CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 91028

Name: Omega-3-Acid Ethyl Esters Capsules USP, 1 gram

Sponsor: Teva Pharmaceuticals USA

Approval Date: April 7, 2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 91028

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 91028

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 091028

Teva Pharmaceuticals USA
Attention: Scott Tomsky
Vice President, U.S. Generics Regulatory Affairs
425 Privet Road
Horsham, PA 19044

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) received on November 10, 2008, and submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Omega-3-Acid Ethyl Esters Capsules USP, 1 gram.

Reference is also made to the Complete Response letter issued by this office on August 13, 2013, and to your amendments dated December 30, 2013; and January 30, March 20, and April 3, 2014.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Omega-3-Acid Ethyl Esters Capsules USP, 1 gram, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Lovaza Capsules, 1 gram, of SmithKline Beecham (SKB). Your dissolution (qualitative capsule rupture) testing (QCRT) should be incorporated into the stability and quality control program using the same method and specifications proposed in your ANDA.

The RLD upon which you have based your ANDA, SKB's Lovaza capsules, is subject to a period of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. Patent No. 5,656,667 (the '667 patent), is scheduled to expire on April 10, 2017.

Your ANDA contains a paragraph IV certification under section 505(j)(2)(A)(vii)(IV) of the Act stating that the '667 patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Omega-3-Acid Ethyl Esters Capsules USP, 1 gram, under this ANDA. You have notified the agency that Teva Pharmaceuticals USA (Teva) complied with the requirements of section 505(j)(2)(B) of the Act, and that litigation was initiated against Teva for infringement of the '667 patent within the statutory 45-day period in the United States District Court for the District of Delaware [Pronova BioPharma Norge AS v. Teva Pharmaceuticals USA, Inc., and Par Pharmaceutical, Inc. and Par Pharmaceutical Companies, Inc., Civil Action No. 09-CV-0286]. You have also notified the agency that the United States Court of Appeals for the Federal Circuit found, in a mandate issued on January 23, 2014, that the asserted claims of the '667 patent were invalid.

With respect to 180-day generic drug exclusivity, we note that Teva was a first applicant for Omega-3-Acid Ethyl Esters Capsules USP, 1 gram, to submit a substantially complete ANDA with a paragraph IV certification. Therefore, with this approval, Teva may be eligible for 180 days of generic drug exclusivity for Omega-3-Acid Ethyl Esters Capsules USP, 1 gram. This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the Act, would begin to run from the date of the commercial marketing identified in section 505(j)(5)(B)(iv). The agency notes that Teva failed to obtain tentative approval of this ANDA within 30 months after the date on which the ANDA was filed. See section 505(j)(5)(D)(i)(IV) (forfeiture of exclusivity for failure to obtain tentative approval). The agency is not, however, making a formal determination at this time of Teva's eligibility for 180-day generic drug exclusivity. It will do so only if a subsequent paragraph IV applicant becomes eligible for full approval (a) within 180 days after a first applicant begins commercial marketing of Omega-3-Acid Ethyl Esters Capsules USP, 1 gram, or (b) at any time prior to the expiration of the listed patent if a first applicant has not begun commercial marketing. Please submit correspondence to this ANDA informing the agency of the date commercial marketing begins.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed

drug also will be required to have a REMS. See section 505-1(i) of the Act.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. You should advise the Office of Generic Drugs of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Office of Prescription Drug Promotion with a completed Form FDA 2253 at the time of their initial use.

The Generic Drug User Fee Amendments of 2012 (GDUFA)(Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

Kathleen Uhl, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT L WEST

04/07/2014

Deputy Director, Office of Generic Drugs, for
Kathleen Uhl, M.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 91028

LABELING

NDC 0093-5401-56

OMEGA-3-ACID ETHYL ESTERS Capsules USP

1 gram*

PHARMACIST: PLEASE DISPENSE WITH ATTACHED PATIENT INFORMATION LEAFLET

℞ only

Swallow capsules whole.

30 CAPSULES

TEVA

* Each capsule contains 1 gram omega-3-acid ethyl ester liquid concentrate consisting of at least 900 mg omega-3-acid ethyl esters, USP.

Each capsule provides:
Eicosapentaenoic acid (EPA) ethyl ester: 465 mg
Docosahexaenoic acid (DHA) ethyl ester: 375 mg

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].
Do not freeze. Protect from light.

Manufactured By:
BANNER PHARMACAPS, INC.
High Point, NC 27265
Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Iss. 8/2013

N 3 0093-5401-56 0

Reference ID: 3434355

NDC 0093-**5401**-89

OMEGA-3-ACID ETHYL ESTERS Capsules USP

1 gram*

PHARMACIST: PLEASE DISPENSE WITH ATTACHED PATIENT INFORMATION LEAFLET

℞ only

Swallow capsules whole.

120 CAPSULES

TEVA

* Each capsule contains 1 gram omega-3-acid ethyl ester liquid concentrate consisting of at least 900 mg omega-3-acid ethyl esters, USP.

Each capsule provides:
Eicosapentaenoic acid (EPA) ethyl ester: 465 mg
Docosahexaenoic acid (DHA) ethyl ester: 375 mg

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Do not freeze. Protect from light.

Manufactured By:
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Iss. 8/2013

N 0093-5401-89 8

Reference ID: 3434355

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use omega-3-acid ethyl esters capsules USP safely and effectively. See full prescribing information for omega-3-acid ethyl esters capsules USP.

OMEGA-3-ACID ETHYL ESTERS capsules USP for oral use

Initial U.S. Approval: 2004

- - RECENT MAJOR CHANGES - -

Indications and Usage, Limitations of Use (1) 06/2013

Warnings and Precautions, Recurrent Atrial Fibrillation or Flutter (5.3) 08/2012

- - INDICATIONS AND USAGE - -

Omega-3-acid ethyl esters capsules USP are a combination of ethyl esters of omega 3 fatty acids, principally EPA and DHA, indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia. (1)

Limitations of Use:

- The effect of omega-3-acid ethyl esters capsules USP on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined. (1)
- The effect of omega-3-acid ethyl esters capsules USP on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia has not been determined. (1)

- DOSAGE AND ADMINISTRATION -

- The daily dose of omega-3-acid ethyl esters capsules USP is 4 grams per day taken as a single 4 gram dose (4 capsules) or as two 2 gram doses (2 capsules given twice daily). (2)
- Patients should be advised to swallow omega-3-acid ethyl esters capsules USP whole. Do not break open, crush, dissolve or chew omega-3-acid ethyl esters capsules USP. (2)

- DOSAGE FORMS AND STRENGTHS -

Capsules: 1 gram (3)

- - - - CONTRAINDICATIONS - - - -

Omega-3-acid ethyl esters capsules are contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to omega-3-acid ethyl esters or any of its components. (4)

- WARNINGS AND PRECAUTIONS -

- In patients with hepatic impairment, monitor ALT and AST levels periodically during therapy. (5.1)
- Omega-3-acid ethyl esters may increase levels of LDL. Monitor LDL levels periodically during therapy. (5.1)
- Use with caution in patients with known hypersensitivity to fish and/or shellfish. (5.2)
- There is a possible association between omega-3-acid ethyl esters and more frequent recurrences of symptomatic atrial fibrillation or flutter in patients with paroxysmal or persistent atrial fibrillation, particularly within the first months of initiating therapy. (5.3)

- - - - ADVERSE REACTIONS - - - -

The most common adverse reactions (incidence > 3% and greater than placebo) were eructation, dyspepsia, and taste perversion. (6)

To report SUSPECTED ADVERSE REACTIONS, contact TEVA USA, PHARMACOVIGILANCE at 1-866-832-8537 or drug.safety@tevapharm.com; or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

- - - DRUG INTERACTIONS - - -

Omega-3-acids may prolong bleeding time. Patients taking omega-3-acid ethyl esters and an anticoagulant or other drug affecting coagulation (e.g., anti-platelet agents) should be monitored periodically. (7.1)

- USE IN SPECIFIC POPULATIONS -

- Pregnancy: Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2013

Iss. 10/2013

OMEGA-3-ACID ETHYL ESTERS CAPSULES USP

℞ only

5401

FULL PRESCRIBING INFORMATION: CONTENTS*

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PATIENT INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Omega-3-acid ethyl esters capsules USP are indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia.

Usage Considerations: Patients should be placed on an appropriate lipid-lowering diet before receiving omega-3-acid ethyl esters capsules USP and should continue this diet during treatment with omega-3-acid ethyl esters capsules USP.

Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal before instituting omega-3-acid ethyl esters capsule USP therapy. Every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (such as beta blockers, thiazides, estrogens) should be discontinued or changed if possible prior to consideration of triglyceride-lowering drug therapy.

Limitations of Use:

The effect of omega-3-acid ethyl esters capsules USP on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined.

The effect of omega-3-acid ethyl esters capsules USP on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia has not been determined.

2 DOSAGE AND ADMINISTRATION

- Assess triglyceride levels carefully before initiating therapy. Identify other causes (e.g., diabetes mellitus, hypothyroidism, or medications) of high triglyceride levels and manage as appropriate [*see Indications and Usage (1)*].
- Patients should be placed on an appropriate lipid-lowering diet before receiving omega-3-acid ethyl esters capsules USP, and should continue this diet during treatment with omega-3-acid ethyl esters capsules USP. In clinical studies, omega-3-acid ethyl esters capsules were administered with meals.

The daily dose of omega-3-acid ethyl esters capsules USP is 4 grams per day. The daily dose may be taken as a single 4 gram dose (4 capsules) or as two 2 gram doses (2 capsules given twice daily).

Patients should be advised to swallow omega-3-acid ethyl esters capsules USP whole. Do not break open, crush, dissolve or chew omega-3-acid ethyl esters capsules USP.

3 DOSAGE FORMS AND STRENGTHS

Omega-3-acid ethyl esters capsules USP are supplied as 1 gram oblong, clear, soft gel capsules filled with slightly yellow to yellow liquid and imprinted with "TV 5401" in white ink.

4 CONTRAINDICATIONS

Omega-3-acid ethyl esters capsules are contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to omega-3-acid ethyl esters or any of its components.

5 WARNINGS AND PRECAUTIONS

5.1 Monitoring: Laboratory Tests

In patients with hepatic impairment, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels should be monitored periodically during therapy with omega-3-acid ethyl esters. In some patients, increases in ALT levels without a concurrent increase in AST levels were observed.

In some patients, omega-3-acid ethyl esters increases LDL-C levels. LDL-C levels should be monitored periodically during therapy with omega-3-acid ethyl esters.

Laboratory studies should be performed periodically to measure the patient's TG levels during therapy with omega-3-acid ethyl esters.

5.2 Fish Allergy

Omega-3-acid ethyl esters contains ethyl esters of omega-3 fatty acids (EPA and DHA) obtained from the oil of several fish sources. It is not known whether patients with allergies to fish and/or shellfish, are at increased risk of an allergic reaction to omega-3-acid ethyl esters. Omega-3-acid ethyl esters should be used with caution in patients with known hypersensitivity to fish and/or shellfish.

5.3 Recurrent Atrial Fibrillation (AF) or Flutter

In a double-blind, placebo-controlled trial of 663 patients with symptomatic paroxysmal AF (n = 542) or persistent AF (n = 121), recurrent AF or flutter was observed in patients randomized to omega-3-acid ethyl esters who received 8 grams/day for 7 days and 4 grams/day thereafter for 23 weeks at a higher rate relative to placebo. Patients in this trial had median baseline triglycerides of 127 mg/dL, had no substantial structural heart disease, were taking no anti-arrhythmic therapy (rate control permitted), and were in normal sinus rhythm at baseline.

At 24 weeks, in the paroxysmal AF stratum, there were 129 (47%) first recurrent symptomatic AF or flutter events on placebo and 141 (53%) on omega-3-acid ethyl esters [primary endpoint, HR 1.19; 95% CI 0.93, 1.35]. In the persistent AF stratum, there were 19 (35%) events on placebo and 34 (52%) events on omega-3-acid ethyl esters [HR 1.63; 95% CI 0.91, 2.18]. For both strata combined, the HR was 1.25; 95% CI 1.00, 1.40. Although the clinical significance of these results is uncertain, there is a possible association between omega-3-acid ethyl esters and more frequent recurrences of symptomatic atrial fibrillation or flutter in patients with paroxysmal or persistent atrial fibrillation, particularly within the first 2 to 3 months of initiating therapy.

Omega-3-acid ethyl esters are not indicated for the treatment of AF or flutter.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse reactions reported in at least 3% and at a greater rate than placebo for patients treated with omega-3-acid ethyl esters based on pooled data across 23 clinical studies are listed in **Table 1**.

Table 1. Adverse Reactions Occurring at Incidence ≥ 3% and Greater Than Placebo in Clinical Studies of Omega-3-Acid Ethyl Esters

Adverse Reaction[a]	Omega-3-Acid Ethyl Esters (N = 655)		Placebo (N = 370)	
	n	%	n	%
Eructation	29	4	5	1
Dyspepsia	22	3	6	2
Taste perversion	27	4	1	< 1

[a] Studies included subjects with HTG and severe HTG.

Additional adverse reactions from clinical studies are listed below:

Digestive System: Constipation, gastrointestinal disorder and vomiting.

Metabolic and Nutritional Disorders: Increased ALT and increased AST.

Skin: Pruritus and rash.

6.2 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the events described below have been identified during post-approval use of omega-3-acid ethyl esters. Because these events are reported voluntarily from a population of unknown size, it is not possible to reliably estimate their frequency or to always establish a causal relationship to drug exposure.

The following events have been reported: anaphylactic reaction, hemorrhagic diathesis.

7 DRUG INTERACTIONS

7.1 Anticoagulants or Other Drugs Affecting Coagulation

Some studies with omega-3-acids demonstrated prolongation of bleeding time. The prolongation of bleeding time reported in these studies has not exceeded normal limits and did not produce clinically significant bleeding episodes. Clinical studies have not been done to thoroughly examine the effect of omega-3-acid ethyl esters and concomitant anticoagulants. Patients receiving treatment with omega-3-acid ethyl esters and an anticoagulant or other drug affecting coagulation (e.g., anti-platelet agents) should be monitored periodically.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

Pregnancy category C

There are no adequate and well-controlled studies in pregnant women. It is unknown whether omega-3-acid ethyl esters can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Omega-3-acid ethyl esters should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus.

Animal Data: Omega-3-acid ethyl esters have been shown to have an embryocidal effect in pregnant rats when given in doses resulting in exposures 7 times the recommended human dose of 4 grams/day based on a body surface area comparison.

In female rats given oral gavage doses of 100, 600, and 2,000 mg/kg/day beginning 2 weeks prior to mating and continuing through gestation and lactation, no adverse effects were observed in the high dose group (5 times human systemic exposure following an oral dose of 4 grams/day based on body surface area comparison).

In pregnant rats given oral gavage doses of 1,000, 3,000, and 6,000 mg/kg/day from gestation day 6 through 15, no adverse effects were observed (14 times human systemic exposure following an oral dose of 4 grams/day based on a body surface area comparison).

In pregnant rats given oral gavage doses of 100, 600, and 2,000 mg/kg/day from gestation day 14 through lactation day 21, no adverse effects were seen at 2,000 mg/kg/day (5 times the human systemic exposure following an oral dose of 4 grams/day based on a body surface area comparison). However, decreased live births (20% reduction) and decreased survival to postnatal day 4 (40% reduction) were observed in a dose-ranging study using higher doses of 3,000 mg/kg/day (7 times the human systemic exposure following an oral dose of 4 grams/day based on a body surface area comparison).

In pregnant rabbits given oral gavage doses of 375, 750, and 1,500 mg/kg/day from gestation day 7 through 19, no findings were observed in the fetuses in groups given 375 mg/kg/day (2 times human systemic exposure following an oral dose of 4 grams/day based on a body surface area comparison). However, at higher doses, evidence of maternal toxicity was observed (4 times human systemic exposure following an oral dose of 4 grams/day based on a body surface area comparison).

8.3 Nursing Mothers

Studies with omega-3-acid ethyl esters have demonstrated excretion in human milk. The effect of this excretion on the infant of a nursing mother is unknown; caution should be exercised when omega-3-acid ethyl esters is administered to a nursing mother. An animal study in lactating rats given oral gavage ^{14}C-ethyl EPA demonstrated that drug levels were 6 to 14 times higher in milk than in plasma.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

A limited number of patients older than 65 years were enrolled in the clinical studies of omega-3-acid ethyl esters. Safety and efficacy findings in subjects older than 60 years did not appear to differ from those of subjects younger than 60 years.

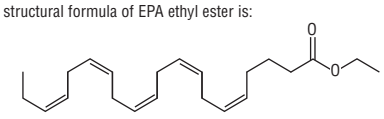
9 DRUG ABUSE AND DEPENDENCE

Omega-3-acid ethyl esters does not have any known drug abuse or withdrawal effects.

11 DESCRIPTION

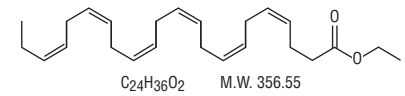
Omega-3-acid ethyl esters, USP, a lipid-regulating agent, is supplied as a liquid-filled gel capsule for oral administration. Each 1 gram capsule of omega-3-acid ethyl esters contains at least 900 mg of the ethyl esters of omega-3 fatty acids. These are predominantly a combination of ethyl esters of eicosapentaenoic acid (EPA - approximately 465 mg) and docosahexaenoic acid (DHA - approximately 375 mg).

The structural formula of EPA ethyl ester is:



$C_{22}H_{34}O_2$ M.W. 330.51

The structural formula of DHA ethyl ester is:



$C_{24}H_{36}O_2$ M.W. 356.55

Omega-3-acid ethyl esters capsules USP also contain the following inactive ingredients: 4 mg alpha-tocopherol, gelatin, glycerin, hypromellose, propylene glycol, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of omega-3-acid ethyl esters is not completely understood. Potential mechanisms of action include inhibition of acyl-CoA:1,2-diacylglycerol acyltransferase, increased mitochondrial and peroxisomal β-oxidation in the liver, decreased lipogenesis in the liver, and increased plasma lipoprotein lipase activity. Omega-3-acid ethyl esters may reduce the synthesis of triglycerides in the liver because EPA and DHA are poor substrates for the enzymes responsible for TG synthesis, and EPA and DHA inhibit esterification of other fatty acids.

12.3 Pharmacokinetics

In healthy volunteers and in patients with hypertriglyceridemia, EPA and DHA were absorbed when administered as ethyl esters orally. Omega-3-acids administered as ethyl esters induced significant, dose-dependent increases in serum phospholipid EPA content, though increases in DHA content were less marked and not dose-dependent when administered as ethyl esters.

Specific Populations: ***Age:*** Uptake of EPA and DHA into serum phospholipids in subjects treated with omega-3-acid ethyl esters was independent of age (< 49 years versus ≥ 49 years).

Gender: Females tended to have more uptake of EPA into serum phospholipids than males. The clinical significance of this is unknown.

Pediatric: Pharmacokinetics of omega-3-acid ethyl esters have not been studied.

Renal or Hepatic Impairment: Omega-3-acid ethyl esters has not been studied in patients with renal or hepatic impairment.

Drug-Drug Interactions: ***Simvastatin:*** In a 14 day study of 24 healthy adult subjects, daily coadministration of simvastatin 80 mg with omega-3-acid ethyl esters 4 grams did not affect the extent (AUC) or rate (C_{max}) of exposure to simvastatin or the major active metabolite, beta-hydroxy simvastatin at steady state.

Atorvastatin: In a 14 day study of 50 healthy adult subjects, daily coadministration of atorvastatin 80 mg with omega-3-acid ethyl esters 4 grams did not affect AUC or C_{max} of exposure to atorvastatin, 2-hydroxyatorvastatin, or 4-hydroxyatorvastatin at steady state.

Rosuvastatin: In a 14 day study of 48 healthy adult subjects, daily coadministration of rosuvastatin 40 mg with omega-3-acid ethyl esters 4 grams did not affect AUC or C_{max} of exposure to rosuvastatin at steady state.

In vitro studies using human liver microsomes indicated that clinically significant cytochrome P450 mediated inhibition by EPA/DHA combinations are not expected in humans.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a rat carcinogenicity study with oral gavage doses of 100, 600, and 2,000 mg/kg/day, males were treated with omega-3-acid ethyl esters for 101 weeks and females for 89 weeks without an increased incidence of tumors (up to 5 times human systemic exposures following an oral dose of 4 grams/day based on a body surface area comparison). Standard lifetime carcinogenicity bioassays were not conducted in mice.

Omega-3-acid ethyl esters were not mutagenic or clastogenic with or without metabolic activation in the bacterial mutagenesis (Ames) test with *Salmonella typhimurium* and *Escherichia coli* or in the chromosomal aberration assay in Chinese hamster V79 lung cells or human lymphocytes. Omega-3-acid ethyl esters were negative in the *in vivo* mouse micronucleus assay.

In a rat fertility study with oral gavage doses of 100, 600, and 2,000 mg/kg/day, males were treated for 10 weeks prior to mating and females were treated for 2 weeks prior to and throughout mating, gestation, and lactation. No adverse effect on fertility was observed at 2,000 mg/kg/day (5 times human systemic exposure following an oral dose of 4 grams/day based on a body surface area comparison).

PATIENT INFORMATION

OMEGA-3-ACID ETHYL ESTERS CAPSULES USP

Read this Patient Information before you start taking omega-3-acid ethyl esters capsules, and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What are omega-3-acid ethyl esters capsules?

Omega-3-acid ethyl esters capsules are a prescription medicine used along with a low fat and low cholesterol diet to lower very high triglyceride (fat) levels in adults.

It is not known if omega-3-acid ethyl esters capsules change your risk of having inflammation of your pancreas (pancreatitis).

It is not known if omega-3-acid ethyl esters capsules prevent you from having a heart attack or stroke.

It is not known if omega-3-acid ethyl esters capsules are safe and effective in children.

Who should not take omega-3-acid ethyl esters capsules?

Do not take omega-3-acid ethyl esters capsules if you are allergic to omega-3-acid ethyl esters or any of the ingredients in omega-3-acid ethyl esters capsules. See the end of this leaflet for a complete list of ingredients in omega-3-acid ethyl esters capsules.

What should I tell my doctor before taking omega-3-acid ethyl esters capsules?

Before you take omega-3-ethyl esters capsules, tell your doctor if you:

- have diabetes.
- have a low thyroid problem (hypothyroidism).
- have a liver problem.
- have a pancreas problem.
- have a certain heart rhythm problem called atrial fibrillation or flutter.
- are allergic to fish or shellfish. It is not known if people who are allergic to fish or shellfish are also allergic to omega-3-acid ethyl esters capsules.
- are pregnant, or plan to become pregnant. It is not known if omega-3-acid ethyl esters capsules will harm your unborn baby.
- are breastfeeding or plan to breastfeed. Omega-3-acid ethyl esters can pass into your breast milk. You and your doctor should decide if you will take omega-3-acid ethyl esters capsules or breastfeed.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicine, vitamins, and herbal supplements.

Omega-3-acid ethyl esters capsules can interact with certain other medicines that you are taking. Using omega-3-acid ethyl esters capsules with medicines that affect blood clotting (anticoagulants or blood thinners) may cause serious side effects.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take omega-3-acid ethyl esters capsules?

- Take omega-3-acid ethyl esters capsules exactly as your doctor tells you to take them.
- You should not take more than 4 capsules of omega-3-acid ethyl esters capsules each day. Either take all 4 capsules at one time, or 2 capsules two times a day.
- Do not change your dose or stop omega-3-acid ethyl esters capsules without talking to your doctor.
- Take omega-3-acid ethyl esters capsules with or without food.
- Take omega-3-acid ethyl esters capsules whole. Do not break, crush, dissolve, or chew omega-3-acid ethyl esters capsules before swallowing. If you cannot swallow omega-3-acid ethyl esters capsules whole, tell your doctor. You may need a different medicine.
- Your doctor may start you on a diet that is low in saturated fat, cholesterol, carbohydrates, and low in added sugars before giving you omega-3-acid ethyl esters capsules. Stay on this diet while taking omega-3-acid ethyl esters capsules.
- Your doctor should do blood tests to check your triglyceride, bad cholesterol and liver function levels while you take omega-3-acid ethyl esters capsules.

Reference ID: 3434355

What are the possible side effects of omega-3-acid ethyl esters capsules?
Omega-3-acid ethyl esters capsules may cause serious side effects, including:

- increases in the results of blood tests used to check your liver function (ALT and AST) and your bad cholesterol levels (LDL-C).
- increases in the frequency of a heart rhythm problem (atrial fibrillation or flutter) may especially happen in the first few months of taking omega-3-acid ethyl esters capsules if you already have that problem.

The most common side effects of omega-3-acid ethyl esters capsules include:

- burping
- upset stomach
- a change in your sense of taste

Talk to your doctor if you have a side effect that bothers you or does not go away.

These are not all the possible side effects of omega-3-acid ethyl esters capsules. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store omega-3-acid ethyl esters capsules?

- Store omega-3-acid ethyl esters capsules at room temperature, 20° to 25°C (68° to 77°F).
- Do not freeze omega-3-acid ethyl esters capsules.
- Safely throw away medicine that is out of date or no longer needed.

Keep omega-3-acid ethyl esters capsules and all medicines out of the reach of children.

General information about the safe and effective use of omega-3-acid ethyl esters capsules

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use omega-3-acid ethyl esters capsules for a condition for which they were not prescribed. Do not give omega-3-acid ethyl esters capsules to other people, even if they have the same symptoms you have. They may harm them.

This Patient Information Leaflet summarizes the most important information about omega-3-acid ethyl esters capsules. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about omega-3-acid ethyl esters capsules that is written for health professionals.

For more information, call 1-888-838-2872.

What are the ingredients in omega-3-acid ethyl esters capsules USP?

Active Ingredient: omega-3-acid ethyl esters, USP

Inactive Ingredients: 4 mg alpha-tocopherol, gelatin, glycerin, hypromellose, propylene glycol, and titanium dioxide.

This patient labeling has been approved by the U.S. Food and Drug Administration.

Manufactured By:
BANNER PHARMACAPS, INC.
High Point, NC 27265

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Iss. 7/2013

14 CLINICAL STUDIES

14.1 Severe Hypertriglyceridemia

The effects of omega-3-acid ethyl esters 4 grams per day were assessed in 2 randomized, placebo-controlled, double-blind, parallel-group studies of 84 adult patients (42 on omega-3-acid ethyl esters, 42 on placebo) with very high triglyceride levels. Patients whose baseline triglyceride levels were between 500 and 2,000 mg/dL were enrolled in these 2 studies of 6 and 16 weeks duration. The median triglyceride and LDL-C levels in these patients were 792 mg/dL and 100 mg/dL, respectively. Median HDL-C level was 23.0 mg/dL.

The changes in the major lipoprotein lipid parameters for the groups receiving omega-3-acid ethyl esters or placebo are shown in **Table 2**.

Table 2. Median Baseline and Percent Change From Baseline in Lipid Parameters in Patients With Severe Hypertriglyceridemia (≥ 500 mg/dL)

Parameter	Omega-3-Acid Ethyl Esters N = 42		Placebo N = 42		Difference
	BL	% Change	BL	% Change	
TG	816	-44.9	788	+6.7	-51.6
Non-HDL-C	271	-13.8	292	-3.6	-10.2
TC	296	-9.7	314	-1.7	-8.0
VLDL-C	175	-41.7	175	-0.9	-40.8
HDL-C	22	+9.1	24	0.0	+9.1
LDL-C	89	+44.5	108	-4.8	+49.3

BL = Baseline (mg/dL); % Change = Median Percent Change from Baseline; Difference = Omega-3-acid ethyl esters Median % Change – Placebo Median % Change

Omega-3-acid ethyl esters 4 grams per day reduced median TG, VLDL-C, and non-HDL-C levels and increased median HDL-C from baseline relative to placebo. Treatment with omega-3-acid ethyl esters to reduce very high TG levels may result in elevations in LDL-C and non-HDL-C in some individuals. Patients should be monitored to ensure that the LDL-C level does not increase excessively.

The effect of omega-3-acid ethyl esters on the risk of pancreatitis in patients with severe hypertriglyceridemia has not been determined.

The effect of omega-3-acid ethyl esters on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia has not been determined.

14.2 Other Clinical Experience

The effects of omega-3-acid ethyl esters 4 grams per day as add-on therapy to treatment with simvastatin were evaluated in a randomized, placebo-controlled, double-blind, parallel-group study of 254 adult patients (122 on omega-3-acid ethyl esters and 132 on placebo) with persistent high triglycerides (200 to 499 mg/dL) despite simvastatin therapy. Patients were treated with open-label simvastatin 40 mg per day for 8 weeks prior to randomization to control their LDL-C to no greater than 10% above NCEP ATP III goal and remained on this dose throughout the study. Following 8 weeks of open-label treatment with simvastatin, patients were randomized to either omega-3-acid ethyl esters 4 grams per day or placebo for an additional 8 weeks with simvastatin co-therapy. The median baseline triglyceride and LDL-C levels in these patients were 268 mg/dL and 89 mg/dL, respectively. Median baseline non-HDL-C and HDL-C levels were 138 mg/dL and 45 mg/dL, respectively.

The changes in the major lipoprotein lipid parameters for the groups receiving omega-3-acid ethyl esters plus simvastatin or placebo plus simvastatin are shown in **Table 3**.

Table 3. Response to the Addition of Omega-3-Acid Ethyl Esters 4 grams per day to Ongoing Simvastatin 40 mg per day Therapy in Patients With High Triglycerides (200 to 499 mg/dL)

Parameter	Omega-3-Acid Ethyl Esters + Simvastatin N = 122			Placebo + Simvastatin N = 132			Difference	P-Value
	BL	EOT	Median % Change	BL	EOT	Median % Change		
Non-HDL-C	137	123	-9.0	141	134	-2.2	-6.8	< 0.0001
TG	268	182	-29.5	271	260	-6.3	-23.2	< 0.0001
TC	184	172	-4.8	184	178	-1.7	-3.1	< 0.05
VLDL-C	52	37	-27.5	52	49	-7.2	-20.3	< 0.05
Apo-B	86	80	-4.2	87	85	-1.9	-2.3	< 0.05
HDL-C	46	48	+3.4	43	44	-1.2	+4.6	< 0.05
LDL-C	91	88	+0.7	88	85	-2.8	+3.5	= 0.05

BL = Baseline (mg/dL); EOT = End of Treatment (mg/dL); Median % Change = Median Percent Change from Baseline; Difference = Omega-3-Acid Ethyl Esters Median % Change - Placebo Median % Change

Omega-3-acid ethyl esters 4 grams per day significantly reduced non-HDL-C, TG, TC, VLDL-C, and Apo-B levels and increased HDL-C and LDL-C from baseline relative to placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

Omega-3-acid ethyl esters capsules USP are available as follows:

1 gram – slightly yellow to yellow liquid, oblong, clear, soft gel capsules, imprinted with "TV 5401" in white ink, in bottles of 30 and 120.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Do not freeze. Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (17.2).

17.1 Information for Patients

- Omega-3-acid ethyl esters capsules should be used with caution in patients with known sensitivity or allergy to fish and/or shellfish [*see Warnings and Precautions (5.2)*].
- Patients should be advised that use of lipid-regulating agents does not reduce the importance of adhering to diet [*see Dosage and Administration (2)*].
- Patients should be advised not to alter omega-3-acid ethyl esters capsules in any way and to ingest intact capsules only [*see Dosage and Administration (2)*].
- Instruct patients to take omega-3-acid ethyl esters capsules as prescribed. If a dose is missed, patients should take it as soon as they remember. However, if they miss one day of omega-3-acid ethyl esters capsules, they should not double the dose when they take it.

17.2 FDA-Approved Patient Labeling

Patient labeling is provided as a tear-off leaflet at the end of this full prescribing information.

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BANNER PHARMACAPS, INC.
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Iss. 10/2013

PATIENT INFORMATION

OMEGA-3-ACID ETHYL ESTERS CAPSULES USP

Read this Patient Information before you start taking omega-3-acid ethyl esters capsules, and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What are omega-3-acid ethyl esters capsules?

Omega-3-acid ethyl esters capsules are a prescription medicine used along with a low fat and low cholesterol diet to lower very high triglyceride (fat) levels in adults.

It is not known if omega-3-acid ethyl esters capsules change your risk of having inflammation of your pancreas (pancreatitis).

It is not known if omega-3-acid ethyl esters capsules prevent you from having a heart attack or stroke.

It is not known if omega-3-acid ethyl esters capsules are safe and effective in children.

Who should not take omega-3-acid ethyl esters capsules?

Do not take omega-3-acid ethyl esters capsules if you are allergic to omega-3-acid ethyl esters or any of the ingredients in omega-3-acid ethyl esters capsules. See the end of this leaflet for a complete list of ingredients in omega-3-acid ethyl esters capsules.

What should I tell my doctor before taking omega-3-acid ethyl esters capsules?

Before you take omega-3-ethyl esters capsules, tell your doctor if you:

- have diabetes.
- have a low thyroid problem (hypothyroidism).
- have a liver problem.
- have a pancreas problem.
- have a certain heart rhythm problem called atrial fibrillation or flutter.
- are allergic to fish or shellfish. It is not known if people who are allergic to fish or shellfish are also allergic to omega-3-acid ethyl esters capsules.
- are pregnant, or plan to become pregnant. It is not known if omega-3-acid ethyl esters capsules will harm your unborn baby.
- are breastfeeding or plan to breastfeed. Omega-3-acid ethyl esters can pass into your breast milk. You and your doctor should decide if you will take omega-3-acid ethyl esters capsules or breastfeed.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicine, vitamins, and herbal supplements.

Omega-3-acid ethyl esters capsules can interact with certain other medicines that you are taking. Using omega-3-acid ethyl esters capsules with medicines that affect blood clotting (anticoagulants or blood thinners) may cause serious side effects.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take omega-3-acid ethyl esters capsules?

- Take omega-3-acid ethyl esters capsules exactly as your doctor tells you to take them.
- You should not take more than 4 capsules of omega-3-acid ethyl esters capsules each day. Either take all 4 capsules at one time, or 2 capsules two times a day.
- Do not change your dose or stop omega-3-acid ethyl esters capsules without talking to your doctor.
- Take omega-3-acid ethyl esters capsules with or without food.
- Take omega-3-acid ethyl esters capsules whole. Do not break, crush, dissolve, or chew omega-3-acid ethyl esters capsules before swallowing. If you cannot swallow omega-3-acid ethyl esters capsules whole, tell your doctor. You may need a different medicine.
- Your doctor may start you on a diet that is low in saturated fat, cholesterol, carbohydrates, and low in added sugars before giving you omega-3-acid ethyl esters capsules. Stay on this diet while taking omega-3-acid ethyl esters capsules.
- Your doctor should do blood tests to check your triglyceride, bad cholesterol and liver function levels while you take omega-3-acid ethyl esters capsules.

What are the possible side effects of omega-3-acid ethyl esters capsules?

Omega-3-acid ethyl esters capsules may cause serious side effects, including:

- increases in the results of blood tests used to check your liver function (ALT and AST) and your bad cholesterol levels (LDL-C).
- increases in the frequency of a heart rhythm problem (atrial fibrillation or flutter) may especially happen in the first few months of taking omega-3-acid ethyl esters capsules if you already have that problem.

The most common side effects of omega-3-acid ethyl esters capsules include:

- burping
- upset stomach
- a change in your sense of taste

Talk to your doctor if you have a side effect that bothers you or does not go away.

These are not all the possible side effects of omega-3-acid ethyl esters capsules. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store omega-3-acid ethyl esters capsules?

- Store omega-3-acid ethyl esters capsules at room temperature, 20° to 25°C (68° to 77°F).
- Do not freeze omega-3-acid ethyl esters capsules.
- Safely throw away medicine that is out of date or no longer needed.

Keep omega-3-acid ethyl esters capsules and all medicines out of the reach of children.

General information about the safe and effective use of omega-3-acid ethyl esters capsules

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use omega-3-acid ethyl esters capsules for a condition for which they were not prescribed. Do not give omega-3-acid ethyl esters capsules to other people, even if they have the same symptoms you have. They may harm them.

This Patient Information Leaflet summarizes the most important information about omega-3-acid ethyl esters capsules. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about omega-3-acid ethyl esters capsules that is written for health professionals.

For more information, call 1-888-838-2872.

What are the ingredients in omega-3-acid ethyl esters capsules USP?

Active Ingredient: omega-3-acid ethyl esters, USP

Inactive Ingredients: 4 mg alpha-tocopherol, gelatin, glycerin, hypromellose, propylene glycol, and titanium dioxide.

This patient labeling has been approved by the U.S. Food and Drug Administration.

Manufactured By:
BANNER PHARMACAPS, INC.
High Point, NC 27265

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Iss. 7/2013

PATIENT INFORMATION

OMEGA-3-ACID ETHYL ESTERS CAPSULES USP

Read this Patient Information before you start taking omega-3-acid ethyl esters capsules, and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What are omega-3-acid ethyl esters capsules?

Omega-3-acid ethyl esters capsules are a prescription medicine used along with a low fat and low cholesterol diet to lower very high triglyceride (fat) levels in adults.

It is not known if omega-3-acid ethyl esters capsules change your risk of having inflammation of your pancreas (pancreatitis).

It is not known if omega-3-acid ethyl esters capsules prevent you from having a heart attack or stroke.

It is not known if omega-3-acid ethyl esters capsules are safe and effective in children.

Who should not take omega-3-acid ethyl esters capsules?

Do not take omega-3-acid ethyl esters capsules if you are allergic to omega-3-acid ethyl esters or any of the ingredients in omega-3-acid ethyl esters capsules. See the end of this leaflet for a complete list of ingredients in omega-3-acid ethyl esters capsules.

What should I tell my doctor before taking omega-3-acid ethyl esters capsules?

Before you take omega-3-ethyl esters capsules, tell your doctor if you:

- have diabetes.
- have a low thyroid problem (hypothyroidism).
- have a liver problem.
- have a pancreas problem.
- have a certain heart rhythm problem called atrial fibrillation or flutter.
- are allergic to fish or shellfish. It is not known if people who are allergic to fish or shellfish are also allergic to omega-3-acid ethyl esters capsules.
- are pregnant, or plan to become pregnant. It is not known if omega-3-acid ethyl esters capsules will harm your unborn baby.
- are breastfeeding or plan to breastfeed. Omega-3-acid ethyl esters can pass into your breast milk. You and your doctor should decide if you will take omega-3-acid ethyl esters capsules or breastfeed.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicine, vitamins, and herbal supplements.

Omega-3-acid ethyl esters capsules can interact with certain other medicines that you are taking. Using omega-3-acid ethyl esters capsules with medicines that affect blood clotting (anticoagulants or blood thinners) may cause serious side effects.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take omega-3-acid ethyl esters capsules?

- Take omega-3-acid ethyl esters capsules exactly as your doctor tells you to take them.
- You should not take more than 4 capsules of omega-3-acid ethyl esters capsules each day. Either take all 4 capsules at one time, or 2 capsules two times a day.
- Do not change your dose or stop omega-3-acid ethyl esters capsules without talking to your doctor.
- Take omega-3-acid ethyl esters capsules with or without food.
- Take omega-3-acid ethyl esters capsules whole. Do not break, crush, dissolve, or chew omega-3-acid ethyl esters capsules before swallowing. If you cannot swallow omega-3-acid ethyl esters capsules whole, tell your doctor. You may need a different medicine.
- Your doctor may start you on a diet that is low in saturated fat, cholesterol, carbohydrates, and low in added sugars before giving you omega-3-acid ethyl esters capsules. Stay on this diet while taking omega-3-acid ethyl esters capsules.
- Your doctor should do blood tests to check your triglyceride, bad cholesterol and liver function levels while you take omega-3-acid ethyl esters capsules.

What are the possible side effects of omega-3-acid ethyl esters capsules?

Omega-3-acid ethyl esters capsules may cause serious side effects, including:

- increases in the results of blood tests used to check your liver function (ALT and AST) and your bad cholesterol levels (LDL-C).

- increases in the frequency of a heart rhythm problem (atrial fibrillation or flutter) may especially happen in the first few months of taking omega-3-acid ethyl esters capsules if you already have that problem.

The most common side effects of omega-3-acid ethyl esters capsules include:

- burping
- upset stomach
- a change in your sense of taste

Talk to your doctor if you have a side effect that bothers you or does not go away.

These are not all the possible side effects of omega-3-acid ethyl esters capsules. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store omega-3-acid ethyl esters capsules?

- Store omega-3-acid ethyl esters capsules at room temperature, 20° to 25°C (68° to 77°F).
- Do not freeze omega-3-acid ethyl esters capsules.
- Safely throw away medicine that is out of date or no longer needed.

Keep omega-3-acid ethyl esters capsules and all medicines out of the reach of children.

General information about the safe and effective use of omega-3-acid ethyl esters capsules

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use omega-3-acid ethyl esters capsules for a condition for which they were not prescribed. Do not give omega-3-acid ethyl esters capsules to other people, even if they have the same symptoms you have. They may harm them.

This Patient Information Leaflet summarizes the most important information about omega-3-acid ethyl esters capsules. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about omega-3-acid ethyl esters capsules that is written for health professionals.

For more information, call 1-888-838-2872.

What are the ingredients in omega-3-acid ethyl esters capsules USP?

Active Ingredient: omega-3-acid ethyl esters, USP

Inactive Ingredients: 4 mg alpha-tocopherol, gelatin, glycerin, hypromellose, propylene glycol, and titanium dioxide.

This patient labeling has been approved by the U.S. Food and Drug Administration.

Manufactured By:
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Iss. 7/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 91028

LABELING REVIEWS

APPROVAL SUMMARY

Office of Generic Drugs

REVIEW OF PROFESSIONAL LABELING (4th cycle)

ANDA Number:	091028
Date of Submission:	December 30, 2013
Applicant:	Teva Pharmaceuticals USA
Established Name and Strength:	Omega-3-Acid Ethyl Esters Capsules USP, 1 gram
Proposed Proprietary Name:	None

Labeling Comments below are considered:

☐ Minor Deficiency *

* Please note that the RPM may change the status from Minor Deficiency to Easily Correctable Deficiency if other disciplines are acceptable.

☒ No Comments **(**Labeling Approval Summary)

RPM Note - Labeling comments to be sent to the firm start below:

The Labeling Review Branch has no further questions/comments at this time based on your labeling submission dated December 30, 2013.

Please continue to monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book and the NF-USP online for recent updates, and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17.

Note RPM - Labeling comments end here

REVISIONS NEEDED POST APPROVAL? Yes

1. CONTAINER

   We encourage you to increase the prominence of “Swallow capsules whole” and relocate to appear above the Pharmacist statement.

2. INSERT

   a. HIGHLIGHTS, RECENT MAJOR CHANGES: Delete “Warnings and Precautions, Recurrent Atrial Fibrillation or Flutter (5.3) 08/2012”.

   b. DESCRIPTION: Please revise the second sentence of the first paragraph to read “Each 1 gram capsule of omega-3-acid ethyl esters contains at least 900 mg of the ethyl esters of

omega-3 fatty acids sourced from fish oils." to be the same as the RLD or comment.

The above post-approval comments are annual reportable and will be communicated to the firm once the review has been signed off.

NOTES/QUESTIONS TO THE CHEMIST/BIO REVIEWER/MICRO REVIEWER:

Review Summary

Labeling Submitted	Date submitted	Final or Draft	Recommendation
CONTAINER Bottles of 30s and 120s	12/30/2013	Final	Acceptable for approval
INSERT	12/30/2013	Final	Acceptable for approval
PATIENT INFORMATION	12/30/2013	Final	Acceptable for approval

REMS required?	**(OTC do NOT require)**		
MedGuides and/or PPIs (505-1(e))	☐ Yes	☒ No	
Communication plan (505-1(e))	☐ Yes	☐ No	
Elements to assure safe use (ETASU) (505-1(f)(3))	☐ Yes	☐ No	
Implementation system if certain ETASU (505-1(f)(4))	☐ Yes	☐ No	
Timetable for assessment (505-1(d))	☐ Yes	☐ No	
ANDA REMS acceptable?	☐ Yes	☐ No	☒ N/A

FOR THE RECORD: Please note the first review cycle was completed by Thuyanh Vu, Labeling Reviewer.

1. **MODEL LABELING:** This review is based on the labeling for Lovaza® (omega-3-acid ethyl esters) Capsule of GlaxoSmithKline, NDA 021654/S-039; approved September 11, 2013.

   The labeling approved on 9/11/2013 does not usually require new labeling. This labeling was approved for manufacturing change or addition. Supplement -039 was submitted to add Catalent (b) (4) as an alternate drug product manufacturing site, and associated labeling revisions. The initial submission did not contain labeling, so this was submitted in an amendment to the application.

   The labeling approved 6/26/2013 (s-037) provides for revised package insert in response to the letter dated 12/18/2012.

   BACKGROUND INFORMATION FROM RPM LABELING REVIEW dated 6/30/2013:

   Lovaza was approved 11/10/2004 for the treatment of severe hypertriglyceridemia.

   Vascepa (icosapent ethyl) Capsules (NDA 202057) was approved 7/26/2012 for the same indication. These are the only 2 currently approved fish oil prescription products available. Following the approval of Vascepa, there were some inconsistencies noted between the package inserts of Vascepa and Lovaza, and a supplement request letter was issued to the sponsor of Lovaza on 12/18/2012, requesting some labeling revisions (letter attached). The firm responded with this labeling supplement.

Editorial revisions were made to the labeling as well as the following sections were revised for consistency between the two labeling.

PI

8.3 Nursing Mothers

Studies with omega-3-acid ethyl esters have demonstrated excretion in human milk. The effect of this excretion on the infant of a nursing mother is unknown; caution should be exercised when VASCEPA is administered to a nursing mother. An animal study in lactating rats given oral gavage ^{14}C-ethyl EPA demonstrated that drug levels were 6 to 14 times higher in milk than in plasma.

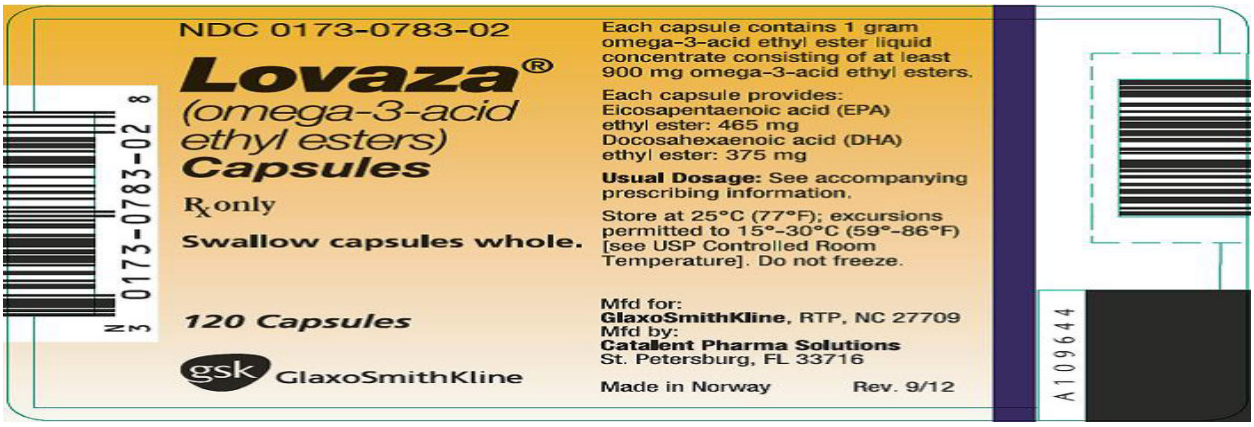
PPI

"What should I tell my doctor before taking LOVAZA?

Before you take LOVAZA, tell your doctor if you:

….are breastfeeding or plan to breastfeed. LOVAZA can pass into your breast milk. You and your doctor should decide if you will take LOVAZA or breastfeed."

S-022 provided for PLR format and inclusion of atorvastatin and rosuvastatin in the Drug Interactions subsection.



MedWatch – (checked January 8, 2014)

Lovaza (omega-3-acid ethyl esters) capsules

Detailed View: Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER)

September 2012

Summary View[1]

5 WARNINGS AND PRECAUTIONS

5.3 Recurrent Atrial Fibrillation (AF) or Flutter

- In a double-blind, placebo-controlled trial of 663 patients with symptomatic paroxysmal AF (n=542) or persistent AF (n=121), recurrent AF or flutter was observed in patients randomized to LOVAZA who received 8 grams/day for 7 days and 4 grams/day thereafter for 23 weeks at a higher rate relative to placebo. .....
- .....Although the clinical significance of these results is uncertain, there is a possible association between LOVAZA and more frequent recurrences of symptomatic atrial fibrillation or flutter in patients with paroxysmal or persistent atrial fibrillation, particularly within the first 2 to 3 months of initiating therapy. LOVAZA is not indicated for the treatment of AF or flutter.

Patient Information Leaflet

What are the possible side effects of LOVAZA?

LOVAZA may cause serious side effects, including:

- increases in the frequency of a heart rhythm problem (atrial fibrillation or flutter) may especially happen in the first few months of taking LOVAZA if you already have that problem.

2. **USP-36:** (checked January 8, 2014)

Omega-3-Acid Ethyl Esters Capsules
ADDITIONAL REQUIREMENTS

• Packaging and Storage: Preserve in tight containers, and store at controlled room temperature. Do not freeze. Protect from light.
• Labeling: The label states the amount of docosahexaenoic acid (DHA) ethyl ester and eicosapentaenoic acid (EPA) ethyl ester, and the minimum amount of total content of omega-3-acid ethyl esters in mg/Capsule. It also states the name and content of any added antioxidant.

3. **PATENT AND EXCLUSIVITY (**checked January 8, 2014)

Patent Data – NDA 021654

No	Expiration	Use Code	Use	How filed	Labeling Impact
5502077	Mar 26, 2013	U-822	Use In Lipid Management	IV	None
5656667	April 10, 2017	U-822	Use In Lipid Management	IV	None
7732488	Jan 30, 2025			IV	None

Exclusivity Data– NDA 021654

Code	Reference	Expiration	Labeling impact
M-87	Inclusion of results from two drug interaction studies with Lipid and Crestor in Clinical Pharmacology section	Sep 16, 2012	**None**

PATENT AMENDMENT UPDATE 12/27/12

While the exclusivity M-87 is still listed in the Orange Book, it is now expired. The language previously protected by this exclusivity is now included in Teva's proposed package insert labeling.

Additionally, the previously listed M-64 and NCE exclusivities are now expired and are no longer listed in the Orange Book.

PATENT AMENDMENT DATED 8/1/2012

STIPULATION OF DISMISSAL WITHOUT PREJUDICE AND ORDER DATED July 22, 2011.

Pursuant to Rule 41(a)(1)(A)(ii), Fed. R. Civ. P., IT IS HEREBY STIPULATED AND AGREED, by and between the parties, through their undersigned counsel of record, that this action (relating to U.S. Patent Nos. 7,678,930; 7,718,698 and 7,732,488) be and hereby is voluntarily dismissed in its entirety without prejudice, including all claims, counterclaims,

Reference ID: 3434355

and requests for relief.

June 15, 2009 amendment informed the Agency that a suit was filed against Teva: Civil Action 09-286-SLR in the United States District Court of the District of Delaware.

4. INACTIVE INGREDIENTS

There is no discrepancy in inactives between the DESCRIPTION and the composition statement. [2.3.P.1-original submission]

Inactive ingredients:
Alpha-tocopherol, gelatin, glycerin, [redacted] (b) (4) White [redacted] (b) (4) titanium dioxide, hypromellose, propylene glycol)

The active ingredient is sensitive to oxygen. Alpha-tocopherol was added by the API manufacturer [redacted] (b) (4) to prevent oxidation. Final fill composition is 4 mg Alpha-tocopherol for every [redacted] (b) (4) mg of API.

5. MANUFACTURING FACILITY

[2.3.P.3- original submission]

Manufacturing and Processing
Banner Pharmacaps, Inc.
4125 Premier Drive
High Point, NC 27252

FROM AMENDMENT DATED 12/30/2013: FACILITY INSPECTIONS SECTION

Teva hereby proposes the following facility as an additional site of drug product packaging and labeling for Omega-3-Acid Ethyl Ester Capsules USP, 1 gram. The facility information is as follows:

Packaging and Labeling
Barr Laboratories Inc.
(an indirect wholly owned subsidiary of Teva Pharmaceuticals USA)
2150 Perrowville Road
Forest, VA 24551
USA
FEI: 3000718267
DUNS: 002931751

Contact Information
Joseph De Vito, Vice President, Quality
[redacted] (b) (6) Fax: 215-591-8987
email: joseph.devito@tevapharm.com

The proposed facility has a current satisfactory cGMP compliance status with the Agency for this type of operation based on its August 12, 2013 – August 23, 2013 inspection.

AMENDMENT DATED 12/30/2013 (3.2.p.3.1.1)
Manufacturing, processing, packaging, labeling, and handling of Omega-3-Acid Ethyl Esters Capsules, 1 g for commercial production will take place at the facilities identified below:

Manufacturing and Processing (same as original submission)

Packaging and Labeling
Teva Pharmaceuticals USA
650 Cathill Road
Sellersville, PA 18960
USA
FEI: 2517175
DUNS: 118234421

Packaging and Labeling
Barr Laboratories Inc.
(an indirect wholly owned subsidiary of Teva Pharmaceuticals USA)
2150 Perrowville Road
Forest, VA 24551
USA
FEI: 3000718267
DUNS: 002931751

6. **FINISHED PRODUCT DESCRIPTION**

RLD: transparent soft gelatin capsules filled with light-yellow oil and bearing the designation REL900

ANDA: [2.3.P.5-original submission]

Slightly yellow to yellow liquid in size 22 oblong clear soft gel capsule, imprinted with (b) (4) in white ink.

CHANGE IN CAPSULE IMPRINT: AMENDMENT DATED 12/30/2013
(Manufacturing Changes Section)

In addition, the updated drug product specifications reflect a minor change to the existing capsule imprint. Specifically, we propose a change in the imprint from (b) (4) to "TV 5401". Please note that there is no change to the ink being used.

7. **STORAGE STATEMENT AND DISPENSING RECOMMENDATIONS**

RLD: Stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Do not freeze.

ANDA: Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Do not freeze.

8. **PRODUCT LINE**

RLD: 1 gram capsules in bottles of 60s and 120s

ANDA: The drug product will be packaged in 30's, and 120's

9. **CONTAINER/CLOSURE**

[2.3.P.7-original submission]
The drug product will be shipped in a 30 capsule/bottle configuration as follows:
Bottle: 120-cc HDPE Bottle (Teva part #333-31-019440)
Cap: 38-mm CRC Cap (Teva part #333-31-021204)

The drug product will be shipped in a 120 capsule/bottle configuration as follows:
Bottle: 400-cc HDPE Bottle (Teva part #333-31-019393)
Cap: 53-mm CRC Cap (Teva part #333-31-021811)

10. **BIOEQUIVALENCE/DISSOLUTION:**

Review is inadequate as of review date 12/14/2012.

Reference ID: 3434365

11. **SPL DATA ELEMENTS**

Updated labeling was provided in SPL format in amendment dated 12/30/2013.

ANDA:
900 mg Omega-3-Acid Ethyl Esters
Color YELLOW (to yellow); Score no score; Shape CAPSULE; Size 22mm; Imprint Code TV; 5401

RLD:
900 mg Omega-3-Acid Ethyl Esters
Color YELLOW (light yellow); Score no score; Shape CAPSULE; Size 24mm; Imprint Code LOVAZA

12. **EXPRESSION OF STRENGTH: We will continue to monitor this issue.**

No updates on the strength for the RLD (checked 1/9/2014)

Agency letter dated 6/18/12 for NDA 021654:
According to Lovaza's approved specification, each capsule contains from 950 mg to 1050 mg of esterified purified fish oil. The principal components are two omega-3 acid ethyl esters, eicosapentaenoic acid (EPA) ethyl ester and docosahexaenoic acid (DHA) ethyl ester. Both are required to be present at a combined concentration of between 800 and 880 mg/capsule. The drug substance specification also includes an acceptance criterion of at least 90% (w/w) total omega-3 ethyl esters – the active ingredients.

Recently reviewed data from your NDA indicate that the total omega-3 ethyl esters content does not deviate significantly from 90% of total capsule fill. For the target 1 gram capsule fill, this amounts to 900 mg of omega-3 ethyl esters. Consequently, we believe that the labeled strength should be changed from 1 gram to 900 mg.

Please revise all labeling to reflect a strength per capsule of 900 mg.

NDA sponsor response dated 8/6/2012:
GSK is not in agreement that the labeled strength of LOVAZA should be changed to 900 mg (see **Attachment 1** for details).

GSK proposes to revise the Dosage Forms and Strengths section of the Prescribing Information to incorporate the language that is currently used on the trade and sample container packaging:
• Each capsule contains 1 gram omega-acid ethyl ester liquid concentrate consisting of at least 900 mg omega-3-acid ethyl esters.
This change to the Prescribing Information would afford a consistent description of the product (in the PI and on the container labels) and would alleviate any potential misunderstandings regarding the amount of active ingredient in a 1 gram capsule. Division consideration and concurrence with this proposal would be much appreciated.

The attachment provided by the firm in the 8/6/2012 amendment provides a detailed explanation of the inactive ingredients.

Email from TL's regarding expression of strength dated 5/7/2013

From: Wu, Ruby (Chi-Ann)
Sent: Tuesday, May 07, 2013 3:29 PM
To: Turner, Betty
Subject: FW: Strength on PDP (Omega-3)

From: Lee, Koung U
Sent: Tuesday, May 07, 2013 2:36 PM
To: Golson, Lillie D; Wu, Ruby (Chi-Ann)
Subject: RE: Strength on PDP (Omega-3)

I agree. What if the RLD gets approved with a different strength?

From: Golson, Lillie D
Sent: Tuesday, May 07, 2013 2:09 PM
To: Wu, Ruby (Chi-Ann); Lee, Koung U
Cc: Golson, Lillie D
Subject: RE: Strength on PDP (Omega-3)

I believe the strength should appear on the PDP as we do with all our products. All vitamins that I buy do have the strength. Might even be better to express as mg rather than grams. There are many others on google image.

<< File: images[2].jpg >> << File: images[1].jpg >> << File: images[3].jpg >>

From: Wu, Ruby (Chi-Ann)
Sent: Tuesday, May 07, 2013 1:18 PM
To: Lee, Koung U; Golson, Lillie D
Subject: Strength on PDP (Omega-3)

Hi Lillie and Koung,

What do you think about the following situation….

RLD Label: (strength not specified on the PDP)

<< File: image[10].jpg >>

OSE review dated 4/27/2004 for the RLD
CONTAINER LABEL
The product strength should appear immediately following or below the established name and be more prominent on the label.
The comment was sent to the firm on 6/4/2004.

The request for the strength on the PDP seemed to have stopped there.

What are your thoughts….should we be the same as the RLD and remain silent on the strength or ask the firm to include the strength "1 gram*" on the PDP

pursuant to the Guidance for Industry?

The **principal display panel** (PDP) is the panel of a label that is most likely to be displayed, presented, shown, or examined by the end user. We recommend that the PDP include the following critical information:

- ☐ Proprietary name
- ☐ **Established name** or **proper name**
- ☐ Product strength
- ☐ Route(s) of administration

☐ Warnings (if any) or cautionary statements (if any)

What are your thoughts?

Ruby

From: Turner, Betty
Sent: Tuesday, May 07, 2013 1:02 PM
To: Wu, Ruby (Chi-Ann)
Subject: RE: ANDA (b) (4)

Hi Ruby,

I like having the strength on the PDP, but would we be following the RLD or is that difference allowed? I do not have a problem with asking the firm to include the strength on the PDP. Do you know of other cases like this?

(b) (4)

If we put the 1 gm on the PDP, I think we will need the asterisk because it consist of at least 900 mg Omega-3-acid ethyl esters.

No rush. Any time is fine with me.

Thanks,
Betty

From: Wu, Ruby (Chi-Ann)
Sent: Tuesday, May 07, 2013 12:41 PM
To: Turner, Betty
Subject: RE: ANDA (b) (4)

Hi Betty,

OSE review dated 4/27/2004

CONTAINER LABEL

The product strength should appear immediately following or below the established name and be more prominent on the label.

The comment was sent to the firm on 6/4/2004.

However, I can't find the amendment where the firm responded to this request.

Personally, I do not see a reason why we shouldn't include the strength. Maybe we can do a "Upon further consideration, we encourage you to include the expression of strength on the principal display panel."

Do you think we need an asterisk after "1 gram*" and before the "Each capsule contains" statement?

What do you think?

Ruby

P.S. I just started my review so probably won't send it back to you until tomorrow.

Please note the email below was taken from the previous review which was completed by labeling reviewer Thuyanh Vu.

The following information was taken from the previous review completed by Thuyanh Vu dated 1/25/2010 in DARRTS.

See email below between John Grace and myself. There was a question of importance with the placement of the "1 gram" on the principal display panel of the generic companies' container labels. I will ask ALL generic companies to delete the "1 gram" from the principal display panel.

John Grace's email from 1/21/10:

There is no requirement for putting on PDP in conjunction with est name.
But amount of active ingredient(s) is to appear on label, "Each capsule contains."

In this case it appears that the amount of active contained in capsules may not be as important as what amount of components is provided.
I don't know, we should follow RLD to avoid confusion

From: Vu, Thuyanh (Ann)
Sent: Thursday, January 21, 2010 9:38 AM
To: Grace, John F
Subject: FW: 21654 (Lovaza) label question about the 1 gram placement on the container label

John,

Could you read the below question? I seem to remember that RLD do not always put the strength on the principal display panel (especially if the drug product only comes in one strength) but generics do? Could you clarify?

Thanks
Ann

Question to Chemist on January 21, 2010,

Suhas replied on 1/21/2010

Hi Ann,

Thanks for the info. I have not reviewed this application yet. I will let you know if there is discrepancy between components and labeling.

Suhas

Suhas,

Teva's labeling differs from the RLD's Lovaza in the DESCRIPTION

Section: Teva's capsule: inactive ingredients: 4 mg alpha-tocopherol,

gelatin..."

RLD's insert: "inactive ingredients: 4 mg α-tocopherol (in a carrier of partially hydrogenated vegetable oils including soybean oil).

Not sure if Teva's is acceptable since it did not specify the carrier.

Thanks
Ann

Date of Review:	January 8, 2014
Primary Reviewer:	Betty Turner
Team Leader:	Chi-Ann Wu

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BETTY B TURNER
01/10/2014

CHI-ANN Y WU
01/10/2014
For Wm. Peter Rickman

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	091028
Date of Submission:	March 8, 2010, March 4, 2011 and December 27, 2012
Applicant's Name:	Teva Pharmaceuticals USA
Established Name and Strength:	Omega-3-Acid Ethyl Esters Capsules USP, 1 gram

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Labeling Comments below are considered:

☐ NOT easily correctable (applicant cannot respond within 10 business days)

☒ Easily correctable (respond within 10 business days)

☐ No Comments **(**Labeling Approval Summary or Tentative Approval Summary)

RPM Note - Labeling comments to be sent to the firm start below:

Labeling Deficiencies determined on August 9, 2013 based on your submission dated March 8, 2010, March 4, 2011 and December 27, 2012:

1. CONTAINER
   a. Upon further consideration, please add the expression of strength "1 gram*" to the principal display panel and add an asterisk immediately before the "*Each capsule contains…" statement on the side panel.

   b. Revise "Each capsule contains 1 g…" to read "*Each capsule contains 1 gram…"

   c. Add "Protect from light" to the storage statement.

2. PHYSICIAN INSERT
   a. GENERAL COMMENT: Due to changes in the insert labeling for the reference listed drug Lovaza® (omega-3-acid ethyl esters) Capsules by GlaxoSmithKline, (NDA 021654/S-037) approved June 26, 2013, please revise your labeling to be in accordance with the reference listed drug labeling. If you are unable to obtain this labeling at the Drugs@FDA website (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm), please contact the labeling reviewer, Betty Turner (betty.turner@fda.hhs.gov).

   b. Please revise "1 g" to read "1 gram" throughout your insert.

   c. Please confirm if the following statement accurately reflects your drug product: These are predominantly a combination of ethyl esters of eicosapentaenoic acid (EPA-

approximately 465 mg) and docosahexaenoic acid (DHA- approximately 375 mg).

3. PATIENT INFORMATION LEAFLET
   Please ensure that your leaflet is in accordance with the RLD approved on June 26, 2013.

4. SPL
   Please submit your labeling in SPL format. Please also update to be in accordance with the most recently approved labeling for the RLD.

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug's labeling with all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the Electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

Note RPM - Labeling comments end here

REMS required?

MedGuides and/or PPIs (505-1(e))	☐ Yes	☒ No
Communication plan (505-1(e))	☐ Yes	☒ No
Elements to assure safe use (ETASU) (505-1(f)(3))	☐ Yes	☒ No
Implementation system if certain ETASU (505-1(f)(4))	☐ Yes	☒ No
Timetable for assessment (505-1(d))	☐ Yes	☒ No

ANDA REMS acceptable?
☐ Yes ☐ No ☒ n/a

	Date submitted	Final or Draft	Recommendation
CONTAINER Bottles of 30s, and 120s	12/27/2012	Draft	Revisions requested
INSERT	12/27/2012	Draft	Revisions requested
PATIENT INFORMATION	12/27/2012	Draft	Revisions requested

REVISIONS NEEDED POST APPROVAL?

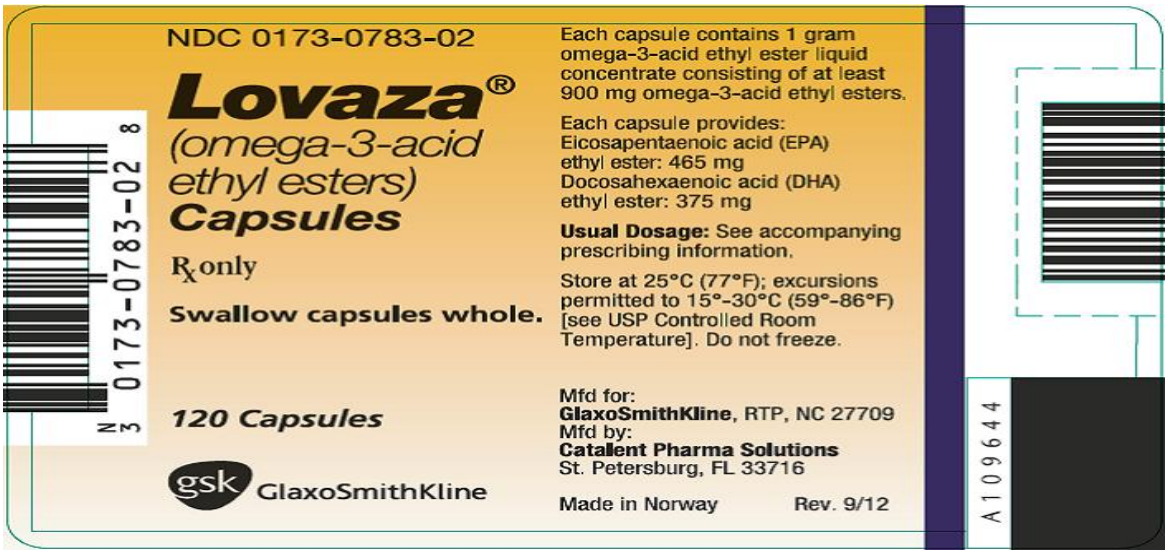
NOTES/QUESTIONS TO THE CHEMIST/BIO REVIEWER/MICRO REVIEWER:

FOR THE RECORD: Please note the first review cycle was completed by Thuyanh Vu, Labeling Reviewer. Portions of this review were taken the review dated 1/25/2010 in DARRTS.

1. **MODEL LABELING**: This review is based on the labeling for Lovaza® (omega-3-acid ethyl esters) Capsule of SmithKline Beecham, NDA 021654/S-037; approved June 26, 2013.

   S-022 provided for PLR format and inclusion of atorvastatin and rosuvastatin in the Drug Interactions subsection.

   S-014, approved on 11/7/07 provided for the revised patient package insert.



2. **USP-36:** (checked August 9, 2013)
   Omega-3-Acid Ethyl Esters Capsules
   ADDITIONAL REQUIREMENTS
   - Packaging and Storage: Preserve in tight containers, and store at controlled room temperature. Do not freeze. Protect from light.
   - Labeling: The label states the amount of docosahexaenoic acid (DHA) ethyl ester and eicosapentaenoic acid (EPA) ethyl ester, and the minimum amount of total content of omega-3-acid ethyl esters in mg/Capsule. It also states the name and content of any added antioxidant.

3. **PATENT AND EXCLUSIVITY** (checked August 9, 2013)
   Patent Data – NDA 021654

No	Expiration	Use Code	Use	**How filed**	**Labeling Impact**

5502077	Mar 26, 2013	U-822	Use In Lipid Management	IV	None
5656667	Apr 10, 2017	U-822	Use In Lipid Management	IV	None
7732488	Jan 30, 2025			IV	None

Exclusivity Data– NDA 021654

Code	Reference	Expiration	**Labeling impact**
M-87	Inclusion of results from two drug interaction studies with Lipid and Crestor in Clinical Pharmacology section	Sep 16, 2012	**None**

PATENT AMENDMENT UPDATE 12/27/12

While the exclusivity M-87 is still listed in the Orange Book, it is now expired. The language previously protected by this exclusivity is now included in Teva's proposed package insert labeling.

Additionally, the previously listed M-64 and NCE exclusivities are now expired and are no longer listed in the Orange Book.

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4. **INACTIVE INGREDIENTS**
There is no discrepancy in inactives between the DESCRIPTION and the composition statement. [2.3.P.1-original submission]

Inactive ingredients:
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The active ingredient is sensitive to oxygen. Alpha-tocopherol was added by the API manufacturer [redacted] to prevent oxidation. Final fill composition is 4 mg Alpha-tocopherol for every [redacted] mg of API.

5. **MANUFACTURING FACILITY**
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[2.3.P.3- original submission]

6. **FINISHED PRODUCT DESCRIPTION**
NDA: transparent soft gelatin capsules filled with light-yellow oil and bearing the designation REL900

ANDA: [2.3.P.5-original submission]
Slightly yellow to yellow liquid in size 22 oblong clear soft gel capsule, imprinted with (b) (4) in white ink.

7. **STORAGE STATEMENT AND DISPENSING RECOMMENDATIONS**

RLD: Stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Do not freeze.

ANDA: Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Do not freeze.

8. **PRODUCT LINE**

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ANDA: The drug product will be packaged in 30's, and 120's

9. **CONTAINER/CLOSURE**
[2.3.P.7-original submission]
The drug product will be shipped in a 30 capsule/bottle configuration as follows:
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Cap: 53-mm CRC Cap (Teva part #333-31-021811)

10. **BIOEQUIVALENCE/DISSOLUTION:**
Review is inadequate as of review date 12/14/2012.

11. **SPL DATA ELEMENTS**
Labeling was provided in SPL format in amendment dated 12/27/2012.

ANDA:
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Color YELLOW (to yellow); Score no score; Shape CAPSULE; Size 22mm; Imprint Code (b) (4)

RLD:
900 mg Omega-3-Acid Ethyl Esters
Color YELLOW (light yellow); Score no score; Shape CAPSULE; Size 24mm; Imprint Code LOVAZA

12. **EXPRESSION OF STRENGTH: We will continue to monitor this issue.**

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According to Lovaza's approved specification, each capsule contains from 950 mg to 1050

mg of esterified purified fish oil. The principal components are two omega-3 acid ethyl esters, eicosapentaenoic acid (EPA) ethyl ester and docosahexaenoic acid (DHA) ethyl ester. Both are required to be present at a combined concentration of between 800 and 880 mg/capsule. The drug substance specification also includes an acceptance criterion of at least 90% (w/w) total omega-3 ethyl esters – the active ingredients.

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Please revise all labeling to reflect a strength per capsule of 900 mg.

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This change to the Prescribing Information would afford a consistent description of the product (in the PI and on the container labels) and would alleviate any potential misunderstandings regarding the amount of active ingredient in a 1 gram capsule. Division consideration and concurrence with this proposal would be much appreciated.

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Sent: Tuesday, May 07, 2013 3:29 PM
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Subject: FW: Strength on PDP (Omega-3)

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Subject: Strength on PDP (Omega-3)

Hi Lillie and Koung,

What do you think about the following situation….

RLD Label: (strength not specified on the PDP)

<< File: image[10].jpg >>

OSE review dated 4/27/2004 for the RLD

CONTAINER LABEL

The product strength should appear immediately following or below the established name and be more prominent on the label.

The comment was sent to the firm on 6/4/2004.

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What are your thoughts….should we be the same as the RLD and remain silent on the strength or ask the firm to include the strength "1 gram*" on the PDP pursuant to the Guidance for Industry?

The **principal display panel** (PDP) is the panel of a label that is most likely to be displayed, presented, shown, or examined by the end user. We recommend that the PDP include the following critical information:

- Proprietary name
- **Established name** or **proper name**
- Product strength
- Route(s) of administration
- Warnings (if any) or cautionary statements (if any)

What are your thoughts?

Ruby

From: Turner, Betty
Sent: Tuesday, May 07, 2013 1:02 PM

To: Wu, Ruby (Chi-Ann)
Subject: RE: ANDA [redacted] (b) (4)

Hi Ruby,

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[redacted] (b) (4)

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No rush. Any time is fine with me.

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Please note the email below was taken from the previous review which was completed by labeling reviewer Thuyanh Vu.

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But amount of active ingredient(s) is to appear on label, "Each capsule contains."

In this case it appears that the amount of active contained in capsules may not be as important as what amount of components is provided.
I don't know, we should follow RLD to avoid confusion

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Sent: Thursday, January 21, 2010 9:38 AM
To: Grace, John F
Subject: FW: 21654 (Lovaza) label question about the 1 gram placement on the container label

John,

Could you read the below question? I seem to remember that RLD do not always put the strength on the principal display panel (especially if the drug product only comes in one strength) but generics do? Could you clarify?

Thanks
Ann

Question to Chemist on January 21, 2010,

Suhas replied on 1/21/2010

Hi Ann,

Thanks for the info. I have not reviewed this application yet. I will let you know if there is discrepancy between components and labeling.

Suhas

Suhas,

Teva's labeling differs from the RLD's Lovaza in the DESCRIPTION

Section: Teva's capsule: inactive ingredients: 4 mg alpha-tocopherol,

gelatin..."

RLD's insert: "inactive ingredients: 4 mg α-tocopherol (in a carrier of partially hydrogenated vegetable oils including soybean oil).

Not sure if Teva's is acceptable since it did not specify the carrier.

Thanks
Ann

Date of Review: August 9, 2013

Primary Reviewer: Betty Turner

Team Leader: Chi-Ann Y Wu

Reference ID: 3355625

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BETTY B TURNER
08/09/2013

CHI-ANN Y WU
08/10/2013
For Wm. Peter Rickman

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 91-028 Date of Submission: June 3, 2009
Applicant's Name: TEVA Pharmaceuticals USA
Established Name: Omega 3-Acid Ethyl Esters Capsule, 1 gram

Labeling Deficiencies:

1. **GENERAL COMMENT**

Please address the M-87 exclusivity.

2. **CONTAINER**: (30's, 120's)
Please delete "1 g" from the principal display panel.

3. **INSERT:**
Please revise your insert in accordance with the most recently approved RLD, Lovaza labeling (021654/S-022). Please refer to the Drugs@FDA website for the RLD labeling.

4. **PATIENT PACKAGE INSERT:**
Acceptable in draft.

Submit labels and labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with the RLD labeling with all differences annotated and explained.

NOTES/QUESTIONS TO THE CHEMIST:

See email below between John Grace and myself. There was a question of importance with the placement of the "1 gram" on the principal display panel of the generic companies' container labels. I will ask ALL generic companies to delete the "1 gram" from the principal display panel.

John Grace's email from 1/21/10:

There is no requirement for putting on PDP in conjunction with est name.
But amount of active ingredient(s) is to appear on label, "Each capsule contains."

In this case it appears that the amount of active contained in capsules may not be as important as what amount of components is provided.
I don't know, we should follow RLD to avoid confusion

From: Vu, Thuyanh (Ann)
Sent: Thursday, January 21, 2010 9:38 AM
To: Grace, John F
Subject: FW: 21654 (Lovaza) label question about the 1 gram placement on the container label

John,

Could you read the below question? I seem to remember that RLD do not always put the strength on the principal display panel (especially if the drug product only comes in one strength) but generics do? Could you clarify?

Thanks
Ann

Question to Chemist on January 21, 2010,

Suhas replied on 1/21/2010

Hi Ann,

Thanks for the info. I have not reviewed this application yet. I will let you know if there is discrepancy between components and labeling.

Suhas

Suhas,

Teva's labeling differs from the RLD's Lovaza in the DESCRIPTION Section:

Teva's capsule: inactive ingredients: 4 mg alpha-tocopherol, gelatin..."

RLD's insert: "inactive ingredients: 4 mg α-tocopherol (in a carrier of partially hydrogenated vegetable oils including soybean oil).

Not sure if Teva's is acceptable since it did not specify the carrier.

Thanks
Ann

FOR THE RECORD:

1. **MODEL LABELING:** This review was based on the labeling for Lovaza of Smithkline Beecham (21-654/S-022, approved on 9/16/09). S-022 provided for PLR format and inclusion of atorvastatin and rosuvastatin in th Drug Interactions subsection. S-014, approved on 11/7/07 provided for the revised patient package insert.

2. PATENTS/EXCLUSIVITIES

Patent Data – NDA 21-654

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5502077	Mar 26, 2013	U-822	Use in Lipid Management	IV	
5656667	Apr 10, 2017	U-822	Use in Lipid Management	IV	
5698594	Aug 4, 2009	U-822	Use in Lipid Management	III	

EXCLUSIVITIES

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
N021654	001	NCE	Nov 10, 2009
N021654	001	M - 64	Jun 12, 2010
N021654	001	M - 87	Sep 16, 2012

M-64: Changes to clinical pharmacology detailing study results

M-87: Inclusion of results from two drug interaction studies with Lipitor and Crestor in Clinical Pharmacology Section.

TEVA certifies that sale of drug product will not begin until after expiry of the M-64 exclusivity.

TEVA has not addressed the M-87 exclusivity, see comment to firm (Not sure if Teva could "carve out" the exclusivity since it does address safety concerns)

3. INACTIVE INGREDIENTS

There is no discrepancy in inactives between the DESCRIPTION and the composition statement. [2.3.P.1-original submission]

Inactive ingredients:

Alpha-tocopherol, gelatin, glycerin, (b) (4) White (b) (4) (b) (4) titanium dioxide, hypromellose, propylene glycol)

The active ingredient is sensitive to oxygen. Alpha-tocopherol was added by the API manufacturer (b) (4) to prevent oxidation. Final fill composition is 4 mg Alpha-tocopherol for every (b) (4) mg of API

4. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Banner Pharmacaps, Inc.
4125 Premier Drive
High Point, NC 27252

[2.3.P.3- original submission]

See comment to firm about discrepancy between drug product manufacturer.
In AF 6/3/09: Firm revised labels to reflect the relationship between manufacturer and distributor.

5. FINISHED DOSAGE FORM

NDA: transparent soft gelatin capsules filled with light-yellow oil and bearing the designation REL900

ANDA: [2.3.P.5-original submission]

Slightly yellow to yellow liquid in size 22 oblong clear soft gel capsule, imprinted with (b) (4) in white ink.

6. CONTAINER/CLOSURE:

[2.3.P.7-original submission]

The drug product will be shipped in a 30 capsule/bottle configuration as follows:
Bottle: 120-cc HDPE Bottle (Teva part #333-31-019440)
Cap: 38-mm CRC Cap (Teva part #333-31-021204)

The drug product will be shipped in a 120 capsule/bottle configuration as follows:
Bottle: 400-cc HDPE Bottle (Teva part #333-31-019393)
Cap: 53-mm CRC Cap (Teva part #333-31-021811)

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

- Not USP: Checked on April 15, 2009)
- RLD: Stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Do not freeze.
- ANDA: Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Do not freeze.

8. SCORING

N/A

9. PACKAGE CONFIGURATION

- RLD: 1 gram capsules in bottles of 60s and 120s
- ANDA: The drug product will be packaged in 30's, and 120's

Date of Review: January 20, 2010	**Date of Submission:** June 3, 2009
Primary Reviewer: Thuyanh Vu	**Date:**
Team Leader: John Grace	**Date:**

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91028	ORIG-1	TEVA PHARMACEUTICALS USA	OMEGA-3-ACID ETHYL ESTERS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THUYANH VU
01/21/2010

JOHN F GRACE
01/25/2010

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 91-028 Date of Submission: November 10, 2008
Applicant's Name: TEVA Pharmaceuticals USA
Established Name: Omega 3-Acid Ethyl Esters Capsule, 1 gram

Labeling Deficiencies:

1. **CONTAINER**: (30's, 120's)
   a. The manufacturer of this product is Banner, yet there is no mention of Banner on the labels. According to 21 CFR 201.1(h)(2), "The appearance on a drug product label of a person's name without qualification is a representation that the named person is the sole manufacturer of the product. That representation is false and misleading, and the drug product is misbranded under section 502(a) of the act, if the person is not the manufacturer of the product in accordance to this section". Please revise your labels by adding "Manufactured for TEVA..." or "Manufactured by Banner..."

   b. We encourage adding the statement "Pharmacist: please dispense with patient package insert".

2. **INSERT:**
   a. DESCRIPTION: Please revise to read "4 mg alpha-tocopherol"

   b. CLINICAL STUDIES: Table 1, please format the rows correctly so that the numbers is shown on one line (e.g "137" vs. "13)
   7"

   c. Revise the subsection "DRUG ABUSE" to "DRUG ABUSE AND DEPENDENCE".

3. **PATIENT PACKAGE INSERT:**
   Please submit the patient package insert.

Submit final printed labeling electronically. We refer you to the http://www.fda.gov/oc/datacouncil/spl.html website for guidance.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

NOTES/QUESTIONS TO THE CHEMIST:

Teva's capsule: inactive ingredients: alpha-tocopherol, gelatin..."

RLD's insert: "inactive ingredients: 4 mg α-tocopherol (in a carrier of partially hydrogenated vegetable oils including soybean oil).

Is this acceptable? This is assigned to a Random Chemist.

FOR THE RECORD:

1. MODEL LABELING: This review was based on the labeling for Lovaza of Smithkline Beecham (S-021, approved on 6/3/08). S-021 provided the change of the proprietary from Omacor to Lovaza. S-014, approved on 11/7/07 provided for the revised patient package insert.

2. PATENTS/EXCLUSIVITIES

Patent Data – NDA 21-654

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5502077	Mar 26, 2013	U-822	Use in Lipid Management	IV	
5656667	Apr 10, 2017	U-822	Use in Lipid Management	IV	
5698594	Aug 4, 2009	U-822	Use in Lipid Management	III	

Exclusivity-Data – NDA 21-654

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021654	001	M-64	Jun 12, 2010
021654	001	NCE	Nov 10, 2009

TEVA certifies that sale of drug product will not begin until after expiry of the above exclusivities.

3. INACTIVE INGREDIENTS

There appears to be a discrepancy in inactives between the DESCRIPTION and the composition statement. [2.3.P.1-original submission]

Inactive ingredients:

Alpha-tocopherol, gelatin, glycerin, [redacted] (b) (4) White [redacted] (b) (4) [redacted] (b) (4) titanium dioxide, hypromellose, propylene glycol)

The active ingredient is sensitive to oxygen. Alpha-tocopherol was added by the API manufacturer [redacted] (b) (4) to prevent oxidation. Final fill composition is 4 mg Alpha-tocopherol for every [redacted] (b) (4) mg of API

4. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Banner Pharmacaps, Inc.
4125 Premier Drive
High Point, NC 27252

[2.3.P.3- original submission]

See comment to firm about discrepancy between drug product manufacturer.

5. FINISHED DOSAGE FORM

NDA: transparent soft gelatin capsules filled with light-yellow oil and bearing the designation REL900

ANDA: [2.3.P.5-original submission]

Slightly yellow to yellow liquid in size 22 oblong clear soft gel capsule, imprinted with (b) (4) in white ink.

6. CONTAINER/CLOSURE:
[2.3.P.7-original submission]

The drug product will be shipped in a 30 capsule/bottle configuration as follows:
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Cap: 38-mm CRC Cap (Teva part #333-31-021204)

The drug product will be shipped in a 120 capsule/bottle configuration as follows:
Bottle: 400-cc HDPE Bottle (Teva part #333-31-019393)
Cap: 53-mm CRC Cap (Teva part #333-31-021811)

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

- Not USP: Checked on April 15, 2009)
- RLD: Stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Do not freeze.
- ANDA: Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Do not freeze.

8. SCORING

N/A

9. PACKAGE CONFIGURATION

- RLD: 1 gram capsules in bottles of 60s and 120s
- ANDA: The drug product will be packaged in 30's, and 120's

Date of Review: April 16, 2009	**Date of Submission:** November 10, 2008
Primary Reviewer: Thuyanh Vu	**Date:**
Team Leader: John Grace	**Date:**

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thuyanh Vu
4/16/2009 03:34:31 PM
LABELING REVIEWER

John Grace
4/21/2009 12:08:02 PM
LABELING REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 91028

CHEMISTRY REVIEWS

CHEMISTRY REVIEW

First Generic: Yes
CMC Review cycle # 4: Acceptable
Labeling: Adequate
Bio: Inadequate
EES: Acceptable

ANDA 91028

Omega-3-acid ethyl esters capsules USP, 1 g

Teva Pharmaceuticals, USA

M A Rahman
Team 34
Division of Chemistry III
Office of Generic Drugs

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Reference ID: 3478520

Chemistry Review Data Sheet

1. **ANDA #: 91028**

2. **REVIEW #: R04**

3. **REVIEW DATE: 03/25/2014**

4. **REVIEWER: MD Rahman, PhD**

5. **PREVIOUS DOCUMENTS: N/A**

Previous Document(s)	Document Date
Original ANDA	November 10, 2008
Amendment	October 27, 2011
Amendment	December 30, 2013
Patent amendment	January 30, 2014

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
Amendment	March 20, 2014

7. **NAME & ADDRESS OF APPLICANT:**

Name:	Teva Pharmaceuticals USA
Address:	1090 Horsham Road, PO Box 1090, North Wales, PA 19454
Representative:	Jean W Zwicker, Senior Director, Regulatory Affairs
Telephone:	215-591-8725
Fax:	215-591-8812

8. **DRUG PRODUCT NAME/CODE/TYPE:**

Proprietary Name: N/A
Non-Proprietary Name (USAN): Omega-3-Acid Ethyl Esters Capsules, 1 gm

9. **LEGAL BASIS FOR SUBMISSION:**

This ANDA # 91028 of Omega-3-Acid Ethyl Esters Capsules USP, 1 gm is being submitted based on the reference listed drug (RLD): Lovaza® Capsules (Omega-3-Acid Ethyl Esters Capsules, 1 gm) is approved for GlaxoSmithKline (NDA# 21654).

10. **PHARMACOL. CATEGORY:** Triglyceride reducing agent

11. **DOSAGE FORM:** Capsules (Soft Gelatin)

Reference ID: 3478520

12. STRENGTH/POTENCY: 1 gm (MDD = 4 gm)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: X **Rx** **OTC**

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

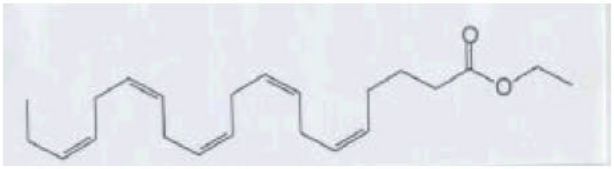
15b. NANOTECHNOLOGY PRODUCT TRACKING:

_____NANO product – Form Completed (See Appendix A.4)

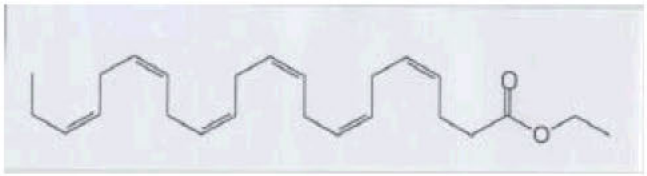
__X__Not a NANO product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Omega-3 acid ethyl esters is a fish-oil fatty acid ester concentrate containing the followings:
Chemical name: Eicosapentaenoic acid ethyl esters (EPA-EE)
CAS Registry Number: 73310-10-8
Molecular Formula: $C_{22}H_{34}O_2$
Molecular Weight: 330.51
Molecular struture



Chemical Name: Docosahexaenoic acid ethyl esters (DHA-EE)
CAS Registry Number: 84494-72-4
Molecular Formula: $C_{24}H_{36}O_2$
Molecular Weight: 356.5
Molecular Structure



Reference ID: 3478520

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Omega-3-Acid Ethyl Esters	1	**adequate**	03/27/2014	Reviewed by MA Rahman
14194	IV	Banner Pharmacaps, Inc	Softgel Capsules	3	**adequate**	08/27/2012	Reviewed by VS Prabhu

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Lovaza® Capsules	NDA# 21654	

Reference ID: 3478520

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable as on 11/22/2013 for DP and 02/03/2014 for DS		District recommendation
Methods Validation	N/A		
Labeling	adequate	01/10/2014	Reviewed by B Turner
BE Study Dissolution	Inadequate Inadequate	03/10/2014 03/06/2014	Reviewed by G Li Reviewed by G Li
Toxicology/Clinical	N/A		
EA	Provided - Adequate	2/4/2014	Laxma Nagavelli
Radiopharmaceutical	N/A		
Samples requested	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

20. EES INFORMATION

Drug Substance			
Function	**Site Information**	**FEI/CFN#**	**Status**
(b) (4)			
Drug Product			
Function	**Site Information**	**FEI/CFN#**	**Status**
Manufacturer of the DP, Omega-3 Acids Ethyl Esters Capsules, I gm	*Banner Pharmacaps Inc, High Point, USA 272658144*	3001451366	Acceptable as on 11/22/2013
Packager of Finished Product	*Teva Pharmaceuticals USA, Inc. Sellersville, USA 189601512*	2517175	Acceptable as on 03/18/2013
(b) (4)			

Reference ID: 3478520

Chemistry Review for ANDA 91028

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

CMC is acceptable in the current review cycle.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:
The drug product, Omega-3-Acid Ethyl Esters is a soft gelatin capsule containing 1 g fish oil and it is now official in the current USP monograph. The drug product is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe hypertriglyceridemia. The mechanism of action of Omega-3-acid ethyl esters is not completely understood. However, the potential mechanism of action include inhibition of acyl-CoA:1, 2-diacylglycerol acyltranferase, increased mitochondrial and peroxisomal β-oxidation in the liver, decreased lipogenesis in the liver, and increased plasma lipoprotein lipase activity. The proposed generic drug product is a softgel capsule containing at least 900 mg of Omega-3-acid ethyl esters, predominantly consisting of ethyl esters of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The drug product also contains α-tocopherol, 4 mg/g as an antioxidant, gelatin NF as a shell, glycerin USP (b) (4) (b) (4) white ink (b) (4) (b) (4) titanium dioxide NF, hypromellose (b) (4) USP and propylene glycol USP (b) (4) The drug product has been developed by the Teva and accordingly the details of the product development reports are provided by the firm in the ANDA submissions which are reviewed in the part B section of this review. The release of API, drug product, packaging and stability are the sponsor's responsibility. The drug product soft gelatin capsules are manufactured by Banner Pharmacap, Inc for the ANDA applicant, Teva USA. The DMF# 14194 from Banner Pharmacap is referenced for manufacturing the softgel capsule for the proposed drug product which is in adequate status.

The drug product, Omega-3-Acid Ethyl Esters Capsules, 1 gm contains polyunsaturated fatty acids which are susceptible to oxidation. Hence, the capsules are processed (b) (4) . The drug product is proposed to be stored in HDPE bottle with CRC closure which is similar with the RLD. The 24 months expiration dates are proposed at controlled room temperature.

The soft gelatin capsules are manufactured by (b) (4)

Reference ID: 3478520

Maximum daily dose is 4 g/day as per labeling insert information.

The drug product: based on the ICH Guideline Q3B (R2), reporting threshold (RT): 0.05%, Identification threshold (IT) for any unspecified impurity: 0.10%; Qualification threshold (QT) for any specified impurity: 0.15%.

Proposed expiry: Firm proposes an expiration period of 24 months for drug product based on 3 months accelerated stability data (40 ± 2 ^{0}C/75 ± 5% RH).

Storage condition: Proposed generic label recommends storage at 20^0 to 25^{0}C (68^0 to 77^{0}F), [USP Controlled Room Temperature]. Do not freeze. Proposed Omega-3-acid ethyl esters capsules, 1 g are slightly yellow to yellow, oblong, clear soft gel capsules imprinted with (b) (4) in white ink, in bottles of 30 and 120. RLD recommends to store at 25^0 C (77^{0}F), excursion permitted to 15^0-30^0 C (59-86^0 F). LOVAZA® (RLD) capsules are transparent soft-gelatin capsules filled with light-yellow oil and bearing the designation LOVAZA.

Drug Substance:
The drug substance, Omega-3-acid ethyl esters USP is light yellow liquid. It is soluble in ethanol, acetone, heptane and methanol and not soluble in water. It is a fish oil fatty acid ester containing (b) (4) EPA (eicosapentanoic acid ethyl ester) and (b) (4) DHA (docosahexaenoic acid ethyl ester) and (b) (4) total Omega-3 as EE. In addition, the drug substance is also consistent of mixture of the ethyl esters of five other omega-3 fatty acids per USP monograph and the proposed drug substance has no control over these fatty acids esters. It has also 4 mg/g α-tocopherol as an antioxidant to protect from oxidation. Omega-3-acid ethyl esters, drug substance are manufactured by (b) (4) (b) (4)

Maximum daily dose is 4 g/day as per labeling insert information.
Impurity Threshold: The drug substance: based on the ICH Guideline Q3A (R2), reporting threshold (RT): 0.03%; Identification threshold (IT) for any unspecified impurity: 0.05%; Qualification threshold (QT) for any specified impurity: 0.05%.

B. Description of How the Drug Product is Intended to be Used

Omega-3-acids ethyl esters Capsules, 1 g to be taken as directed. The daily dose of Omega-3-acid ethyl esters capsule is 4 grams per day taken as a single 4 grams dose (4 capsules) or as two 2-gram doses (2 capsules given twice daily). The patients are advised to shallow Omega-3-acid ethyl esters capsules whole and do not break open, crush, dissolve or chew. Patient should be on an appropriate lipid-lowering diet before receiving Omega-3-acid ethyl esters capsules. Proposed drug products will be available in (b) (4) count and 120's count HDPE bottles and caps. See the drug product labeling for further information.

C. Basis for Approvability or Not-Approval Recommendation

The CMC review is currently acceptable per the review team recommendations. Sponsor is following the DBE proposed method for quantitative capsule rupture testing (QCRT). ANDA approvability is pending Division review and other disciplines. This CMC review may require an addendum based on recommendations made by other review disciplines.

Following this page, 33 Pages Withheld in Full as (b)(4)

Reference ID: 3478520

Administrative

B. Endorsement Block
Reviewer: M D Rahman, PhD, 03/26/2014
Team Leader: Laxma R Nagavelli, PhD/3/26/2014
Division Director: Vilayat Sayeed, PhD/3/27/2014
Project Manager Name/Date: Leigh Ann Sears/3/27/2014 sy for

TYPE OF LETTER: CMC Acceptable

Reference ID: 3478520

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MD A RAHMAN
03/27/2014

STEVEN W YANG on behalf of LEIGH A SEARS
03/27/2014

LAXMA R NAGAVELLI
03/27/2014
CMC Acceptable pending Bio

VILAYAT A SAYEED
03/28/2014

First Generic:
CMC: Not Acceptable NA Minor
Labeling: Adequate
Bio: Inadequate
EES: Pending

ANDA 91028

Omega-3-acid ethyl esters capsules USP, 1 g

Teva Pharmaceuticals, USA

M A Rahman
Team 34
Division of Chemistry III
Office of Generic Drugs

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Reference ID: 3450595

Chemistry Review Data Sheet

1. **ANDA #: 91028**

2. **REVIEW #: R03**

3. **REVIEW DATE: 01/26/2014**

4. **REVIEWER: MD Rahman, PhD**

5. **PREVIOUS DOCUMENTS: N/A**

Previous Document(s)	Document Date
Original ANDA	November 10, 2008
Amendment	October 27, 2011

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
Patent amendment	January 30, 2014
Amendment	December 30, 2013

7. **NAME & ADDRESS OF APPLICANT:**

Name:	Teva Pharmaceuticals USA
Address:	1090 Horsham Road, PO Box 1090, North Wales, PA 19454
Representative:	Jean W Zwicker, Senior Director, Regulatory Affairs
Telephone:	215-591-8725
Fax:	215-591-8812

8. **DRUG PRODUCT NAME/CODE/TYPE:**

Proprietary Name: N/A
Non-Proprietary Name (USAN): Omega-3-Acid Ethyl Esters Capsules, 1 gm

9. **LEGAL BASIS FOR SUBMISSION:**

This ANDA # 91028 of Omega-3-Acid Ethyl Esters Capsules USP, 1 gm is being submitted based on the reference listed drug (RLD): Lovaza® Capsules (Omega-3-Acid Ethyl Esters Capsules, 1 gm) is approved for GlaxoSmithKline (NDA# 21654).

10. **PHARMACOL. CATEGORY:** Triglyceride reducing agent

11. **DOSAGE FORM:** Capsules (Soft Gelatin)

12. **STRENGTH/POTENCY:** 1 gm (MDD = 4 gm)

Reference ID: 3450595

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: X **Rx** ___ **OTC**

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X___Not a SPOTS product

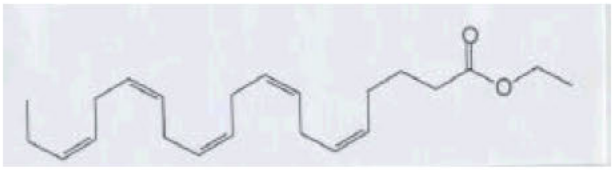
15b. NANOTECHNOLOGY PRODUCT TRACKING:

_____NANO product – Form Completed (See Appendix A.4)

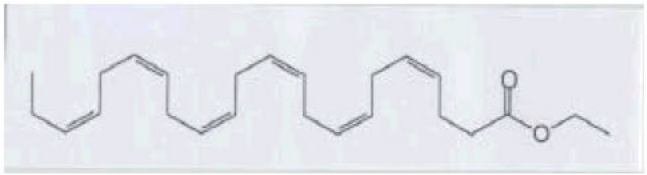
___X___Not a NANO product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Omega-3 acid ethyl esters is a fish-oil fatty acid ester concentrate containing the followings:
Chemical name: Eicosapentaenoic acid ethyl esters (EPA-EE)
CAS Registry Number: 73310-10-8
Molecular Formula: $C_{22}H_{34}O_2$
Molecular Weight: 330.51
Molecular struture



Chemical Name: Docosahexaenoic acid ethyl esters (DHA-EE)
CAS Registry Number: 84494-72-4
Molecular Formula: $C_{24}H_{36}O_2$
Molecular Weight: 356.5
Molecular Structure



Reference ID: 3450595

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Omega-3-Acid Ethyl Esters	1	Inadequate	02/07/2014	Reviewed by MA Rahman
14194	IV	Banner Pharmacaps, Inc	Softgel Capsules	3	**adequate**	08/27/2012	Reviewed by VS Prabhu

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

Reference ID: 3450595

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable as on 04/10/2009 for DP but pending for DS		
Methods Validation	N/A		
Labeling	adequate	01/10/2014	Reviewed by B Turner
BE Study Dissolution	Inadequate Inadequate	12/14/2012 05/04/2009	Reviewed by G li Reviewed by K Ren
Toxicology/Clinical	N/A		
EA	Provided - Adequate	2/4/2014	Laxma Nagavelli
Radiopharmaceutical	N/A		
Samples requested	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

20. EES INFORMATION

Drug Substance			
Function	**Site Information**	**FEI/CFN#**	**Status**
(b) (4)			
Drug Product			
Function	**Site Information**	**FEI/CFN#**	**Status**
Manufacturer of the DP, Omega-3 Acids Ethyl Esters Capsules, I gm	*Banner Pharmacaps Inc, High Point, USA 272658144*	3001451366	Acceptable as on 04/10/2009
Packager of Finished Product	*Teva Pharmaceuticals USA, Inc. Sellersville, USA 189601512*	2517175	Acceptable as on 03/24/2009

Reference ID: 3450595

Chemistry Review for ANDA 91028

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable, NA-Minor

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:

The drug product, Omega-3-Acid Ethyl Esters is a soft gelatin capsule containing 1 g fish oil and it is now official in the current USP monograph. The drug product is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe hypertriglyceridemia. The mechanism of action of Omega-3-acid ethyl esters is not completely understood. However, the potential mechanism of action include inhibition of acyl-CoA:1, 2-diacylglycerol acyltranferase, increased mitochondrial and peroxisomal β-oxidation in the liver, decreased lipogenesis in the liver, and increased plasma lipoprotein lipase activity. The proposed generic drug product is a softgel capsule containing at least 900 mg of Omega-3-acid ethyl esters, predominantly consisting of ethyl esters of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The drug product also contains α-tocopherol, 4 mg/g as an antioxidant, gelatin NF as a shell, glycerin USP (b) (4) (b) (4) and white ink (b) (4), titanium dioxide NF, hypromellose (b) (4) USP and propylene glycol USP (b) (4). The drug product has been developed by the Teva and accordingly the details of the product development reports are provided by the firm in the ANDA submissions which are reviewed in the part B section of this review. The release of API, drug product, packaging and stability are the sponsor's responsibility. The drug product soft gelatin capsules are manufactured by Banner Pharmacap, Inc for the ANDA applicant, Teva USA. The DMF# 14194 from Banner Pharmacap is referenced for manufacturing the softgel capsule for the proposed drug product which is in adequate status.

The drug product, Omega-3-Acid Ethyl Esters Capsules, 1 gm contains polyunsaturated fatty acids which are susceptible to oxidation. Hence, the capsules are processed (b) (4) The drug product is proposed to be stored in HDPE bottle with CRC closure which is similar with the RLD. The 24 months expiration dates are proposed at controlled room temperature.

The soft gelatin capsules are manufactured by (b) (4)

Maximum daily dose is 4 g/day as per labeling insert information.

Reference ID: 3450595

The drug product: based on the ICH Guideline Q3B (R2), reporting threshold (RT): 0.05%, Identification threshold (IT) for any unspecified impurity: 0.10%; Qualification threshold (QT) for any specified impurity: 0.15%.

Proposed expiry: Firm proposes an expiration period of 24 months for drug product based on 3 months accelerated stability data (40 ± 2 ^{0}C/75 ± 5% RH).

Storage condition: Proposed generic label recommends storage at 20^0 to 25^{0}C (68^0 to 77^{0}F), [USP Controlled Room Temperature]. Do not freeze. Proposed Omega-3-acid ethyl esters capsules, 1 g are slightly yellow to yellow, oblong, clear soft gel capsules imprinted with (b) (4) in white ink, in bottles of 30 and 120. RLD recommends to store at 25^0 C (77 F), excursion permitted to 15^0-30^0 C (59-86^0 F). LOVAZA® (RLD) capsules are transparent soft-gelatin capsules filled with light-yellow oil and bearing the designation LOVAZA.

Drug Substance:
The drug substance, Omega-3-acid ethyl esters USP is light yellow liquid. It is soluble in ethanol, acetone, heptane and methanol and not soluble in water. It is a fish oil fatty acid ester containing (b) (4) EPA (eicosapentanoic acid ethyl ester) and (b) (4) DHA (docosahexaenoic acid ethyl ester) and (b) (4) total Omega-3 as EE. In addition, the drug substance is also consistent of mixture of the ethyl esters of five other omega-3 fatty acids per USP monograph and the proposed drug substance has no control over these fatty acids esters. It has also 4 mg/g α-tocopherol as an antioxidant to protect from oxidation. Omega-3-acid ethyl esters, drug substance are manufactured by (b) (4) (b) (4) .

Maximum daily dose is 4 g/day as per labeling insert information.
Impurity Threshold: The drug substance: based on the ICH Guideline Q3A (R2), reporting threshold (RT): 0.03%; Identification threshold (IT) for any unspecified impurity: 0.05%; Qualification threshold (QT) for any specified impurity: 0.05%.

B. Description of How the Drug Product is Intended to be Used

Omega-3-acids ethyl esters Capsules, 1 g to be taken as directed. The daily dose of Omega-3-acid ethyl esters capsule is 4 grams per day taken as a single 4 grams dose (4 capsules) or as two 2-gram doses (2 capsules given twice daily). The patients are advised to shallow Omega-3-acid ethyl esters capsules whole and do not break open, crush, dissolve or chew. Patient should be on an appropriate lipid-lowering diet before receiving Omega-3-acid ethyl esters capsules. Proposed drug products will be available in (b) (4) count and 120's count HDPE bottles and caps. See the drug product labeling for further information.

C. Basis for Approvability or Not-Approval Recommendation

The application is Not Approval due to minor CMC deficiencies.

Reference ID: 3450595

Following this page, 39 Pages Withheld in Full as (b)(4)

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 91028 **APPLICANT: Teva Pharmaceuticals, USA**

DRUG PRODUCT: Omega-3-Acid Ethyl Esters Capsules, 1 gm

The deficiencies presented below represent Minor deficiencies.

Deficiencies

1. The drug master file (b) (4) for Omega-3acid ethyl esters is currently inadequate. The DMF holder, (b) (4) has been notified. Please do not respond to this letter until the DMF holder has informed you that they have responded to all the deficiencies. Please update your drug substance specifications in consultation with your DMF holder and provide updated methods and validations as applicable.

2. We acknowledge that you have updated your drug product release and stability specification to comply with the current USP monograph. (b) (4)

Please update the release and stability specifications accordingly.

Sincerely yours,

{See appended electronic signature}

Vilayat A Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

ADMINISTRATIVE

B. Endorsement Block
Reviewer: M D Rahman, PhD, 01/30/2014; 02/03/2014
Team Leader: Laxma R Nagavelli, PhD/2/1/2014; 2/4/2014
Division Director: Vilayat Sayeed, PhD/2/7/2014
Project Manager Name/Date: Leigh Ann Sears/2/7/2014

TYPE OF LETTER: NA Minor

Reference ID: 3450595

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MD A RAHMAN
02/07/2014

LEIGH A SEARS
02/07/2014

LAXMA R NAGAVELLI
02/07/2014

VILAYAT A SAYEED
02/07/2014

ANDA 91028

Omega-3-acid ethyl esters capsules USP, 1 gm

Teva Pharmaceuticals USA

M A Rahman
Team 34
Division of Chemistry III
Office of Generic Drugs

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8. DRUG PRODUCT NAME/CODE/TYPE: 1
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Reference ID: 3349353

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III. List of Deficiencies To Be Communicated ..... **Error! Bookmark not defined.**

A. Deficiencies 78

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response: 78

Reference ID: 3349353

Chemistry Review Data Sheet

1. **ANDA #: 91028**

2. **REVIEW #: R02**

3. **REVIEW DATE: 01/24/2012**

4. **REVIEWER: MD Rahman, PhD**

5. **PREVIOUS DOCUMENTS: N/A**

Previous Document(s)	Document Date

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
Original ANDA	November 10, 2008
Amendment	October 27, 2011

7. **NAME & ADDRESS OF APPLICANT:**

Name:	Teva Pharmaceuticals USA
Address:	1090 Horsham Road, PO Box 1090, North Wales, PA 19454
Representative:	Jean W Zwicker, Senior Director, Regulatory Affairs
Telephone:	215-591-8725
Fax:	215-591-8812

8. **DRUG PRODUCT NAME/CODE/TYPE:**

Proprietary Name: N/A
Non-Proprietary Name (USAN): Omega-3-Acid Ethyl Esters Capsules, 1 gm

9. **LEGAL BASIS FOR SUBMISSION:**

This ANDA # 91028 of Omega-3-Acid Ethyl Esters Capsules USP, 1 gm is being submitted based on the reference listed drug (RLD): Lovaza® Capsules (Omega-3-Acid Ethyl Esters Capsules, 1 gm) is approved for GlaxoSmithKline (NDA# 21654).

Teva Pharmaceuticals USA certifies that there are four patents which claim the reference drug Lovaza® Capsules:

Reference ID: 3349353

U.S. Patent #	Expiration Date
5,502,077	March 26, 2013
5,656,667	April 10, 2017
5,698,594	August 4, 2009
7,732,488	January 30, 2025

Teva submits the following certifications to these patents:

Paragraph II Certification
Paragraph IV Certification

Teva also certifies that there is an exclusivity currently listed for RLD in the orange book is now expired.

- Exclusivity M-87, which is defined as "inclusion of results from two drug interaction studies with Lipitor and Crestor in Clinical Pharmacology section" expired on September 16, 2012.

10. PHARMACOL. CATEGORY: Triglyceride reducing agent

11. DOSAGE FORM: Capsules (Soft Gelatin)

12. STRENGTH/POTENCY: 1 gm (MDD = 4 gm)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: X **Rx** ___ **OTC**

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

_____NANO product – Form Completed (See Appendix A.4)

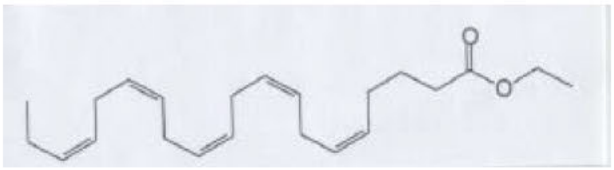
__X__Not a NANO product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

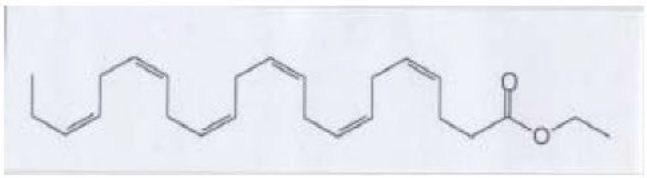
Omega-3 acid ethyl esters is a fish-oil fatty acid ester concentrate containing the followings:
Chemical name: Eicosapentaenoic acid ethyl esters (EPA-EE)
CAS Registry Number: 73310-10-8
Molecular Formula: $C_{22}H_{34}O_2$
Molecular Weight: 330.51
Molecular struture

Reference ID: 3349353

Chemistry Review Data Sheet



Chemical Name: Docosahexaenoic acid ethyl esters (DHA-EE)
CAS Registry Number: 84494-72-4
Molecular Formula: $C_{24}H_{36}O_2$
Molecular Weight: 356.5
Molecular Structure



Reference ID: 3349353

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Omega-3-Acid Ethyl Esters	1	Inadequate	7/17/2013	Reviewed by MA Rahman
14194	IV	Banner Pharmacaps, Inc	Softgel Capsules	3	**adequate**	08/27/2012	Reviewed by VS Prabhu

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

Reference ID: 3349353

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable as on 04/10/2009 for DP but pending for DS		
Methods Validation	N/A		
Labeling	Inadequate	01/25/2012	Reviewed by T Vu
BE Study Dissolution	Inadequate Inadequate	12/14/2012 05/04/2009	Reviewed by G li Reviewed by K Ren
Toxicology/Clinical	N/A		
EA	Not provided		
Radiopharmaceutical	N/A		
Samples requested	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

20. EES INFORMATION

Drug Substance			
Function	**Site Information**	**FEI/CFN#**	**Status**
(b) (4)			
Drug Product			
Function	**Site Information**	**FEI/CFN#**	**Status**
Manufacturer of the DP, Omega-3 Acids Ethyl Esters Capsules, I gm	*Banner Pharmacaps Inc, High Point, USA 272658144*	3001451366	Acceptable as on 04/10/2009
(b) (4)			
Packager of Finished Product	*Teva Pharmaceuticals USA, Inc. Sellersville, USA 189601512*	2517175	Acceptable as on 03/24/2009

Reference ID: 3349353

Chemistry Review for ANDA 91028

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable, NA-Minor

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:

The drug product, Omega-3-Acid Ethyl Esters is a soft gelatin capsule containing 1 g fish oil and it is now official in the current USP monograph. The drug product is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe hypertriglyceridemia. The mechanism of action of Omega-3-acid ethyl esters is not completely understood. However, the potential mechanism of action include inhibition of acyl-CoA:1, 2-diacylglycerol acyltranferase, increased mitochondrial and peroxisomal β-oxidation in the liver, decreased lipogenesis in the liver, and increased plasma lipoprotein lipase activity. The proposed generic drug product is a softgel capsule containing at least 900 mg of Omega-3-acid ethyl esters, predominantly consisting of ethyl esters of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The drug product also contains α-tocopherol, 4 mg/g as an antioxidant, gelatin NF as a shell, glycerin USP (b) (4) (b) (4) and white ink (b) (4) (b) (4) titanium dioxide NF, hypromellose (b) (4) USP and propylene glycol USP (b) (4) The drug product has been developed by the Teva and accordingly the details of the product development reports are provided by the firm in the ANDA submissions which are reviewed in the part B section of this review. The release of API, drug product, packaging and stability are the sponsor's responsibility. The drug product soft gelatin capsules are manufactured by Banner Pharmacap, Inc for the ANDA applicant, Teva USA. The DMF# 14194 from Banner Pharmacap is referenced for manufacturing the softgel capsule for the proposed drug product which is in adequate status.

The drug product, Omega-3-Acid Ethyl Esters Capsules, 1 gm contains polyunsaturated fatty acids which are susceptible to oxidation. Hence, the capsules are processed (b) (4) The drug product is proposed to be stored in HDPE bottle with CRC closure which is similar with the RLD. The 24 months expiration dates are proposed at controlled room temperature.

The soft gelatin capsules are manufactured (b) (4)

Reference ID: 3349353

Maximum daily dose is 4 g/day as per labeling insert information.

The drug product: based on the ICH Guideline Q3B (R2), reporting threshold (RT): 0.05%, Identification threshold (IT) for any unspecified impurity: 0.10%; Qualification threshold (QT) for any specified impurity: 0.15%.

Proposed expiry: Firm proposes an expiration period of 24 months for drug product based on 3 months accelerated stability data (40 ± 2 ^{0}C/75 ± 5% RH).

Storage condition: Proposed generic label recommends storage at 20^0 to 25^{0}C (68^0 to 77^{0}F), [USP Controlled Room Temperature]. Do not freeze. Proposed Omega-3-acid ethyl esters capsules, 1 g are slightly yellow to yellow, oblong, clear soft gel capsules imprinted with (b) (4) in white ink, in bottles of 30 and 120. RLD recommends to store at 25^0 C (77 F), excursion permitted to 15^0-30^0 C (59-86^0 F). LOVAZA® (RLD) capsules are transparent soft-gelatin capsules filled with light-yellow oil and bearing the designation LOVAZA.

Drug Substance:
The drug substance, Omega-3-acid ethyl esters USP is light yellow liquid. It is soluble in ethanol, acetone, heptane and methanol and not soluble in water. It is a fish oil fatty acid ester containing (b) (4) EPA (eicosapentanoic acid ethyl ester) and (b) (4) DHA (docosahexaenoic acid ethyl ester) and (b) (4) total Omega-3 as EE. In addition, the drug substance is also consistent of mixture of the ethyl esters of five other omega-3 fatty acids per USP monograph and the proposed drug substance has no control over these fatty acids esters. It has also 4 mg/g α-tocopherol as an antioxidant to protect from oxidation. Omega-3-acid ethyl esters, drug substance are manufactured by (b) (4)
(b) (4)

Maximum daily dose is 4 g/day as per labeling insert information.
Impurity Threshold: The drug substance: based on the ICH Guideline Q3A (R2), reporting threshold (RT): 0.03%; Identification threshold (IT) for any unspecified impurity: 0.05%; Qualification threshold (QT) for any specified impurity: 0.05%.

B. Description of How the Drug Product is Intended to be Used

Omega-3-acids ethyl esters Capsules, 1 g to be taken as directed. The daily dose of Omega-3-acid ethyl esters capsule is 4 grams per day taken as a single 4 grams dose (4 capsules) or as two 2-gram doses (2 capsules given twice daily). The patients are advised to shallow Omega-3-acid ethyl esters capsules whole and do not break open, crush, dissolve or chew. Patient should be on an appropriate lipid-lowering diet before receiving Omega-3-acid ethyl esters capsules. Proposed drug products will be available in (b) (4) count and 120's count HDPE bottles and caps. See the drug product labeling for further information.

C. Basis for Approvability or Not-Approval Recommendation

The application is Not Approval due to minor CMC deficiencies.

Reference ID: 3349353

Following this page, 70 Pages Withheld in Full as (b)(4)

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 91028 **APPLICANT: Teva Pharmaceuticals USA**

DRUG PRODUCT: Omega-3-Acid Ethyl Esters Capsules, 1 gm

The deficiencies presented below represent Minor deficiencies.

A. Deficiencies

1. The drug master file (b) (4) for Omega-3acid ethyl esters is currently inadequate. The DMF holder, (b) (4) has been notified. Please do not respond to this letter until the DMF holder has informed you that they have responded to all the deficiencies. Please update your drug substance specifications in consultation with your DMF holder and provide updated methods and validations as applicable.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please list the API and other excipients in the composition table as USP or NF grade as applicable.

2. For future ANDA submissions, please provide answer to all Question-based Review questions. If the question is not applicable, please provide a response that the question is not applicable and why it is not applicable.

3. Please make all applicable changes to your drug product release specifications to comply with the division of bioequivalence recommendations.

4. Please update the drug product name and other relevant information to comply with the current USP monograph for the drug product.

Reference ID: 3349353

5. Please provide updated stability data at controlled room temperature using the revised stability specifications.

Sincerely yours,

{See appended electronic signature}

Vilayat A Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

ADMINISTRATIVE

B. Endorsement Block
Reviewer: M D Rahman, PhD, 02/04/2013; 02/26/2013; 04/22/2013; 05/14/2013; 7/16/2013; 7/25/2013
Team Leader: Laxma R Nagavelli, PhD; 2/12/2013; 3/16/2013; 5/2/2013; 5/25/2013; 7/17/2013; 7/25/2013
Division Director: Vilayat Sayeed, PhD/7/26/2013
Project Manager Name/Date: Leigh Ann Sears, PM/7/30/13

TYPE OF LETTER: NA Minor

Reference ID: 3349353

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/s/

MD A RAHMAN
07/30/2013

LEIGH A SEARS
07/30/2013

LAXMA R NAGAVELLI
07/30/2013

VILAYAT A SAYEED
07/30/2013

ANDA 091028

Omega-3-Acid Ethyl Esters Capsules, 1 g

TEVA Pharmaceuticals USA

Haitao Li
Office of Generic Drugs
Division of Chemistry III
Team 34

Reference ID: 2957317

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Reference ID: 2957317

Chemistry Review Data Sheet

1. ANDA #: 091028

2. REVIEW #: 1

3. REVIEW DATE: 6/7/11

4. REVIEWER: Haitao Li, Ph.D

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission Reviewed	Document Date
Original	November 10, 2008

7. NAME & ADDRESS OF APPLICANT:

Name:	TEVA Pharmaceuticals USA
Address:	1090 Horsham Road PO Box 1090 North Wales, PA 19454
Representative:	Philip Erickson
Telephone:	(215) 591-3000
Fax:	(215) 591-8812

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A

b) Non-Proprietary Name (USAN): Omega-3-Acid Ethyl Esters Capsules

9. LEGAL BASIS FOR SUBMISSION:

Reference Listed Drug: Lovaza™ Capsules
RLD Company: SmithKline Beecham, NDA # 021654

The firm provided Paragraph IV certification.

10. PHARMACOLOGICAL CATEGORY: indicated as an adjunct to diet to reduce very high (≥ 500 mg/dL) triglyceride (TG) levels.

11. DOSAGE FORM: Soft gelatin capsules

Reference ID: 2957317

12. STRENGTH/POTENCY: 1g

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed
__X__Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING

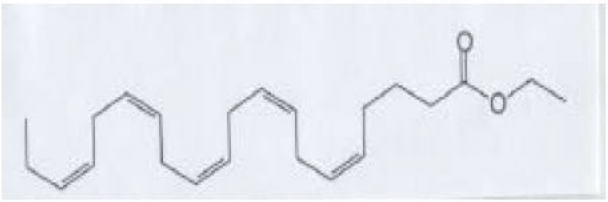
_____Nano product – Form Completed
__X__Not a NANO product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Eicosapentaenoic Acid Ethyl Ester (EPA-EE)

CAS Registry Number: 73310-10-8

Molecular Structure:



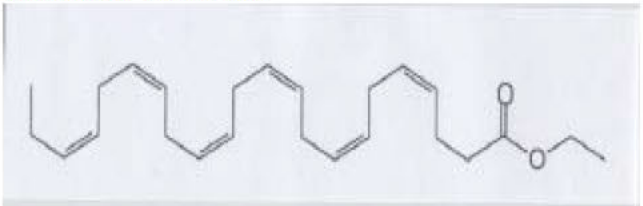
Molecular Formula: $C_{22}H_{34}O_2$

Molecular Weight: 330.51

Chemical Name: Docosahexaenoic Acid Ethyl Ester (DHA-EE)

CAS Registry Number: 84494-72-4

Molecular Structure:



Reference ID: 2957317

Molecular Formula: $C_{24}H_{36}O_2$

Molecular Weight: 356.5

Reference ID: 2957317

Background:

Lovaza (Omega-3-acid ethyl esters) soft gelatin capsules was approved on November 10, 2004, as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe hypertriglyceridemia.

The USP 34 for Omega-3 Acid Ethyl Esters defines the drug substance to contain 7 omega-3 acid ethyl esters. The Agency considers that a pharmaceutically equivalent API contains two quantitatively major components, EPA EE and DHA EE, in the ranges specified in the USP. Quantitative ranges are not specified for three additional omega-3 acid EEs present greater than 1% w/w in the RLD, Lovaza (GSK). These three compounds are SDA EE, HPA EE, and DPA EE.

Pursuant to CMC request, the firm provided quantitative levels of the seven omega-3 acid EEs in multiple batches of the RLD and one batch of the test product. The firm has not provided comparable results for the quantitation of components using in-house analytical method against the USP recommended method. For setting the quantitative ranges of the components for the proposed drug product, the firm needs to provide data for six batches RLD using the official (USP) analytical method.

Reviewer's comment:

The firm is requested to provide responses to the following listed deficiencies (see letter) prior to full CMC review of the application.

III. List of Deficiencies to be communicated:

ANDA: 091028
APPLICANT: TEVA Pharmaceuticals USA
DRUG PRODUCT: Omega-3-Acid Ethyl Esters Capsules, 1 g

The deficiencies presented below represent a Minor deficiency.

A. Deficiencies:

(b) (4)

Upon receiving the above requested data a complete CMC review of the application will be undertaken.

Sincerely yours,

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

Endorsements:

HFD-630/ H. Li, Review Chemist/6/7/2011
HFD-630/ L. Nagavelli, Team Leader /6/7/2011
HFD-617/L. Sears, PM/ 6/07/2011

V:\Chemistry Division III\Team 12\Final Version For DFS Folder\ANDA\91028R01.doc

TYPE OF LETTER: NOT APPROVABLE - Minor

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/s/

HAITAO LI
06/07/2011

LEIGH A SEARS
06/07/2011

LAXMA R NAGAVELLI
06/07/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 91028

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE
DISSOLUTION ACKNOWLEDGEMENT REVIEW

ANDA No.	091028
Drug Product Name	Omega-3-Acid Ethyl Esters Capsules
Strength (s)	1 gram
Applicant Name	Teva Pharmaceuticals USA
Applicant Address	425 Privet Road Horsham, PA 19044
US Agent Name and the mailing address	Scott D. Tomsky 425 Privet Road Horsham, PA 19044
US Agent's Telephone Number	(215) 591-3142
US Agent's Fax Number	(215) 591-8812
Original Submission Date(s)	November 10, 2008
Submission Date(s) of Amendment(s) Under Review	April 3, 2014 (Dissolution Acknowledgment)
First Generic	No
Reviewer	Martin Yoon, Pharm.D.
OVERALL DISSOLUTION REVIEW RESULT	**ADEQUATE**

EXECUTIVE SUMMARY

This is a review of the QCRT method and/or specifications acknowledgement from Teva Pharmaceuticals USA on April 3, 2014. Teva Pharmaceuticals USA has accepted the following FDA-recommended QCRT method and specifications:

Apparatus:	USP II (paddle) with (b) (4) Helix Coil sinkers
Speed of Rotation:	100 rpm
Medium:	Tier I: 8% Labrasol in 0.1 N HCl without enzyme Tier II: 8% Labrasol in 0.1 N HCl with pepsin (750,000 units/L)
Volume:	900 mL
Temperature:	37°C ± 0.5°C
Specifications:	EPA: NLT (b) (4) % (Q) in 90 minutes and DHA: NLT % (Q) in 90 minutes

RECOMMENDATIONS

From a bioequivalence point of view, Teva Pharmaceuticals USA has met the requirements for in vitro dissolution testing. The dissolution testing section of the application is adequate and we have no further questions at this time.

DISSOLUTION COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 091028

APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Omega-3-Acid Ethyl Esters Capsules, 1 gram

The Division of Bioequivalence I (DBI) has completed its review of your submissions acknowledged on the cover sheet and has no further questions at this time. We acknowledge that you will conduct the dissolution testing of your test product using the following FDA-recommended QCRT method and specifications:

Apparatus:	USP II (paddle) with (b) (4) Helix Coil sinkers
Speed of Rotation:	100 rpm
Medium:	Tier I: 8% Labrasol in 0.1 N HCl without enzyme Tier II: 8% Labrasol in 0.1 N HCl with pepsin (750,000 units/L)
Volume:	900 mL
Temperature:	37°C ± 0.5°C
Specifications:	EPA: NLT (b) (4)% (Q) in 90 minutes and DHA: NLT % (Q) in 90 minutes

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

COMPLETED ASSIGNMENT FOR 91028 ID: 22244

Reviewer: Yoon, Martin **Date Completed:**
Verifier: Solana-Sodeinde, Diana **Date Verified:**
Division: Division of Bioequivalence
Description: Dissolution Acknowledgement Review for ANDA 091028, Omega-3-Acid Ethyl Esters Capsules, 1 gram

---

Productivity:

ID	***Letter Date***	***Productivity Category***	***Sub Category***	***Productivity***	***Subtotal***
22244	4/4/2014	Dissolution Data (REGULAR)	Dissolution Acknowledgement	1	1
				Total:	1

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/s/

MARTIN YOON
04/04/2014

DIANA A SOLANA-SODEINDE on behalf of DALE P CONNER
04/04/2014

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	091028	
Drug Product Name	Omega-3-Acid Ethyl Esters Capsules	
Strength(s)	1 g	
Applicant Name	Teva Pharmaceuticals USA	
Address	425 Privet Road Horsham, PA 19044	
Applicant's Point of Contact	Scott D. Tomsky VP US Generics Regulatory Affairs	
Contact's Telephone Number	(215) 591-3142; email: scott.tomsky@tevapharm.com	
Contact's Fax Number	(215) 591-8812	
Original Submission Date(s)	November 10, 2008 (Original submission) October 1, 2009 (Dissolution amendment-already reviewed) December 30, 2013 (Complete response amendment-already reviewed)	
First Generic	No	
Submission Date(s) of Amendment(s) Under Review	March 20, 2014 February 7, 2014 (ECD telephone request)	
Reviewer	Ke Ren. Ph.D.	
Study Number (s)	2008-1779	2008-1829
Study Type (s)	Fasting and Fed study (RLD only)	Fed Study (Test and RLD)
Strength (s)	4 X 1 g	4 X 1 g
Clinical Site	Pharma Medica Research Inc.	Allied Research International (Formerly Cetero Research)
Clinical Site Address	4770 Sheppard Avenue East Toronto, Ontario, Canada M1S 3V6	1405 NW 167th Street Miami Gardens, Florida 33169
Analytical Site	(b) (4)	
Analytical Site Address		

OVERALL REVIEW RESULT	**ADEQUATE**		
WAIVER REQUEST RESULT	**N/A**		
OSI REPORT RESULT	**N/A** (In Vitro Option)		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1, 8 , 17 and 19	**Dissolution**	**1 gram**	**INADEQUATE** (*pending only the QCRT acknowledgment from the firm*)
17 and 19	***In vitro* BE Study**	**1 gram**	**ADEQUATE**
1	**Pilot Study (fasting and fed)**	**1 gram**	**INADEQUATE** (*for information only*)
1	**Pivotal Fed Study**	**1 gram**	**INADEQUATE** (*for information only*)

Review of an Amendment

1 EXECUTIVE SUMMARY

This application is referencing NDA 021654 for Lovaza® (omega-3-acid ethyl esters) Capsules, 1 g, from GlaxoSmithKline.

On November 10, 2008, Teva Pharmaceuticals USA originally submitted the results of a pilot *in vivo* study (Study # 2008-1779), a fed pivotal *in vivo* bioequivalence (BE; Study # 2008-1829) study and an *in vitro* non-quantitative capsule rupture test, comparing its test product, Omega-3-Acid Ethyl Esters Capsules, 1.0 gram, to the corresponding reference listed-drug (RLD) product, GlaxoSmithkline's Lovaza® (omega-3-acid ethyl esters) Capsules, 1.0 gram, to support its application.[1] However, per the current draft individual drug product Guidance for the Omega-3-Acid Ethyl Esters Capsules,[2] deficiencies were found in both *in vivo* and *in vitro* study portions: (1) The firm did not submit recommended fasting and fed studies and (2) did not submit method development report and modification of existing quantitative capsule rupture testing (QCRT).[3]

On December 30, 2013, the firm acknowledged its selection of *In Vitro* Study option per the above Guidance to establish the BE between its test and the RLD products in the current amendment submission and responded to the deficiencies identified in the OGD's complete response letter of August 13, 2013. This application is considered qualified for the in vitro QCRT BE testing option, based on the test formulation submitted in the amendment dated December 30, 2013.

The firm submitted three different QCRT methods using either paddle or flow-through cell.

- Method 1 (firm-proposed method):

Apparatus:	USP II (paddle) with sinkers
Speed of Rotation:	100 rpm
Medium:	Tier I: 8% Labrasol in 0.1 N HCl without enzyme Tier II: 8% Labrasol in 0.1 N HCl with pepsin (750, 000 units)
Volume:	900 mL

- Method 2

Apparatus:	USP IV, Flow-through Cell
Flow:	(b) (4)
Medium:	

[1] DARRTS, ANDA 091028 REV-BIOEQ-01 (General Review); Submit/Final Date 12/14/2012

[2] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM320011.pdf (recommended on September, 2012)

[3] DARRTS, ANDA 091028 COR-ANDAACTION-09(Complete Response); Submit/Final Date 08/13/2013

Reference ID: 3488451

- Method 3

Apparatus:	USP II (paddle) with sinkers
Speed of Rotation:	(b) (4)
Medium:	

Summary of similarity factor f2 values using conventional method:

Data from Firm's QCRT Method 1--Tier I

Conventional Method (f2 similarity calculation)	**f2 $_{EPA}$**	Test vs. Reference	24.99
	f2 $_{DHA}$	Test vs. Reference	26.54

Data from Firm's QCRT Method 1—Tier II

Conventional Method (f2 similarity calculation)	**f2 $_{EPA}$**	Test vs. Reference	50.88
	f2 $_{DHA}$	Test vs. Reference	50.44

Data from Firm's QCRT Method 2

Conventional Method (f2 similarity calculation)	**f2 $_{EPA}$**	Test vs. Reference	51.141
	f2 $_{DHA}$	Test vs. Reference	52.364

Data from Firm's QCRT Method 3

Conventional Method (f2 similarity calculation)	**f2 $_{EPA}$**	Test vs. Reference	52.91
	f2 $_{DHA}$	Test vs. Reference	77.67

Summary of similarity factor f2 values using bootstrapping method:

Data from Firm's QCRT Method 1—Tier I

Bootstrapping Method	f2_bar_EPA	24.99
	f2_boot_mean_EPA	**25.05**
	f2_5th_EPA	28.74
	f2_95th_EPA	31.20
	f2_bar_DHA	26.55
	f2_boot_mean_DHA	**26.69**
	f2_5th_DHA	21.22
	f2_95th_DHA	33.16

Data from Firm's QCRT Method 1—Tier II

Bootstrapping Method	f2_bar_EPA	50.88
	f2_boot_mean_EPA	**48.192**
	f2_5th_EPA	47.71
	f2_95th_EPA	54.77
	f2_bar_DHA	50.44
	f2_boot_mean_DHA	**47.98**
	f2_5th_DHA	40.20
	f2_95th_DHA	55.23

Data from Firm's QCRT Method 2

Bootstrapping Method	f2_bar_EPA	51.14
	f2_boot_mean_EPA	**46.94**
	f2_5th_EPA	31.62
	f2_95th_EPA	61.31
	f2_bar_DHA	52.36
	f2_boot_mean_DHA	**47.17**
	f2_5th_DHA	35.65
	f2_95th_DHA	57.44

Data from Firm's QCRT Method 3

Bootstrapping Method	f2_bar_EPA	52.91
	f2_boot_mean_EPA	**53.33**
	f2_5th_EPA	46.41
	f2_95th_EPA	61.85
	f2_bar_DHA	77.67
	f2_boot_mean_DHA	**76.84**
	f2_5th_DHA	63.93
	f2_95th_DHA	91.39

The QCRT testing data from the test and reference products from all three methods are comparable based on f2 calculation (f2 values are greater than 50 (i.e., f2= 53.33 for EPA component and f2= 76.84 for DHA component) using the bootstrapping method for Method 3 and f2 values are close to 50 (i.e., Method 2: f2= 46.94 for EPA component and f2= 47.17 for DHA component; Method 1 at Tier II: f2= 48.192 for EPA component and f2= 47.98 for DHA component) using the bootstrapping method for Method 2 and Method 1 at Tier II). Based on the f2 values and the similarity of the capsule fill in the Test and RLD products, the reviewer concludes that the Test and RLD products are bioequivalent.

The application is acceptable pending the firm's acknowledgment of the recommended QCRT method and specification for its product [See the separate review for regulatory QCRT method and specification, DARRTS ANDA 091028 Ren, Ke 04/02/2014 N/A 04/02/2014 REV-BIOEQ-02 (Dissolution Review) Archive].

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3 BACKGROUND INFORMATION

- In the original submission (submission date November 10, 2008), the firm submitted the results of a pilot *in vivo* study (Study #2008-1779), a fed pivotal *in vivo* bioequivalence (BE; Study #2008-1829) study and an *in vitro* non-quantitative capsule rupture test, comparing its test product, Omega-3-Acid Ethyl Esters Capsules, 1.0 g, to the RLD product, GlaxoSmithkline's Lovaza® (omega-3-acid ethyl esters) Capsules, 1.0 g, to support its application.

The results of the original pivotal fed BE study (Study # 2008-1829) are included below:

Eicosapentaenoic Acid (EPA; Free fatty acids)

Baseline Adjusted **Omega-3-acid ethyl esters Capsules, 4 x 1 g** **Fed Bioequivalence Study No. 2008-1829, N=80 (Male=32 and Female=48)** **Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals**					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	5.14	5.41	0.95	90.25	99.94
Cmax (ng/mL)	0.81	0.87	0.92	84.58	100.67

EPA (Total lipids)

Baseline Adjusted **Omega-3-acid ethyl esters Capsules, 4 x 1 g** **Fed Bioequivalence Study No. 2008-1829, N=80 (Male=32 and Female=48)** **Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals**					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (µg·hr/mL)	947.89	959.67	0.99	94.23	103.53
Cmax (µg /mL)	72.68	75.44	0.96	90.56	102.49

Docosahexaenoic Acid (DHA; Free fatty acids)

Baseline Adjusted **Omega-3-acid ethyl esters Capsules, 4 x 1 g** **Fed Bioequivalence Study No. 2008-1829, N=80 (Male=32 and Female=48)** **Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals**					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	12.369	12.688	0.97	90.76	104.71
Cmax (ng/mL)	2.364	2.515	0.94	85.27	103.56

DHA (Total lipids)

Baseline Adjusted Omega-3-acid ethyl esters Capsules, 4 x 1 g Fed Bioequivalence Study No. 2008-1829, N=80 (Male=32 and Female=48) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (µg ·hr/mL)	290.59	290.30	1.00	88.92	112.68
Cmax (µg /mL)	44.06	44.86	0.98	89.87	107.36

- However, the firm's pivotal fed study was not acceptable per current Guidance. According to the current BE guidance for Omega-3-Acid Ethyl Esters Capsules posted on September 2012, the 90% confidence intervals for BE of fed study are based on: (1) EPA ethyl esters and (2) DHA ethyl esters. In addition, a fasting BE study is recommended and its 90% confidence intervals for BE are based on: (1) baseline-adjusted EPA total lipids and (2) baseline-adjusted DHA total lipid.

- Also, in the same original submission the firm's *in vitro* non-quantitative capsule rupture testing data were generated per USP <2040> Rupture Test for Soft Gelatin Capsules [500 mL of water using Apparatus II (paddle) at 50 rpm, by visual determination of capsule ruptures] and was found inadequate pending its development of a QCRT method.[4]

- On October 1, 2009, the firm submitted a subsequent dissolution amendment[5] in response to the deficiency letter dated May 6, 2009.[6] The firm had provided results of a then newly developed QCRT, which was found non-discriminatory QCRT profiles between the test and reference product. Thus the QCRT was still inadequate pending the firm's modification of the then-current QCRT method.[7]

- December 30, 2013, the firm submitted the amendment in response to the Office of Generic Drugs' (OGD's) "Complete Response Letter" of August 13, 2013.[8] The firm addressed these deficiencies identified by the DBI. However, there were two different analytical instrumental conditions used in the QCRT and in vitro BE testing. In addition, the firm did not submit results of individual component of EPA and DHA release for the QCRT and in vitro BE testing. The firm was asked to provide clarification on the different analytical instrumental conditions and individual component dissolution data through its response to the DBI's Easily-Correctable-Deficiency (ECD) telephone request dated February 7, 2014[9]. The firm did not respond to the deficiency comments in the DBI's ECD request within 10 business days. Therefore, these aforementioned bio deficiencies and an additional deficiency regarding the sinkers used in the testing have been incorporated into the OGD's "Complete Response Letter" of March 11, 2014.

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[4] DARRTS, ANDA 091028, REV-BIOEQ-02(Dissolution Review) Original-1 Archive: Submit/Final Date: 5/4/2009
[5] DARRTS, ANDA 091028, Supporting Document #8 Quality/Quality Information; Bioequivalence/Response to Information Request, Original-1 View EDR; Submit/Final Date: 10/01/2009.
[6] DARRTS, ANDA 091028, COR-ANDAE-01(Bio Incomplete Deficiencies) Original-1 Archive; Submit/Final Date: 5/6/2009.
[7] DARRTS, ANDA 091028, REV-BIOEQ-01(General Review) Original-1 Archive: Submit/Final Date: 12/14/2012
[8] DARRTS, ANDA 091028, COR-ANDAACTION-09(Complete Response) Original-1 Archive; Submit/Final Date: 08/13/2013.
[9] DARRTS ANDA 091028 Yoon, Martin 02/07/2014 FAX 02/07/2014 COR-ECD-01(Easily Correctable Bioequivalence Deficiency) Archive

Please note the same deficiencies have been issued in the dissolution-only review and full ANDA review.

- In this current amendment, the firm submitted its responses for each of the deficiencies issued by the OGD (dated March 11, 2014)[10].

4 SUBMISSION SUMMARY

4.1 Drug Product Information, PK/PD Information, and Relevant DBE History

The drug information has not changed since the most recent review completed in March 2014. For more information, please refer to the following reviews:

- DARRTS ANDA 091028 Gainese, Robert T 03/11/2014 FAX 03/1132014 COR-ANDAACTION-09 (Complete Response) Archive
- DARRTS ANDA 091028 Gong, Li 03/10/2014 N/A 03/10/2014 REV-BIOEQ-21 (Primary Review) Archive
- DARRTS ANDA 091028 Gong, Li 03/06/2014 N/A 03/06/2014 REV-BIOEQ-02 (Dissolution Review) Archive
- DARRTS ANDA 091028 Yoon, Martin 02/07/2014 FAX 02/07/2014 COR-ECD-01 (Easily Correctable Bioequivalence Deficiency) Archive
- DARRTS ANDA 091028 Gong, Li 12/14/2012 N/A 12/14/2012 REV-BIOEQ-01(General Review) Archive
- DARRTS ANDA 091028 Ren, Ke 05/04/2009 N/A 05/04/2009 REV-BIOEQ-02 (Dissolution Review) Archive

4.2 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	-
Single-dose fed	No	-
Steady-state	No	-
In vitro dissolution	No	1 (reviewed in a separate dissolution amendment review document)
Waiver requests	No	-
BCS Waivers	No	-
Vasoconstrictor Studies	No	-
Clinical Endpoints	No	-
Failed Studies	No	-
Amendments	Yes	1

[10] DARRTS ANDA 091028 Gainese, Robert T 03/11/2014 FAX 03/1132014 COR-ANDAACTION-09 (Complete Response) Archive

4.3 Review of Amendment Submissions

The firm's responses to the four (4) deficiencies and the reviewer's evaluations of those responses are provided in this section of the review.

DBI Deficiency Comment #1

With respect to the Quantitative Capsule Rupture Testing (QCRT) and in vitro bioequivalence (BE) studies submitted on December 30, 2013, you have referenced two different analytical methods. Specifically, the analytical method used in your method validation (Project lD 0013: Code: 2000040) differs from that used in the QCRT [Report No. QDP0060815] and in the in vitro BE testing (POPV 0313 0791, POPV 0313 0852, POPV 0313 0853, POPV 0313 0892, POPV_0313_0891), as follows:

Analytical method used in your method validation (Project ID O013: Code: 2000040):

Column:	(b) (4)
Detection:	
Flow Rate:	
Injection Volume:	
Column Temperature:	
Run Time:	

Analytical method used in your quantitative capsule rupture testing (QCRT) using USP Apparatus II (paddles) or USP apparatus IV [Report No. QDP0060815] and in the in vitro bioequivalence (BE) testing (POPV_0313_0791, POPV_0313_0852, POPV_0313_0853, POPV_0313_0892, POPV_0313_0891):

Column:	(b) (4)
Detection:	
Flow Rate:	
Injection Volume:	
Column Temperature:	
Auto sampler Temperature:	
Run Time (Apparatus II):	
Run Time (Apparatus IV):	

Please clearly identify which instrument conditions were used during the QCRT testing [Report No.QDP0060815] and the in vitro BE testing. If the method used in these studies differs from that already validated, then please provide additional validation as necessary. Also, please provide your Standard Operating Procedure (SOP) for each of the above methods as well as for the method validation procedure.

Firm's Response:

Upon review of the documentation which was submitted in our December 30, 2013 Minor Amendment, **a typographical error** was identified in Appendix 2 of Report No. QDP0060815 (page 98) which incorrectly stated the run time as (b) (4). Please note the run time for the design of experiments (b) (4) (b) (4) Please find in Module 3.2.P.5.6 a copy of the updated report which reflects the corrected run times.

Teva has developed various quantitative capsule rupture test (QCRT) methods to support *in vitro* BE testing, all of which have been validated in accord with our standard operating procedures. At the time of our December 30, 2013 Minor Amendment, separate documents containing solely the analytical methods for the QCRT testing were not available. Instead, the methods were embedded within the method validation report (QDP0068549) and the Summary of *In Vitro* Evaluation Report (QDP0060815). Separate documents housing the analytical methods have since been created to support the QCRT. As noted in our December 30, 2013 Amendment, it is Teva's belief that the method which utilizes USP Apparatus II with the surfactant Labrasol remains the most appropriate for our drug product. However, the methods which utilize the surfactant (b) (4) are also provided herein for your review.

<u>Analytical Methods and Method Validation Report for method using Labrasol:</u>

- Module 3.2.P.5.2 Analytical Method (QDP0004603)
  USP Apparatus II with the surfactant Labrasol (without enzyme) – Tier I
  USP Apparatus II with the surfactant Labrasol (with enzyme) – Tier II

- Module 3.2.P.5.3 and Module 3.2.R.3.P
  Analytical Method Validation Report (QDP0068549)
  USP Apparatus II with the surfactant Labrasol (without enzyme) – Tier I
  USP Apparatus II with the surfactant Labrasol (with enzyme) – Tier II

<u>Analytical Methods and Method Validation Report for method using (b) (4) (App II)</u>

- Module 3.2.P.5.2 Analytical Method (QDP0074613)
  USP Apparatus II with the surfactant (b) (4)

- Module 3.2.P.5.3 and Module 3.2.R.3.P
  Analytical Method Validation Report (QDP0057280)
  USP Apparatus II with the surfactant (b) (4)

Analytical Methods and Validation Report for method using [redacted] (b) (4) (App IV)

- Module 3.2.P.5.2 Analytical Method (QDP0074614)
  USP Apparatus IV with the surfactant [redacted] (b) (4)

- Module 3.2.P.5.3 and Module 3.2.R.3.P
  Analytical Method Validation Report (QDP0057757)
  USP Apparatus IV with the surfactant [redacted] (b) (4)

Additionally, please note that the validation reports for the methods using the surfactant [redacted] (b) (4) were inadvertently omitted from our December 30, 2013 Minor Amendment, and are provided herein, as noted above, for completeness of the file.

The following table summarizes the development work regarding the QCRT testing performed by Teva, and provides the parameters, instruments and conditions used for the method validation and comparative dissolution profile testing. To aid your review, this table also connects the DOE reports to their corresponding Method Validation Reports and Comparative Profile Testing reports:

Methodology		**Validation Report No.**	**Design Of Experiments**	**Reason for the method development**
Dissolution Parameters **Method: QDP0004603**		Report No. **QDP0068549** Comparative Dissolution Report No. **QDP0068622** – Tier I (without enzyme) Comparative Dissolution Report No. **QDP0068624** – Tier II (with enzyme) Submitted in 12/30/13 Minor Amendment	Report No. **QDP0069171** Submitted in 12/30/13 Re- submission/ After Action - Minor Amendment	This report was generated to evaluate the use of USP Apparatus II using varying levels of Labrasol in 0.1 N HCl with and without enzyme, in response to a request made by the Division of Bioequivalence in the 8/13/2013 complete response letter
Apparatus: USP Apparatus II				
Dissolution Medium - Tier I: 8% Labrasol in 0.1 N HCl without enzyme				
Dissolution Medium - Tier II: 8% Labrasol in 0.1 N HCl with enzyme (pepsin, 750,000 units)				
Rotation	100 rpm			
Sinker:	[redacted] (b) (4) Helix			
Volume:	900 mL			
Temperature:	37 ± 0.5°C			
Distance from bottom:	2.5 cm			
Time Point (Single):	120 minutes			
Time Points (Profile):	10, 15, 30, 45, 60, 90, 120 minutes			
Chromatographic Parameters				
Detection:	[redacted] (b) (4)			
Flow Rate:				
Injection Volume:				
Column Temperature:				
Run Time:	[redacted] (b) (4)			

Following this page, 1 Page Withheld in Full as (b)(4)

Reviewer's Comments: The firm's response to the Deficiency #1 is **adequate.**

- In the previous amendment (submission date December 30, 2013), the firm explored and evaluated three different QCRT methods: USP II using Labrasol as surfactant, USP IV using [redacted] as surfactant, and USP II using [redacted] as surfactant. The firm submitted the complete method optimization reports. However, the firm referenced two different analytical instrumental conditions used in the respective QCRT and in vitro BE studies. The firm was asked to provide clarifications.

- In the current amendment, the firm indicated that a typographical error was identified in the Appendix 2 Report No. QDP0060815 which incorrectly stated the run time as [redacted][11]. The run time for the design of experiments [redacted] The firm submitted the updated report which reflects the corrected run time information in Module 3.2.P.5.6 (pages 502 and 507).

- The firm has developed three different QCRT methods. All three QCRT methods were validated for its system suitability, specificity, precision, accuracy, linearity and range, robustness, filter equivalence, API equivalence and standard and sample solution stability. The QCRT validation report for Method 1 has been reviewed in the previous dissolution-only review[12]. Please refer to section 4.4 of the current document for a review of the validation of analytical method for Method 2 and Method 3.

  - Method 1 (firm-proposed method for release and stability testing):

Apparatus:	USP II (paddle)
Speed of Rotation:	100 rpm
Sinkers:	[redacted], Helix
Medium:	Tier I: 8% Labrasol in 0.1 N HCl without enzyme Tier II: 8% Labrasol in 0.1 N HCl with pepsin (750, 000 units)
Volume:	900 mL
Temperature:	37°C ± 0.5°C
Specifications	NLT [redacted]% (Q) in [redacted] minutes for EPA, DHA and Total

  - Method 2

Apparatus:	USP IV, Flow-through Cell
Flow:	[redacted]
System Mode	
Medium:	
Temperature:	37°C ± 0.5°C

[11] DARRTS ANDA 091028 submitted date: 12/30/2013 Module 3.2.P.4 Control of Drug Product, page 318.
[12] DARRTS ANDA 091028 Gong, Li 03/06/2014 N/A 03/06/2014 REV-BIOEQ-02 (Dissolution Review) Archive

Specification	The firm did not propose specification. Method not proposed for routine use.

- Method 3

Apparatus:	USP II (paddle)
Speed of Rotation:	(b) (4)
Sinkers:	(b) (4) Helix or equivalent which can hold the capsules freely
Medium:	(b) (4)
Temperature:	37°C ± 0.5°C
Specification	The firm did not propose specification. Method not proposed for routine use.

Please refer to deficiency #2 for the dissolution data comparisons. The firm submitted dissolution method and method validation report for each method in Module 3.2.P.5.6.

DBI Deficiency Comment #2

In your QCRT testing [Report No. QDP0060815] and in vitro BE testing submitted December 30, 2013, you submitted data reflecting the sum of Eicosapentaenoic Acid Ethyl Ester (EPA) + Docosahexaenoic Acid Ethyl Ester (DHA) release. Please submit the release data from the referenced studies for each individual component rather than for the sum of the two components. Please submit the data from 12 individual dosage units of the Test and Reference products from the referenced studies. In addition, please submit all mean data, range, %CV, and the dates of these studies in eCTD format (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120957.pdf). Finally, please submit the temperature and humidity at which the test and reference product lots were stored between manufacture of the test product (or acquisition of the reference product) and the time of the aforementioned studies.

Firm's Response:

As requested, all reports contained within the December 30, 2013 amendment have been updated to report the results for each individual component (EPA= 465 mg and DHA= 375 mg). In addition, the data for the combined release of EPA and DHA have been re-calculated against a theoretical total of omega-3 content of 840 mg (465 mg EPA + 375 mg DHA) instead of 1000 mg.

The following reports are provided in support of our response:

Module 3.2.P.5.3 and Module 3.2.R.3.P Analytical Method Validation Report for Dissolution Test (Apparatus II) for Omega-3-Acid Ethyl Ester Capsules, 1 gram (QDP0068549) details the validation of USP Apparatus II using 8% Labrasol in 0.1 N HCl without enzyme (Tier I) and with enzyme (pepsin) (Tier II).

Module 3.2.P.5.3 and Module 3.2.R.3.P Analytical Method Validation Report for Dissolution Test (Apparatus II) for Omega-3-Acid Ethyl Ester Capsules, 1 gram (QDP0057280) details the validation of USP Apparatus II using (b) (4) as surfactant (b) (4)

Module 3.2.P.5.3 and Module 3.2.R.3.P Analytical Method Validation Report for Dissolution Test (Apparatus IV) for Omega-3-Acid Ethyl Ester Capsules, 1 gram (QDP0057757) details the validation of USP Apparatus IV using (b) (4) as surfactant (b) (4)

Module 3.2.P.5.6 Special Study Dissolution Profile Report for Omega-3 Ethyl Esters Capsules 1 g (QDP0069171) details the use of USP Apparatus II with different levels of Labrasol in 0.1 N HCl at various speeds without enzyme (Tier I) and with enzyme (pepsin) (Tier II). This study led to our conclusion that the method using USP Apparatus II with Labrasol is the most appropriate for our drug product.

Module 3.2.P.5.6 Omega-3-Acid Ethyl Ester Capsules, 1 gram Comparative Dissolution Profile (Tier II Dissolution Medium) (QDP0068624) details the comparative dissolution profile of the test product and RLD in Tier II dissolution conditions using USP Apparatus II with surfactant Labrasol, with enzyme (pepsin).

Module 3.2.P.5.6 Summary of *In Vitro* Evaluation of Teva's Omega-3-Acid Ethyl Esters Capsules and RLD, LOVAZA® Capsules for Establishing Bioequivalence (QDP0060815) details the use of USP Apparatus II and USP Apparatus IV using (b) (4) (b) (4) as surfactant (b) (4)

The mean data, range, %CV, and dates of the studies have been added to the updated reports. As requested, the data have been summarized in eCTD format and are included in Module 2.7 in both Word and PDF formats. Please note report QDP0069171 indicates that the results of experiments 1, 2, and 5 showed either no or very low release for Total EPA and DHA, which indicate that the method is not suitable for its intended use. As such, no recalculations were performed and no tables were drafted for these three experiments.

As indicated in our December 30, 2013 Amendment, we believe we have developed a discriminating method for evaluating Teva's product against the RLD, and that this method demonstrates that the test product is bioequivalent to the RLD. It is our recommendation that the USP Apparatus II method with Labrasol (Tier I and Tier II methods), as discussed in Module 3.2.P.5.2 (QDP0004603), be deemed appropriate for the Quantitative Capsule Rupture test. Please refer to the following updated

documentation in support of the QCRT for routine drug product release and stability testing:

Module 3.2.P.5.1	Drug Product Release Specifications
Module 3.2.P.5.2	Drug Product Analytical Procedure
Module 3.2.P.5.6	Drug Product Justification of Specification
Module 3.2.P.8.2	Finished Product Stability Protocol
Module 3.2.P.8.2	Drug Product Stability Specifications

We propose the following dissolution conditions and Q value in the QCRT method for both release and stability:

Dissolution:

Media: Tier I: 8% Labrasol in 0.1 N HCl
Tier II: 8% Labrasol in 0.1 N HCl with Enzyme (pepsin 750,000 units)
Apparatus: USP Apparatus II
Rotation Speed: 100 rpm
Sinker: (b) (4) Helix Coil Type or equivalent
Volume: 900 mL
Temperature: 37 ± 0.5°C
Specification: EPA: NLT (b) (4)% (Q) released in (b) (4) minutes
DHA: NLT (b) (4)% (Q) released in minutes
Total: NLT (b) (4)% (Q) released in (b) (4) minutes

Regarding drug product storage conditions, please note that Teva's bulk capsules were stored in Teva's Sellersville warehouse and the RLD capsules were stored in Teva's Pomona facility. The temperature and humidity at which the test and reference products were stored between manufacture of the test procedure (or acquisition of the reference product) and testing in the studies discussed above are as follows:

Sellersville, PA
Temperature: 20°C -25°C, maximum operating range of 17°C - 28°C Relative Humidity: < 60%

Pomona, NY
Temperature: 15°C – 30°C; Relative Humidity: 10 % – 60 %

Reviewer's Comments: The firm's response to the Deficiency #2 is **adequate.**

- In the previous amendment (submission date December 30, 2013), all dissolution data were expressed as the combined release of EPA (g) and DHA (g) divided by 1 g of Omega-3-Acid Ethyl Esters Capsules. The firm was asked to provide the release data for each component rather than for the sum of the two components.

- In the current amendment, the firm submitted the release data for each component using three different QCRT methods. The firm re-calculated the release data based on each individual component with its respective amounts (EPA= 465 mg and DHA 375 mg).

Firm Proposed QCRT method—Tier I

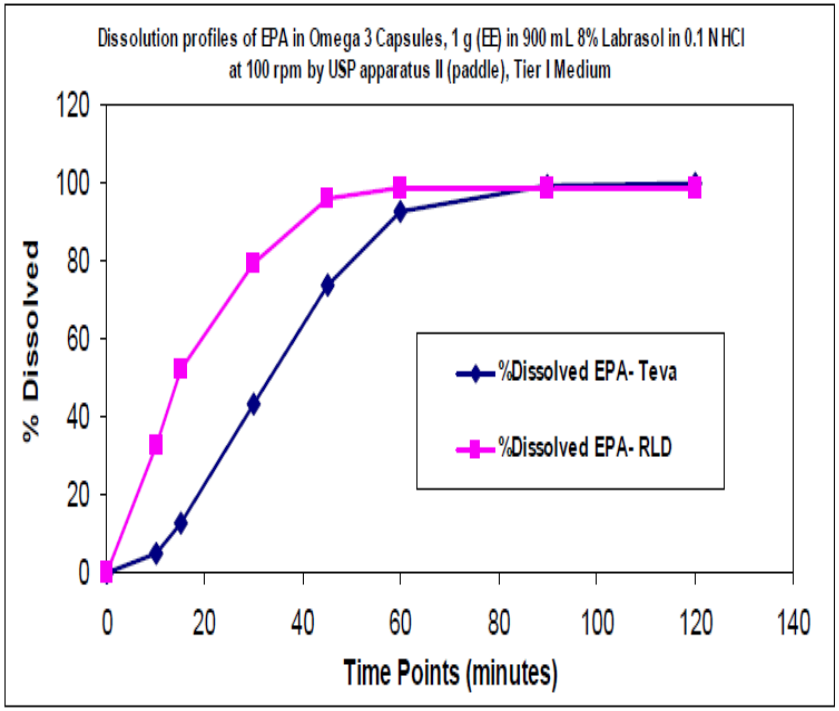
Dissolution Conditions	**Apparatus:**	USP Apparatus 2
	Speed of Rotation:	100 rpm
	Medium:	8% Labrasol in 0.1N HCl (Tier I Dissolution Medium)
	Volume:	900 mL with sinkers ([redacted], Helix Coil Type)
	Temperature:	37±0.5°C
Firm's Proposed Specifications	NLT [redacted]% (Q) released in [redacted] minutes for EPA, DHA, and Total	
Dissolution Testing & Method Validation Site (Name, Address)	Barr Laboratories, 223 Quaker Road, Pomona, NY 10970-0519	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 10	15	30	45	60	90	120
Study Report #: QDP0068622	10/17/13 10/21/13	**Omega-3-Acid Ethyl Ester Capsules USP, 1 gram** Batch # 150000584 Mfg Date: April 2, 2013	1000 mg Capsule	12	**EPA**							
					Mean	5	13	43	74	93	100	100
					Range	[redacted]						
					%CV	41.3	23.7	37.5	27.5	11.1	2.3	2.5
	10/17/13	**Lovaza** Lot 3ZP1602 Expiration Date: 4/2017	1000 mg Capsule	12	Mean	33	52	80	96	99	99	99
					Range	[redacted]						
					%CV	51.7	44.6	19.8	5.3	0.0	0.0	0.8
	10/17/13 10/21/13	**Omega-3-Acid Ethyl Ester Capsules USP, 1 gram** Batch # 150000584 Mfg Date: April 2, 2013	1000 mg Capsule	12	**DHA**							
					Mean	5	12	41	74	93	99	100
					Range	[redacted]						
					%CV	31.5	25.4	41.4	30.5	10.6	1.8	1.6
	10/17/13	**Lovaza** Lot 3ZP1602 Expiration Date: 4/2017	1000 mg Capsule	12	Mean	30	49	75	91	93	93	93
					Range	[redacted]						
					%CV	54.4	46.5	21.1	5.7	0.0	0.0	0.0
	10/17/13 10/21/13	**Omega-3-Acid Ethyl Ester Capsules USP, 1 gram** Batch # 150000584 Mfg Date: April 2, 2013	1000 mg Capsule	12	**EPA+DHA**							
					Mean	5	13	42	74	93	100	100
					Range	[redacted]						
					%CV	37.3	28.0	38.4	28.3	11.0	1.2	1.7
	10/17/13	**Lovaza** Lot 3ZP1602 Expiration Date: 4/2017	1000 mg Capsule	12	Mean	31	50	78	93	96	96	96
					Range	[redacted]						
					%CV	53.0	45.7	20.3	5.6	0.0	0.0	0.4

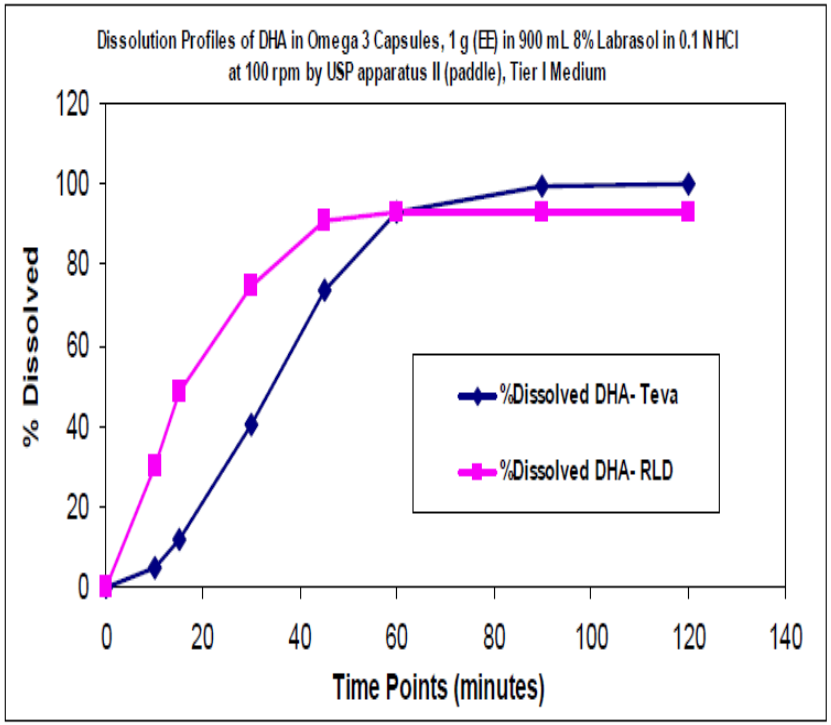
Reference ID: 3483451

Dissolution Profiles:

Tier I- EPA Component



Tier I- DHA Component



Firm Proposed QCRT method—Tier II

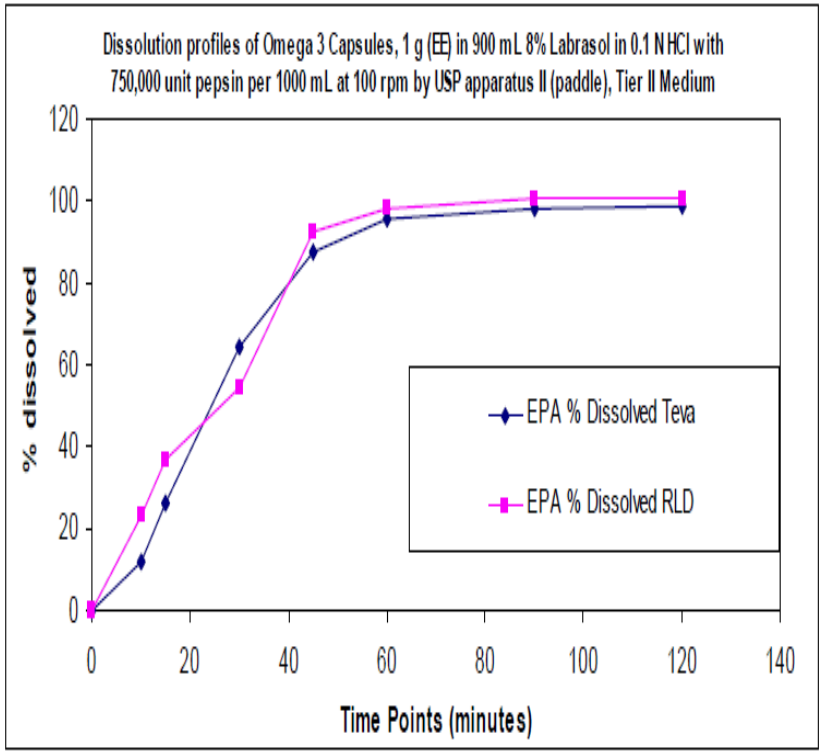
Dissolution Conditions	**Apparatus:**	USP Apparatus 2
	Speed of Rotation:	100 rpm
	Medium:	8% Labrasol in 0.1N HCl with Pepsin (Tier II Dissolution Medium)
	Volume:	900 mL with sinkers ((b) (4) Helix Coil Type)
	Temperature:	37±0.5°C
Firm's Proposed Specifications	NLT (b) (4)% (Q) released in (b) (4) minutes for EPA, DHA, and Total	
Dissolution Testing & Method Validation Site (Name, Address)	Barr Laboratories, 223 Quaker Road, Pomona, NY 10970-0519	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 10	15	30	45	60	90	120
Study Report #: QDP0068624	10/18/13 10/21/13 10/23/13	**Omega-3-Acid Ethyl Ester Capsules USP, 1 gram** Batch # 150000584 Mfg Date: April 2, 2013	1000 mg Capsule	12	**EPA**							
					Mean	12	26	64	87	96	98	99
					Range	(b) (4)						
					%CV	71.6	53.4	38.7	16.5	7.3	2.0	2.0
	10/17/13	**Lovaza** Lot 3ZP1602 Expiration Date: 4/2017	1000 mg Capsule	12	Mean	23	37	55	93	98	101	101
					Range	(b) (4)						
					%CV	28.8	22.5	37.1	13.1	4.7	2.0	1.8
	10/17/13 10/21/13	**Omega-3-Acid Ethyl Ester Capsules USP, 1 gram** Batch # 150000584 Mfg Date: April 2, 2013	1000 mg Capsule	12	**DHA**							
					Mean	12	25	65	88	96	99	99
					Range	(b) (4)						
					%CV	72.2	53.3	40.9	18.1	8.9	1.8	2.2
	10/17/13	**Lovaza** Lot 3ZP1602 Expiration Date: 4/2017	1000 mg Capsule	12	Mean	21	35	51	90	95	97	97
					Range	(b) (4)						
					%CV	29.9	22.6	37.5	13.4	6.5	3.3	3.5
	10/17/13 10/21/13	**Omega-3-Acid Ethyl Ester Capsules USP, 1 gram** Batch # 150000584 Mfg Date: April 2, 2013	1000 mg Capsule	12	**EPA+DHA**							
					Mean	12	26	65	88	96	99	98
					Range	(b) (4)						
					%CV	69.2	53.5	40.0	17.3	7.7	2.1	2.2
	10/17/13	**Lovaza** Lot 3ZP1602 Expiration Date: 4/2017	1000 mg Capsule	12	Mean	22	36	53	91	97	99	99
					Range	(b) (4)						
					%CV	29.1	22.9	37.4	13.0	5.3	0.6	0.8

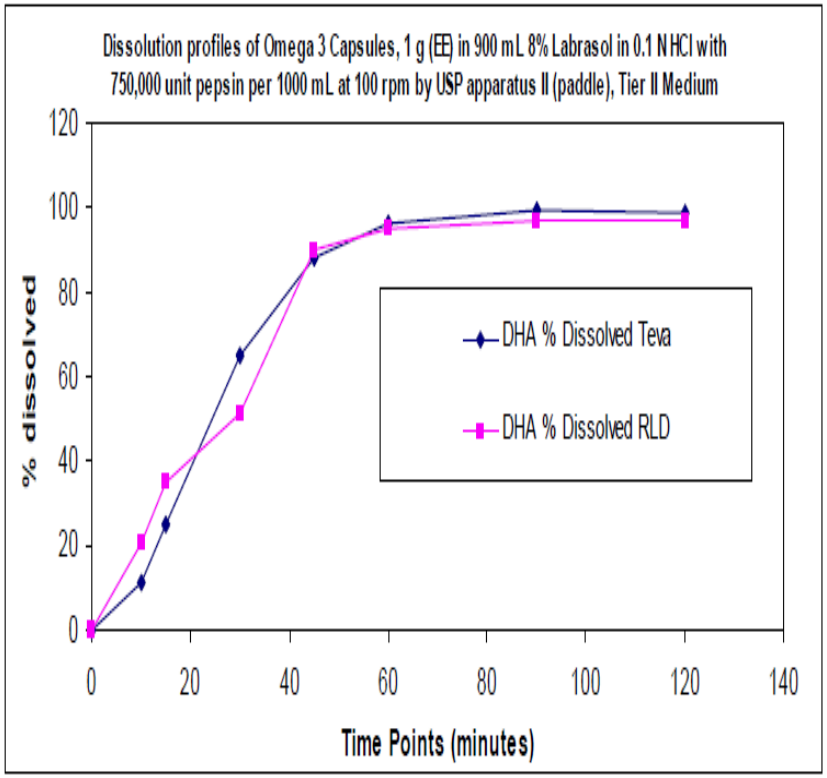
Reference ID: 3483451

Dissolution Profiles:

Tier II- EPA Component



Tier II- DHA Component



Reference ID: 3483451

Dissolution Method using [redacted] and Apparatus II

Dissolution Conditions	**Apparatus:**	USP Apparatus 2
	Speed of Rotation:	[redacted]
	Medium:	[redacted]
	Volume:	900 mL with sinkers ([redacted] Helix Coil Type)
	Temperature:	37±0.5°C
Firm's Proposed Specifications		N/A (method not proposed for routine use)
Dissolution Testing & Method Validation Site (Name, Address)		Barr Laboratories, 223 Quaker Road, Pomona, NY 10970-0519

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)						
						15	30	45	60	90	120	135
Study Report #: QDP0060815	03/21/13	**Omega-3-Acid Ethyl Ester Capsules USP, 1 gram** Batch # 30200001A Mfg Date: March 6, 2012	1000 mg Capsule	12	**EPA**							
					Mean	65	81	87	91	94	94	94
					Range	[redacted]						
					%CV	8.0	4.5	4.5	4.2	3.2	3.5	3.0
	03/18/13	**Lovaza** Lot 2ZP1263 Expiration Date: 10/2015	1000 mg Capsule	12	Mean	74	89	95	98	100	101	101
					Range	[redacted]						
					%CV	8.4	5.0	4.0	2.8	1.3	1.3	1.3
	03/21/13	**Omega-3-Acid Ethyl Ester Capsules USP, 1 gram** Batch # 30200001A Mfg Date: March 6, 2012	1000 mg Capsule	12	**DHA**							
					Mean	64	81	87	90	93	94	95
					Range	[redacted]						
					%CV	7.7	5.0	4.5	4.3	3.7	3.4	3.6
	03/18/13	**Lovaza** Lot 2ZP1263 Expiration Date: 10/2015	1000 mg Capsule	12	Mean	69	82	88	91	93	94	94
					Range	[redacted]						
					%CV	8.6	5.7	3.6	2.1	1.5	1.6	1.6
	03/21/13	**Omega-3-Acid Ethyl Ester Capsules USP, 1 gram** Batch # 30200001A Mfg Date: March 6, 2012	1000 mg Capsule	12	**EPA+DHA**							
					Mean	64	81	87	91	93	94	95
					Range	[redacted]						
					%CV	7.8	4.5	4.4	4.0	3.2	3.3	3.1
	03/18/13	**Lovaza** Lot 2ZP1263 Expiration Date: 10/2015	1000 mg Capsule	12	Mean	72	86	92	95	97	98	98
					Range	[redacted]						
					%CV	8.5	5.1	3.5	2.3	1.5	1.3	1.3

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Dissolution Method using [redacted] and Apparatus IV

Dissolution Conditions	**Apparatus:**	USP Apparatus 4
	Flow Rate	[redacted]
	Run Time	
	Medium:	
	Glass Bead Load	
	Temperature:	37±0.5 C
Firm's Proposed Specifications		N/A (method not proposed for routine use)
Dissolution Testing & Method Validation Site (Name, Address)		Barr Laboratories, 223 Quaker Road, Pomona, NY 10970-0519

Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Mfg. Date) (Reference – Exp. Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 10	20	30	40	50	60	90	120
Study Report #: QDP0060815	03/1913 03/21/13	**Omega-3-Acid Ethyl Ester Capsules USP, 1 gm** Batch # 30200001A Mfg. Date:03/06/12	1000 mg Capsule	12		**EPA**							
					Mean	14	62	83	88	90	92	94	94
					Range	[redacted]							
					%CV	66.5	33.8	22.3	15.9	11.7	9.3	6.7	7.0
	03/1913 03/21/13	**Lovaza** Lot 2ZP1263 Expiration Date: 10/2015	1000 mg Capsule	12	Mean	31	72	84	88	91	95	99	99
					Range	[redacted]							
					%CV	62.9	42.6	31.7	24.9	18.7	10.9	3.3	2.7
	03/1913 03/21/13	**Omega-3-Acid Ethyl Ester Capsules USP, 1 gm** Batch # 30200001A Mfg. Date:03/06/12	1000 mg Capsule	12		**DHA**							
					Mean	14	64	85	90	93	94	97	97
					Range	[redacted]							
					%CV	68.0	33.9	22.3	15.7	11.1	8.4	5.3	5.9
	03/1913 03/21/13	**Lovaza** Lot 2ZP1263 Expiration Date: 10/2015	1000 mg Capsule	12	Mean	29	68	80	84	86	90	93	94
					Range	[redacted]							
					%CV	63.6	42.8	32.1	25.1	19.5	11.1	3.0	2.7
	03/1913 03/21/13	**Omega-3-Acid Ethyl Ester Capsules USP, 1 gm** Batch # 30200001A Mfg. Date:03/06/12	1000 mg Capsule	12		**EPA+DHA**							
					Mean	14	63	83	89	91	93	95	96
					Range	[redacted]							
					%CV	68.0	34.1	22.1	15.7	11.4	8.7	5.9	6.3
	03/1913 03/21/13	**Lovaza** Lot 2ZP1263 Expiration Date: 10/2015	1000 mg Capsule	12	Mean	30	70	82	86	88	93	96	93
					Range	[redacted]							
					%CV	63.2	42.6	31.8	25.0	18.9	10.8	2.6	2.0

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- The table below included three QCRT method validation effective dates and dissolution conducted dates:

Method	Validation Dates	Dissolution Conducted Dates
Method 1	December 18, 2013	October 17- 23, 2013
Method 2	April 26, 2013	March 19- 21, 2013
Method 3	April 26, 2013	March 18- 21, 2013

The QCR testing dates were prior to the approved dates for dissolution method validation. Since there are only 1- 2 months apart, the reviewer deems that the firm used the validated conditions in the comparative testing. In future submissions, the firm should be informed that the dissolution validation should be completed prior to comparative QCR testing.

- The data comparisons of the firm's three different QCRT methods are shown in the following tables:

Reference ID: 3483451

Testing Date	Method*	Lot #	10 mins	15 mins	20 mins	30 mins	40 mins	45 mins	50 mins	60 mins	90 mins	120 mins	135 mins
EPA: mean% (%CV)													
10/17-21/2013	Method 1 (Tier I)	T: Bulk # 150000401; package lot #150000584	5 (41.3)	13 (23.7)	--	43 (37.5)	--	74 (27.5)	--	93 (11.1)	100 (2.3)	100 (2.5)	--
10/17/2013		R: 3ZP1602	33 (51.7)	52 (44.6)	--	80 (19.8)	--	96 (5.3)	--	99 (0)	99 (0)	99 (0.8)	--
10/18-23/2013	Method 1 (Tier II)	T: Bulk # 150000401; package lot #150000584	12 (71.6)	26 (53.4)		64 (38.7)		87 (16.5)		96 (7.3)	98 (2.0)	99 (2.0)	--
10/17/2013		R: 3ZP1602	23 (28.8)	37 (22.5)		55 (37.1)		93 (13.1)		98 (4.7)	101 (2.0)	101 (1.8)	--
03/19-21/2013	Method 2	T: Bulk # 150000401; package lot 30200001A	14 (66.5)	--	62 (33.8)	83 (22.3)	88 (15.9)	--	90 (11.7)	92 (9.3)	94 (6.7)	94 (7.0)	--
03/19-21/2013		R: 2ZP1263	31 (62.9)	--	72 (42.6)	84 (31.7)	88 (24.9)	--	91 (18.7)	95 (10.9)	99 (3.3)	99 (2.7)	--
03/21/2013	Method 3	T: Bulk # 150000401; package lot 30200001A	--	65 (8.0)	--	81 (4.5)	--	87 (4.5)	--	91 (4.2)	94 (3.2)	94 (3.5)	94 (3.0)
03/18/2013		R: 2ZP1263	--	74 (8.4)	--	89 (5.0)	--	95 (4.0)	--	98 (2.8)	100 (1.3)	101 (1.3)	101 (1.3)

* Method 1: 900 mL of 8%Labrasol in 0.1 N HCl without enzyme (Tier I) or 8%Labrasol in 0.1 N HCl with pepsin (750,000 units, Tier II) using USP Apparatus II (paddle) with sinkers at 100 rpm;
Method 2: [redacted] (b) (4) using USP Apparatus IV (flow-through cell) [redacted] (b) (4)
Method 3: 900 mL of [redacted] (b) (4) using USP Apparatus II (paddle) at [redacted] (b) (4)

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Notes: Per bio review [DARRTS ANDA 091028 Gong, Li 03/10/2014 N/A 03/10/2014 REV-BIOEQ-21 (Primary Review) Archive], the firm's test API data from its newly manufactured commercial batch (bulk lot #150000401) met the quantitative ranges recommended by the current Guidance. Package lots #30200001A and 150000584 are from the same bulk lot (#150000401)[13].

Testing Date	Method*	Lot #	10 mins	15 mins	20 mins	30 mins	40 mins	45 mins	50 mins	60 mins	90 mins	120 mins	135 mins
DHA: mean% (%CV)													
10/17-21/2013	Method 1 (Tier I)	T: Bulk # 150000401; package lot #150000584	5 (31.5)	12 (25.4)	--	41 (41.4)	--	74 (30.5)	--	93 (10.6)	99 (1.8)	100 (1.6)	--
10/17/2013		R: 3ZP1602	30 (54.4)	49 (46.5)	--	75 (21.1)	--	91 (5.7)	--	93 (0)	93 (0)	93 (0)	--
10/17-21/2013	Method 1 (Tier II)	T: Bulk # 150000401; package lot #150000584	12 (72.2)	25 (53.3)	--	65 (40.9)	--	88 (18.1)	--	96 (8.9)	99 (1.8)	99 (2.2)	--
10/17/2013		R: 3ZP1602	21 (29.9)	35 (22.6)	--	51 (37.5)	--	90 (13.4)	--	95 (6.5)	97 (3.3)	97 (3.50	--
03/19-21/2013	Method 2	T: Bulk # 150000401; package lot 30200001A	14 (68)	--	64 (33.9)	85 (22.3)	90 (15.7)	--	93 (11.1)	94 (8.4)	97 (5.3)	97 (5.9)	--
03/19-21/2013		R: 2ZP1263	29 (63.6)	--	68 (42.8)	80 (32.1)	84 (25.1)	--	86 (19.5)	90 (11.1)	93 (3.0)	94 (2.7)	--
03/21/2013	Method 3	T: Bulk # 150000401; package lot 30200001A	--	64 (7.7)	--	81 (5.0)	--	87 (4.5)	--	90 (4.3)	93 (3.7)	94 (3.4)	95 (3.6)
03/18/2013		R: 2ZP1263	--	69 (8.6)	--	82 (5.7)	--	88 (3.6)	--	91 (2.1)	93 (1.5)	94 (1.6)	94 (1.6)

[13] DARRTS ANDA 091028 Gong, Li 03/10/2014 N/A 03/10/2014 REV-BIOEQ-21 (Primary Review) Archive, page 39 and DARRTS ANDA 091028 Gong, Li 03/06/2014 N/A 03/06/2014 REV-BIOEQ-02 (Dissolution Review) Archive, page 27- 30.

* Method 1: 900 mL of 8%Labrasol in 0.1 N HCl without enzyme (Tier I) or 8%Labrasol in 0.1 N HCl with pepsin (750,000 units, Tier II) using USP Apparatus II (paddle) with sinkers at 100 rpm;
Method 2: (b) (4) using USP Apparatus IV (flow-through cell) (b) (4)
Method 3: 900 mL of (b) (4) using USP Apparatus II (paddle) at (b) (4)

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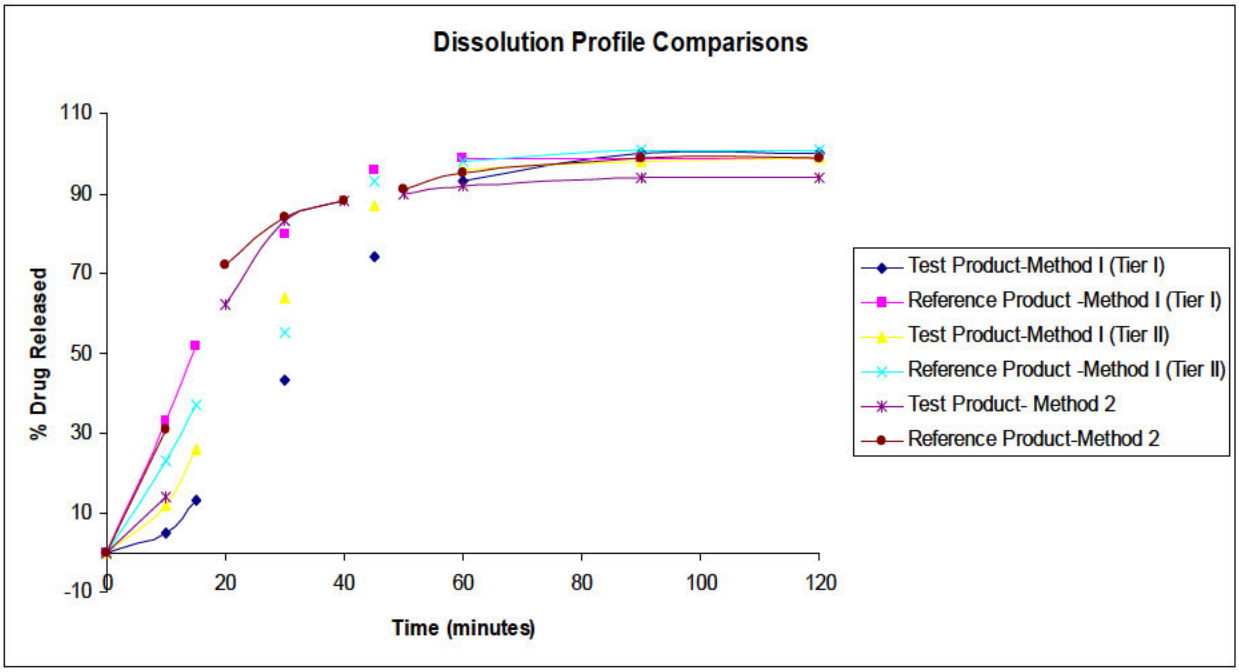
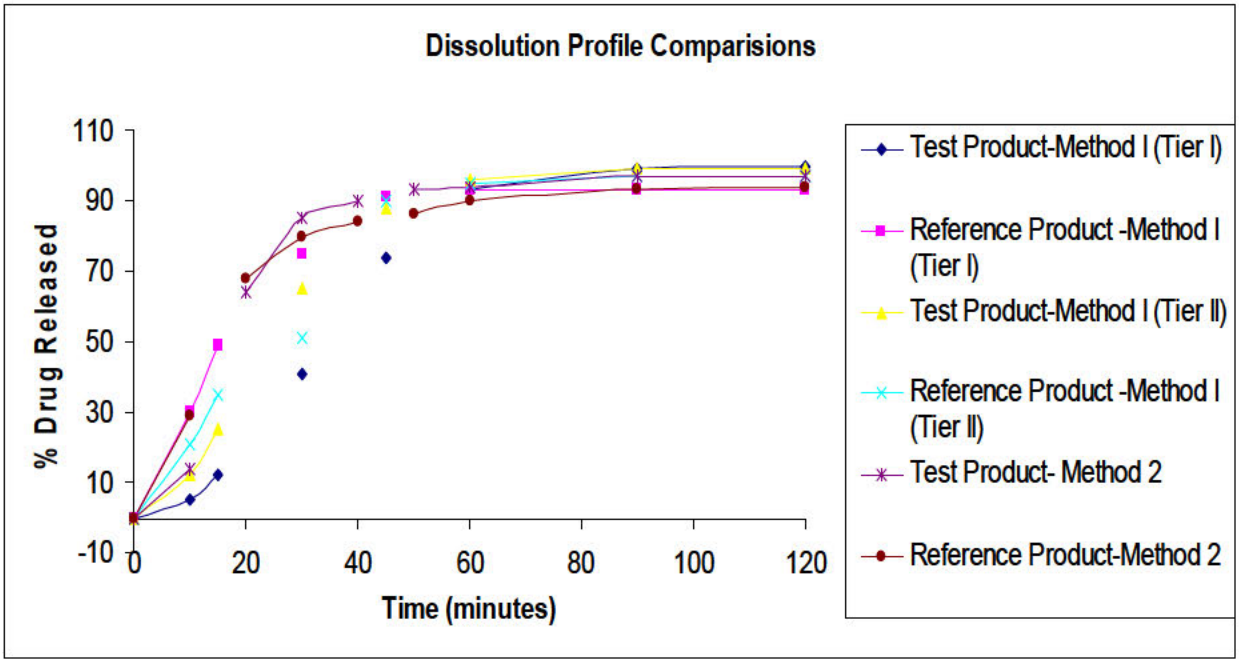
- The QCRT data using Method 1 and Method 2 for the test and reference products are shown in the graphs below:

EPA Component



DHA Component



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- The firm submitted the complete method optimization reports in the previous amendment (submission date December 30, 2013). However, all results were given as combined EPA and DHA measurements. In the current amendment, the firm has submitted addendum of complete method optimization reports, which include the separate EPA and DHA measurements (located at Module 3) and dissolution summary table (located at Module 2).

  - First, per firm's method optimization report, the firm explored QCRT method using USP Apparatus II (paddle) under 12 conductions: different concentrations of Labrasol and different paddle speeds.

Study #	**Paddle Speed (RPM)**	**Surfactant Level (%)**
1	(b) (4)	
2		
3		
4		
5		
6		
7		
8		
9		
10		
11	100	8% Labrasol in 0.1 N HCl with Pepsin (750,000 units/L)
12	100	8% Labrasol in 0.1 N HCl with Pepsin (750,000 units/L), using 17-month-old Test lot (Lot #30200001A)

  - Secondary, the firm explored QCRT method using USP Apparatus II (paddle) under (b) (4) different paddle speeds, different pHs in the dissolution medium and volume of the medium and different amounts of enzyme.

(b) (4)

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- Based on firm's method optimization reports mentioned above and QCRT data submitted, the reviewer agrees with the firm's final method conditions, as follows:

QCRT conditions using USP Apparatus II with Labrasol surfactant

Parameters	Condition used after optimization
Medium Surfactant	Labrasol
Surfactant Concentration	8%
Medium	Tier I: 8% Labrasol in 0.1 N HCl Tier II: 8% Labrasol in 0.1 N HCl with Pepsin (750, 000 units)
Paddle Speed	100 RPM
Medium Volume	900 mL
Temperature	37ºC ± 0.5ºC

QCRT conditions using USP Apparatus II with (b) (4) surfactant

Parameters	Condition used after optimization
Medium Surfactant	(b) (4)
Surfactant Concentration	
Medium pH	
Buffer	
Paddle Speed	
Medium Volume	
Enzyme	
Temperature	37ºC ± 0.5ºC

QCRT conditions using USP Apparatus IV with (b) (4) surfactant

Parameters	Condition used after optimization
Medium Surfactant	(b) (4)
Surfactant Concentration	
Medium pH	
Buffer	
Flow Rate	
Volume of Beads	
Glass Bead Size	
Enzyme	
Temperature	37ºC ± 0.5ºC

- The release data contained in the addendum were re-calculated based on each individual component with its respectively amounts (EPA= 465 mg and DHA= 375 mg). In addition, the re-calculated data for the combined release of EPA+DHA was calculated against a theoretical total of omega-3 content of 840 mg (465 mg EPA + 375 mg DHA).

- The individual unit data (located at Module 3) correspond to the data provided in the summary tables (located at Module 2) with respect to the dissolution data, lot numbers and manufacturing/expiration dates of the test product and RLD. The dissolution testing dates of the test and reference products were provided in the individual unit data. These dates match with those provided in the dissolution data summary tables. The information in this bullet point refers to the comparative (test vs. RLD) testing using all three QCRT methods.

- Based on the firm-provided *in vitro* dissolution summary data tables, the QCRT Method 1 were performed about 6 months since manufacture date of the test product, 1 g (lot # 150000584, manufacture in April, 2013; testing performance in October, 2013). The QCRT Method 2 and Method 3 were performed about 12 months since manufacture date of the test product, 1 g (lot # 30200001A, manufacture in March, 2012; testing performance in March, 2013). The reference product, 1 g (lot# 3ZP1602, expire April 2017 and lot #2ZP1263, expire October 2015), used in the QCRT testing were all before the RLD expiration dates

- The firm stored and handled the test and reference product as per the reference label[14] and as per USP recommendations[15] for the comparative (test vs. RLD) testing using all three QCRT methods.

- The reviewer is able to conduct the similarity factor f2 values calculation for the test versus the reference products of the reported individual (e.g. EPA, DHA) component values of the drug release from the Omega-3-Acid Ethyl Esters capsules using three QCRT methods.

Data from Firm's QCRT Method 1--Tier I:

Conventional Method (f2 similarity calculation)	**$f2_{EPA}$**	Test vs. Reference	24.99
	$f2_{DHA}$	Test vs. Reference	26.54

[14] http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=5ada82f0-a5fd-46c9-aecc-f106f614c9f0#nlm34068-7 ; search term: lovaza; last accessed March 30, 2014.
[15] USP: Section 10.30.50 Controlled Room Temperature; last accessed March 30, 2014.

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Data from Firm's QCRT Method 1—Tier II:

Conventional Method (f2 similarity calculation)	**$f2_{EPA}$**	Test vs. Reference	50.88
	$f2_{DHA}$	Test vs. Reference	50.44

Data from Firm's QCRT Method 2:

Conventional Method (f2 similarity calculation)	**$f2_{EPA}$**	Test vs. Reference	51.141
	$f2_{DHA}$	Test vs. Reference	52.364

Data from Firm's QCRT Method 3:

Conventional Method (f2 similarity calculation)	**$f2_{EPA}$**	Test vs. Reference	52.91
	$f2_{DHA}$	Test vs. Reference	77.67

As per the above f2 values, the test and RLD products show comparable drug release profiles when tested under the firm's proposed three QCRT methods except Method 1 at Tier I.

- Furthermore, the reviewer calculated the similarity factor f2 between the test and reference products using bootstrapping method for the dissolution profile comparison. For general information on this approach, please refer to Shah et al. In Vitro Dissolution Profile Comparison- Statistics and Analysis of the Similarity Factor f2. Pharmaceutical Research (1998) Vol. 15, No.6, page 889-896. For the bootstrapping method, sampling with replacement is used for creating 10,000 replicates of test and reference products. The means of the test and reference units at each time point for each replicate are obtained and used for f2 calculation.

Data from Firm's QCRT Method 1—Tier I

Bootstrapping Method	f2_bar_EPA	24.99
	f2_boot_mean_EPA	**25.05**
	f2_5^{th}_EPA	28.74
	f2_95^{th}_EPA	31.20
	f2_bar_DHA	26.55
	f2_boot_mean_DHA	**26.69**
	f2_5^{th}_DHA	21.22
	f2_95^{th}_DHA	33.16

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Data from Firm's QCRT Method 1—Tier II

Bootstrapping Method	f2_bar_EPA	50.88
	f2_boot_mean_EPA	**48.192**
	f2_5th_EPA	47.71
	f2_95th_EPA	54.77
	f2_bar_DHA	50.44
	f2_boot_mean_DHA	**47.98**
	f2_5th_DHA	40.20
	f2_95th_DHA	55.23

Data from Firm's QCRT Method 2

Bootstrapping Method	f2_bar_EPA	51.14
	f2_boot_mean_EPA	**46.94**
	f2_5th_EPA	31.62
	f2_95th_EPA	61.31
	f2_bar_DHA	52.36
	f2_boot_mean_DHA	**47.17**
	f2_5th_DHA	35.65
	f2_95th_DHA	57.44

Data from Firm's QCRT Method 3

Bootstrapping Method	f2_bar_EPA	52.91
	f2_boot_mean_EPA	**53.33**
	f2_5th_EPA	46.41
	f2_95th_EPA	61.85
	f2_bar_DHA	77.67
	f2_boot_mean_DHA	**76.84**
	f2_5th_DHA	63.93
	f2_95th_DHA	91.39

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The above results shows a comparable dissolution profile between test and reference product using Method 3, as reflected by f2= 53.33 for EPA component and f2= 76.84 for DHA component. However, f2 values are less than 50 using Method 1 and Method 2 (e.g., f2= 48.192 for EPA component and f2= 47.98 for DHA component using Method 1 at Tier I; f2= 46.94 for EPA component and f2= 47.17 for DHA component using Method 2).

- In summary, the reviewer deems the test product to be bioequivalent to the RLD product based on the three QCRT methods data given that 1) f2 values are greater than 50 calculated by the conventional method for three QCRT methods except Method I at Tier I; 2) f2 values are greater than 50 using bootstrapping method for Method 3 and f2 values are close to 50 using bootstrapping method for Method 2 and Method 1 at Tier II and 3) the capsule fills of the test and reference products are considered very similar.

DBI Deficiency Comment #3

You did not provide your Standard Operating Procedures (SOPs) for the QCR testing and in vitro BE studies. Please submit these documents/information.

Firm's Response:

Please refer to our response to bioequivalence comment #1 above. The analytical methods for the QCR testing and *in vitro* BE studies are provided as follows:

- Module 3.2.P.5.2 Analytical Method (QDP0004603)
  USP Apparatus II with the surfactant Labrasol (without enzyme) – Tier I
  USP Apparatus II with the surfactant Labrasol (with enzyme) – Tier II

- Module 3.2.P.5.2 Analytical Method (QDP0074613)
  USP Apparatus II with the surfactant (b) (4)

- Module 3.2.P.5.2 Analytical Method (QDP0074614)
  USP Apparatus IV with the surfactant (b) (4)

Reviewer's Comments: Per DBI's request, in the current amendment, the firm provided the dissolution methods for three different QCR testing. The firm's response to the Deficiency #3 is **adequate.**

DBI Deficiency Comment #4

You have used sinkers in study #s QDP0068549, QDP0069171, QDP0068622, QDP0068624, QDP0060815, and study # POPV_0313_0791. Please provide the following information for the sinkers: 1) a detailed description of the sinker used in the dissolution method (including a diagram, dimensions and manufacturing information)

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and 2) confirmation that the sinker is consistent with those described in USP Chapter <711> with respect to composition and dimensions.

Firm's Response:

The sinker chosen for use in the referenced studies is the [redacted] sinker device manufactured by [redacted] Please find the sinker specifications, including diagram and manufacturing information, in Module 3.2.P.5.6.

This sinker device conforms with the details described in USP Chapter <711> with respect to composition and dimensions. USP <711> states that the use of "a small, loose piece of nonreactive material, such as not more than a few turns of wire helix, may be attached to dosage units that would otherwise float. An alternative sinker device is shown in Figure 2a. Other validated sinker devices may be used."

The USP <711> alternate sinker device was considered, however, it was deemed not appropriate for this product for several reasons. The USP<711> alternate sinker device is intended for use with capsule sizes [redacted] Teva's Omega-3-Acid Ethyl Ester Capsules USP, 1g [redacted] for use with the USP <711>alternative sinker device.

It is important to note that the USP <711> alternate sinker device is similar to the [redacted] helix coil type sinker device with respect to composition (material and finish), inside diameter, and wire diameter. [redacted] Please note the [redacted] sinker has been validated for Teva's Omega-3-Acid Ethyl Esters Capsules USP, 1 gram. The USP <711> and [redacted] Helix Coil Sinker specifications are summarized as follows:

Sinker Device Comparison

	Alternate USP <711> Basket Requirements	**Capsule Sinker Specifications Helix Coil Type** [redacted]
Material	316 Stainless Steel	[redacted]
Finish	Electropolish	
Inside Length	25 – 26 mm	
Inside Diameter	12.0 +/- 0.2 mm	

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Wire Diameter	1.0 mm		(b) (4)
Pitch	3.0 – 3.5 mm		
End Mesh Spacing/ End Coil Inside Dia.	3.5 – 4.0 mm		
Maximum Width	About 14.0 mm (inside diameter + 2x wire diameter)*		
Wire Supports	10		
Number of Coils	About 7.1 - 8.7*		
Weight	4.0 gm		
Maximum Capsule Size	00		

* actual values are calculated based on specifications.

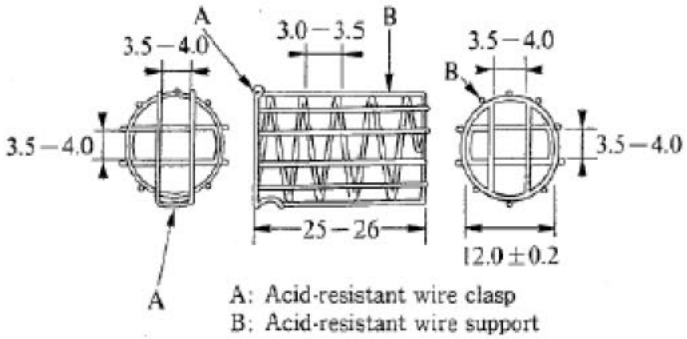
- USP <711> Alternate Sinker Maximum Width = inside diameter + 2x wire diameter = 12.0 mm*2(1.0 mm) = about 14.0 mm
- Helix Coil Type Sinker Maximum Width = inside diameter + 2x wire diameter =11.811 mm*2(1.0922 mm) = 13.9954 mm = about 14.0 mm
- USP <711> Alternate Sinker Number of Coils = inside length/pitch = 25-26 mm/3.0-3.5 mm = 7.142857143 - 8.666666667 = about 7.1 – 8.7 mm

Reviewer's Comments: The reviewer listed the scheme and descriptions of the firm's sinker and the USP's alternative sinker as follows:

Firm's sinkers:

(b) (4)

USP's alternative sinker



The firm's response to the Deficiency #4 is **adequate.**

4.4 Validation of Analytical Method Used for Method 2 and Method 3

Method 2:

Dissolution Testing Conditions:

Apparatus:	USP IV, Flow-through Cell
Flow:	(b) (4)
Medium:	

Analytical Method: HPLC

HPLC Parameters	
Mobile phase:	(b) (4)
Column:	
Flow rate:	
Wavelength:	
Injection volume:	
Column Temperature	
Auto sampler Temperature	
Run Time	

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(b) (4)

Method 3:

Dissolution Testing Conditions:

Apparatus:	USP II (paddle) with sinkers
Speed of Rotation:	100 rpm
Medium:	(b) (4)

Analytical Method: HPLC

HPLC Parameters	
Mobile phase:	(b) (4)
Column:	
Flow rate:	

Reference ID: 3483451

Wavelength:	(b) (4)
Injection volume:	
Column Temperature	
Auto sampler Temperature	
Run Time	

(b) (4)

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Reviewer Comments:

1. The analytical method validation for QCRT Methods 2 and 3 is acceptable.

2. The analytical method validation for QCRT Method 1 was found acceptable in a previous review of this application dated 3/6/2014. It is noted in said review that no interference was detected at the retention time of the EPA peak and DHA peak from dissolution medium and the soft capsule shell solution. In this regard, the current reviewer notes that the firm did not submit the specificity study on the interference of other ethyl esters with EPA and DHA (e.g., moroctic acid ethyl ester, heneicosapentaenoic acid ethyl ester, docosapentaenoic acid ethyl ester, eicosatetraenoic acid ethyl ester, alpha-linolenic acid ethyl ester and alpha-tocopherol). However, the consistency of retention times and relative chromatographic peak heights of EPA and DHA from the working standard solution as compared with sample solution indicates that the method was specific in its detection of the EPA and DHA even in the presence of the other Omega-3 Ethyl Ester components.

Reference ID: 3483451

4.5 Deficiency Comments

None

4.6 Recommendations

1. Per the current draft Individual Product BE Guidance for Omega-3-Acid Ethyl Esters Capsules, recommended on September 2012, the Division of Bioequivalence I (DBI) acknowledges that the firm, Teva Pharmaceuticals USA, intends to take *In Vitro* method option to establish the bioequivalence (BE) between the test product, Omega-3-Acid Ethyl Esters Capsules, 1 g (Lot# 150000401), and the RLD, GlaxoSmithKline's Lovaza® (omega-3-acid ethyl esters) Capsules, 1 g (Lot# 2ZP1263).

2. The firm's *in vitro* drug release testing (QCRT) for the purpose of BE determination is **adequate.**

4.7 Comments for Other OGD Disciplines

Discipline	Comment
None	--

4.8 Pending Consults (Clinical, Statistical, Science Staff, Chemistry etc.)

Discipline	Comment
None	--

Following this page, 12 Pages Withheld in Full as (b)(4)

Reference ID: 3483451

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:	091028
APPLICANT:	Teva Pharmaceuticals USA
DRUG PRODUCT:	Omega-3-Acid Ethyl Esters Capsules, 1 g

The Division of Bioequivalence I (DBI) has completed its review of your submission(s) acknowledged on the cover sheet and has no further questions at this time.

The dates of the Quantitative Capsule Rupture Testing (QCRT) studies (October 2013 with Labrasol method, and March 2013 with (b) (4) method) were prior to the approval dates for the method validation studies (December 2013 and April 2013, respectively). In future submissions, please be advised that the validation should be completed prior to comparative QCRT studies.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

6 OUTCOME PAGE

ANDA: 091028

Reviewer: Ren, Ke **Date Completed:**

Verifier: **Date Verified:**

Division: Division of Bioequivalence

Description: Omega-3-Acid Ethyl Esters Capsules, 1 g,Teva Pharmaceuticals USA

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
22228	3/24/2014	Other (REGULAR)	Study Amendment	1	1
				Total:	1

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/s/

KE REN
04/04/2014

UTPAL M MUNSHI
04/04/2014

HOAINHON N CARAMENICO
04/04/2014

HOAINHON N CARAMENICO on behalf of DALE P CONNER
04/04/2014

DIVISION OF BIOEQUIVALENCE
DISSOLUTION ACKNOWLEDGEMENT REVIEW

ANDA No.	091028
Drug Product Name	Omega-3-Acid Ethyl Esters Capsules
Strength (s)	1 gram
Applicant Name	Teva Pharmaceuticals USA
Applicant Address	425 Privet Road Horsham, PA 19044
US Agent Name and the mailing address	Scott D. Tomsky 425 Privet Road Horsham, PA 19044
US Agent's Telephone Number	(215) 591-3142
US Agent's Fax Number	(215) 591-8812
Original Submission Date(s)	November 10, 2008
Submission Date(s) of Amendment(s) Under Review	April 3, 2014 (Dissolution Acknowledgment)
First Generic	No
Reviewer	Martin Yoon, Pharm.D.
OVERALL DISSOLUTION REVIEW RESULT	**ADEQUATE**

EXECUTIVE SUMMARY

This is a review of the QCRT method and/or specifications acknowledgement from Teva Pharmaceuticals USA on April 3, 2014. Teva Pharmaceuticals USA has accepted the following FDA-recommended QCRT method and specifications:

Apparatus:	USP II (paddle) with (b) (4) Helix Coil sinkers
Speed of Rotation:	100 rpm
Medium:	Tier I: 8% Labrasol in 0.1 N HCl without enzyme Tier II: 8% Labrasol in 0.1 N HCl with pepsin (750,000 units/L)
Volume:	900 mL
Temperature:	37°C ± 0.5°C
Specifications:	EPA: NLT (b) (4)% (Q) in 90 minutes and DHA: NLT % (Q) in 90 minutes

RECOMMENDATIONS

From a bioequivalence point of view, Teva Pharmaceuticals USA has met the requirements for in vitro dissolution testing. The dissolution testing section of the application is adequate and we have no further questions at this time.

DISSOLUTION COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 091028

APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Omega-3-Acid Ethyl Esters Capsules, 1 gram

The Division of Bioequivalence I (DBI) has completed its review of your submissions acknowledged on the cover sheet and has no further questions at this time. We acknowledge that you will conduct the dissolution testing of your test product using the following FDA-recommended QCRT method and specifications:

Apparatus:	USP II (paddle) with (b) (4) Helix Coil sinkers
Speed of Rotation:	100 rpm
Medium:	Tier I: 8% Labrasol in 0.1 N HCl without enzyme Tier II: 8% Labrasol in 0.1 N HCl with pepsin (750,000 units/L)
Volume:	900 mL
Temperature:	37°C ± 0.5°C
Specifications:	EPA: NLT (b) (4)% (Q) in 90 minutes and DHA: NLT % (Q) in 90 minutes

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

COMPLETED ASSIGNMENT FOR 91028 ID: 22244

Reviewer: Yoon, Martin **Date Completed:**
Verifier: Solana-Sodeinde, Diana **Date Verified:**
Division: Division of Bioequivalence
Description: Dissolution Acknowledgement Review for ANDA 091028, Omega-3-Acid Ethyl Esters Capsules, 1 gram

---

Productivity:

ID	***Letter Date***	***Productivity Category***	***Sub Category***	***Productivity***	***Subtotal***
22244	4/4/2014	Dissolution Data (REGULAR)	Dissolution Acknowledgement	1	1
				Total:	1

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/s/

MARTIN YOON
04/04/2014

DIANA A SOLANA-SODEINDE on behalf of DALE P CONNER
04/04/2014

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	091028
Drug Product Name	Omega-3-Acid Ethyl Esters Capsules
Strength (s)	1 g
Applicant Name	Teva Pharmaceuticals USA
Applicant Address	425 Privet Road Horsham, PA 19044
US Agent Name and the mailing address	Scott D. Tomsky VP US Generics Regulatory Affairs
US Agent's Telephone Number	(215) 591-3142
US Agent's Fax Number	(215) 591-8812
Original Submission Date(s)	November 10, 2008 December 30, 2013 (Dissolution amendment- already reviewed)
Submission Date(s) of Amendment(s) Under Review	February 7, 2014 (ECD telephone request) March 20, 2014
First Generic	No
Reviewer	Ke Ren. Ph.D.
OVERALL DISSOLUTION REVIEW RESULT	**INADEQUATE (pending dissolution specifications acknowledgement)**

Study Site(s) Information

Study Number (s)	2008-1779	2008-1829
Study Type (s)	Fasting and Fed Studies (RLD only)	Fed Study (Test and RLD)
Strength(s)	1 g	1 g
Clinical Site	Pharma Medica Research Inc.	Allied Research International (Formerly Cetero Research)
Clinical Site Address	4770 Sheppard Avenue East Toronto, Ontario, Canada M1S 3V6	1405 NW 167th Street Miami Gardens, Florida 33169
OSI Inspection Status of Clinical Site	**N/A (see comment below)**	
Analytical Site	(b) (4)	
Analytical Address		
OSI Inspection Status of Analytical Site	**N/A (see comment below)**	

Reviewer's Comments: Since the firm opted to follow the in vitro option for evidence of bioequivalence, the inspections for the clinical and analytical sites of the in vivo studies are not relevant.

I. EXECUTIVE SUMMARY

This is a review of dissolution-only amendment dated March 20, 2014 (Supporting document #19).

Based on the most recent dissolution-only review [DARRTS ANDA 091028 Gong, Li 03/06/2014 N/A 03/06/2014 REV-BIOEQ-02(Dissolution Review) Archive], four deficiencies were identified and issued to the firm:

1. *The firm was asked to provide clarifications about two different analytical instrumental conditions used in the quantitative capsule rupture testing (QCRT) and in vitro bioequivalence (BE) testing.*

2. *The firm was asked to submit results of individual component of Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) release for its QCRT and in vitro BE testing, rather than providing sum of EPA+ DHA data.*

3. *The firm was asked to provide the Standard Operating Procedures (SOPs) for the QCR methods and in vitro BE studies.*

4. *The firm was asked to provide detailed description of the sinkers used in the dissolution testing*

The current amendment (dated March 20, 2014) contains the firm's responses to the deficiencies specified above. The Division of Bioequivalence I (DBI) finds the firm's responses acceptable.

The firm will be asked to acknowledge the following FDA-recommended QCRT method and specifications for its product:

Apparatus:	USP II (paddle) with sinkers
Speed of Rotation:	100 rpm
Medium:	Tier I: 8% Labrasol in 0.1 N HCl without enzyme Tier II: 8% Labrasol in 0.1 N HCl with pepsin (750, 000 units)
Volume:	900 mL
Temperature:	37°C ± 0.5°C
Specifications	NLT (b)(4)% (Q) in 90 minutes for EPA and DHA

The dissolution testing is **inadequate** pending the firm's acknowledgement of FDA-recommended QCRT method and specifications above.

II. TABLE CONTENTS

I. EXECUTIVE SUMMARY 2
II. TABLE CONTENTS 2
III. BACKGROUND INFORMATION ON THE DISSOLUTION TESTING 3
IV. DISSOLUTION AMENDMENT REVIEW 4
V. DEFICIENCY COMMENTS FOR DISSOLUTION TESTING 38
VI. DISSOLUTION RECOMMENDATIONS 38
VII. OUTCOME 40

III. BACKGROUND INFORMATION ON THE DISSOLUTION TESTING

- In the original submission (submitted on November 10, 2008), the firm conducted a comparative non-quantitative capsule rupture testing on its test product, Omega-3- Acid Ethyl Esters Capsules, 1.0 g, and the reference-listed drug (RLD), GlaxoSmithkline's Lovaza® (omega-3-acid ethyl esters) Capsules, 1.0 g. The data were generated per USP <2040> Rupture Test for Soft Gelatin Capsules [500 mL of water using Apparatus II (paddle) at 50 rpm, by visual determination of capsule ruptures]. The *in vitro* testing was found inadequate. The firm was asked to develop its own quantitative capsule rupture method[1].

- In the amendment (submitted on October 1, 2009), the firm had provided results of a then newly developed QCRT, which was found non-discriminatory QCRT profiles between the test and reference product, pending the firm's modification of the then-current QCRT method[2].

- On December 30, 2013, the firm submitted the amendment in response to the Office of Generic Drugs' (OGD's) "Complete Response Letter" of August 13, 2013, which included QCRT deficiencies. The firm addressed these deficiencies identified by the DBI. However, there were two different analytical instrumental conditions used in the QCRT and in vitro BE testing. In addition, the firm did not submit results of individual component of EPA and DHA release for the QCRT and in vitro BE testing. The firm was asked to provide clarification on the different analytical instrumental conditions and individual component dissolution data through its response to the DBI's Easily-Correctable-Deficiency (ECD) telephone request dated February 7, 2014[3]. The firm did not response the deficiency comments in the DBI's ECD request within 10 business days. Therefore, these aforementioned bio deficiencies and an additional deficiency regarding the sinkers used in the testing have been incorporated into the OGD's "Complete Response Letter" of March 11, 2014.

- In this current amendment, the firm submitted its responses for each of the deficiencies issued by the OGD (dated March 11, 2014)[4].

[1] DARRTS ANDA 091028 Ren, Ke 05/04/2009 N/A 05/04/2009 REV-BIOEQ-02 (Dissolution Review) Archive
[2] DARRTS, ANDA 091028, REV-BIOEQ-01(General Review) Original-1 Archive; Submit/Final Date:12/14/2
[3] DARRTS ANDA 091028 Yoon, Martin 02/07/2014 FAX 02/07/2014 COR-ECD-01(Easily Correctable Bioequivalence Deficiency) Archive
[4] DARRTS ANDA 091028 Gainese, Robert T 03/11/2014 FAX 03/1132014 COR-ANDAACTION-09 (Complete Response) Archive

IV. DISSOLUTION AMENDMENT REVIEW

The firm's responses to the four (4) deficiencies and the reviewer's evaluations of those responses are provided in this section of the review.

DBI Deficiency Comment #1

With respect to the Quantitative Capsule Rupture Testing (QCRT) and in vitro bioequivalence (BE) studies submitted on December 30, 2013, you have referenced two different analytical methods. Specifically, the analytical method used in your method validation (Project lD 0013: Code: 2000040) differs from that used in the QCRT [Report No. QDP0060815] and in the in vitro BE testing (POPV 0313 0791, POPV 0313 0852, POPV 0313 0853, POPV 0313 0892, POPV_0313_0891), as follows:

Analytical method used in your method validation (Project ID O013: Code: 2000040):

Column:

Detection:
Flow Rate:
Injection Volume:
Column Temperature:
Run Time:

(b) (4)

Analytical method used in your quantitative capsule rupture testing (QCRT) using USP Apparatus II (paddles) or USP apparatus IV [Report No. QDP0060815] and in the in vitro bioequivalence (BE) testing (POPV_0313_0791, POPV_0313_0852, POPV_0313_0853, POPV_0313_0892, POPV_0313_0891):

Column:

Detection:
Flow Rate:
Injection Volume:
Column Temperature:
Auto sampler Temperature:
Run Time (Apparatus II):
Run Time (Apparatus IV):

(b) (4)

Please clearly identify which instrument conditions were used during the QCRT testing [Report No.QDP0060815] and the in vitro BE testing. If the method used in these studies differs from that already validated, then please provide additional validation as necessary. Also, please provide your Standard Operating Procedure (SOP) for each of the above methods as well as for the method validation procedure.

Firm's Response:

Upon review of the documentation which was submitted in our December 30, 2013 Minor Amendment, **a typographical error** was identified in Appendix 2 of Report No. QDP0060815 (page 98) which incorrectly stated the run time as (b) (4). Please note the run time for the design of experiments (b) (4) (b) (4) Please find in Module 3.2.P.5.6 a copy of the updated report which reflects the corrected run times.

Teva has developed various quantitative capsule rupture test (QCRT) methods to support *in vitro* BE testing, all of which have been validated in accord with our standard operating procedures. At the time of our December 30, 2013 Minor Amendment, separate documents containing solely the analytical methods for the QCRT testing were not available. Instead, the methods were embedded within the method validation report (QDP0068549) and the Summary of *In Vitro* Evaluation Report (QDP0060815). Separate documents housing the analytical methods have since been created to support the QCRT. As noted in our December 30, 2013 Amendment, it is Teva's belief that the method which utilizes USP Apparatus II with the surfactant Labrasol remains the most appropriate for our drug product. However, the methods which utilize the surfactant (b) (4) are also provided herein for your review.

<u>Analytical Methods and Method Validation Report for method using Labrasol:</u>

- Module 3.2.P.5.2 Analytical Method (QDP0004603)
  USP Apparatus II with the surfactant Labrasol (without enzyme) – Tier I
  USP Apparatus II with the surfactant Labrasol (with enzyme) – Tier II

- Module 3.2.P.5.3 and Module 3.2.R.3.P
  Analytical Method Validation Report (QDP0068549)
  USP Apparatus II with the surfactant Labrasol (without enzyme) – Tier I
  USP Apparatus II with the surfactant Labrasol (with enzyme) – Tier II

<u>Analytical Methods and Method Validation Report for method using (b) (4) (App II)</u>

- Module 3.2.P.5.2 Analytical Method (QDP0074613)
  USP Apparatus II with the surfactant (b) (4)

- Module 3.2.P.5.3 and Module 3.2.R.3.P
  Analytical Method Validation Report (QDP0057280)
  USP Apparatus II with the surfactant (b) (4)

<u>Analytical Methods and Validation Report for method using (b) (4) (App IV)</u>

- Module 3.2.P.5.2 Analytical Method (QDP0074614)
  USP Apparatus IV with the surfactant (b) (4)

- Module 3.2.P.5.3 and Module 3.2.R.3.P
  Analytical Method Validation Report (QDP0057757)
  USP Apparatus IV with the surfactant (b) (4)

Additionally, please note that the validation reports for the methods using the surfactant [redacted] (b) (4) were inadvertently omitted from our December 30, 2013 Minor Amendment, and are provided herein, as noted above, for completeness of the file.

The following table summarizes the development work regarding the QCRT testing performed by Teva, and provides the parameters, instruments and conditions used for the method validation and comparative dissolution profile testing. To aid your review, this table also connects the DOE reports to their corresponding Method Validation Reports and Comparative Profile Testing reports:

Methodology		Validation Report No.	Design Of Experiments	Reason for the method development
Dissolution Parameters Method: QDP0004603		Report No. **QDP0068549** Comparative Dissolution Report No. **QDP0068622** – Tier I (without enzyme) Comparative Dissolution Report No. **QDP0068624** – Tier II (with enzyme) Submitted in 12/30/13 Minor Amendment	Report No. **QDP0069171** Submitted in 12/30/13 Re- submission/ After Action - Minor Amendment	This report was generated to evaluate the use of USP Apparatus II using varying levels of Labrasol in 0.1 N HCl with and without enzyme, in response to a request made by the Division of Bioequivalence in the 8/13/2013 complete response letter
Apparatus: USP Apparatus II				
Dissolution Medium - Tier I: 8% Labrasol in 0.1 N HCl without enzyme				
Dissolution Medium - Tier II: 8% Labrasol in 0.1 N HCl with enzyme (pepsin, 750,000 units)				
Rotation	100 rpm			
Sinker:	[redacted] (b) (4) Helix			
Volume:	900 mL			
Temperature:	37 ± 0.5ºC			
Distance from bottom:	2.5 cm			
Time Point (Single):	120 minutes			
Time Points (Profile):	10, 15, 30, 45, 60, 90, 120 minutes			
Chromatographic Parameters				
Detection:	[redacted] (b) (4)			
Flow Rate:				
Injection Volume:				
Column Temperature:				
Run Time: [redacted] (b) (4)				

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Reviewer's Comments: The firm's response to the Deficiency #1 is **adequate.**

- In the previous amendment (submission date December 30, 2013), the firm explored and evaluated three different QCRT methods: USP II using Labrasol as surfactant, USP IV using (b) (4) as surfactant, and USP II using (b) (4) as surfactant. The firm submitted the complete method optimization reports. However, the firm referenced two different analytical instrumental conditions used in the respective QCRT and in vitro BE studies. The firm was asked to provide clarifications.

- In the current amendment, the firm indicated that a typographical error was identified in the Appendix 2 Report No. QDP0060815 which incorrectly stated the run time as (b) (4)[5]. The run time for the design of experiments (b) (4). The firm submitted the updated report which reflects the corrected run time information in Module 3.2.P.5.6 (pages 502 and 507).

- The firm has developed three different QCRT methods. All three QCRT methods were validated for its system suitability, specificity, precision, accuracy, linearity and range, robustness, filter equivalence, API equivalence and standard and sample solution stability. The QCRT validation report for Method 1 has been reviewed in the previous dissolution-only review[6]. The QCRT validation reports for Method 2 and Method 3 will be reviewed in the full ANDA review.

  - Method 1 (firm proposed method):

Apparatus:	USP II (paddle)
Speed of Rotation:	100 rpm
Sinkers:	(b) (4) Helix
Medium:	Tier I: 8% Labrasol in 0.1 N HCl without enzyme Tier II: 8% Labrasol in 0.1 N HCl with pepsin (750, 000 units)
Volume:	900 mL
Temperature:	37°C ± 0.5°C
Specifications	NLT (b) (4) % (Q) in (b) (4) minutes for EPA, DHA and Total

  - Method 2

Apparatus:	USP IV, Flow-through Cell
Flow:	(b) (4)
System Mode	
Medium:	
Temperature:	37°C ± 0.5°C

[5] DARRTS ANDA 091028 submitted date: 12/30/2013 Module 3.2.P.4 Control of Drug Product, page 318.
[6] DARRTS ANDA 091028 Gong, Li 03/06/2014 N/A 03/06/2014 REV-BIOEQ-02 (Dissolution Review) Archive

Specification	The firm did not propose specification. Method not proposed for routine use.

- Method 3

Apparatus:	USP II (paddle)
Speed of Rotation:	(b) (4)
Sinkers:	(b) (4) Helix or equivalent which can hold the capsules freely
Medium:	(b) (4)
Temperature:	37°C ± 0.5°C
Specification	The firm did not propose specification. Method not proposed for routine use.

The firm believes that Method 1 remains the most appropriate for the test drug product. Please refer to deficiency #2 for the dissolution data comparisons. The firm submitted dissolution method and method validation report for each method in Module 3.2.P.5.6.

DBI Deficiency Comment #2

In your QCRT testing [Report No. QDP0060815] and in vitro BE testing submitted December 30, 2013, you submitted data reflecting the sum of Eicosapentaenoic Acid Ethyl Ester (EPA) + Docosahexaenoic Acid Ethyl Ester (DHA) release. Please submit the release data from the referenced studies for each individual component rather than for the sum of the two components. Please submit the data from 12 individual dosage units of the Test and Reference products from the referenced studies. In addition, please submit all mean data, range, %CV, and the dates of these studies in eCTD format (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120957.pdf). Finally, please submit the temperature and humidity at which the test and reference product lots were stored between manufacture of the test product (or acquisition of the reference product) and the time of the aforementioned studies.

Firm's Response:

As requested, all reports contained within the December 30, 2013 amendment have been updated to report the results for each individual component (EPA= 465 mg and DHA= 375 mg). In addition, the data for the combined release of EPA and DHA have been re-calculated against a theoretical total of omega-3 content of 840 mg (465 mg EPA + 375 mg DHA) instead of 1000 mg.

The following reports are provided in support of our response:

Module 3.2.P.5.3 and Module 3.2.R.3.P Analytical Method Validation Report for Dissolution Test (Apparatus II) for Omega-3-Acid Ethyl Ester Capsules, 1 gram (QDP0068549) details the validation of USP Apparatus II using 8% Labrasol in 0.1 N HCl without enzyme (Tier I) and with enzyme (pepsin) (Tier II).

Module 3.2.P.5.3 and Module 3.2.R.3.P Analytical Method Validation Report for Dissolution Test (Apparatus II) for Omega-3-Acid Ethyl Ester Capsules, 1 gram (QDP0057280) details the validation of USP Apparatus II using (b) (4) as surfactant (b) (4)

Module 3.2.P.5.3 and Module 3.2.R.3.P Analytical Method Validation Report for Dissolution Test (Apparatus IV) for Omega-3-Acid Ethyl Ester Capsules, 1 gram (QDP0057757) details the validation of USP Apparatus IV using (b) (4) as surfactant (b) (4)

Module 3.2.P.5.6 Special Study Dissolution Profile Report for Omega-3 Ethyl Esters Capsules 1 g (QDP0069171) details the use of USP Apparatus II with different levels of Labrasol in 0.1 N HCl at various speeds without enzyme (Tier I) and with enzyme (pepsin) (Tier II). This study led to our conclusion that the method using USP Apparatus II with Labrasol is the most appropriate for our drug product.

Module 3.2.P.5.6 Omega-3-Acid Ethyl Ester Capsules, 1 gram Comparative Dissolution Profile (Tier II Dissolution Medium) (QDP0068624) details the comparative dissolution profile of the test product and RLD in Tier II dissolution conditions using USP Apparatus II with surfactant Labrasol, with enzyme (pepsin).

Module 3.2.P.5.6 Summary of *In Vitro* Evaluation of Teva's Omega-3-Acid Ethyl Esters Capsules and RLD, LOVAZA® Capsules for Establishing Bioequivalence (QDP0060815) details the use of USP Apparatus II and USP Apparatus IV using (b) (4) (b) (4) as surfactant with and without enzyme (pancreatin).

The mean data, range, %CV, and dates of the studies have been added to the updated reports. As requested, the data have been summarized in eCTD format and are included in Module 2.7 in both Word and PDF formats. Please note report QDP0069171 indicates that the results of experiments 1, 2, and 5 showed either no or very low release for Total EPA and DHA, which indicate that the method is not suitable for its intended use. As such, no recalculations were performed and no tables were drafted for these three experiments.

As indicated in our December 30, 2013 Amendment, we believe we have developed a discriminating method for evaluating Teva's product against the RLD, and that this method demonstrates that the test product is bioequivalent to the RLD. It is our recommendation that the USP Apparatus II method with Labrasol (Tier I and Tier II methods), as discussed in Module 3.2.P.5.2 (QDP0004603), be deemed appropriate for

the Quantitative Capsule Rupture test. Please refer to the following updated documentation in support of the QCRT for routine drug product release and stability testing:

Module 3.2.P.5.1	Drug Product Release Specifications
Module 3.2.P.5.2	Drug Product Analytical Procedure
Module 3.2.P.5.6	Drug Product Justification of Specification
Module 3.2.P.8.2	Finished Product Stability Protocol
Module 3.2.P.8.2	Drug Product Stability Specifications

We propose the following dissolution conditions and Q value in the QCRT method for both release and stability:

Dissolution:

Media: Tier I: 8% Labrasol in 0.1 N HCl
Tier II: 8% Labrasol in 0.1 N HCl with Enzyme (pepsin 750,000 units)

Apparatus: USP Apparatus II

Rotation Speed: 100 rpm

Sinker: (b) (4) Helix Coil Type or equivalent

Volume: 900 mL

Temperature: 37 ± 0.5°C

Specification: EPA: NLT (b) (4)% (Q) released in (b) (4) minutes
DHA: NLT (b) (4)% (Q) released in (b) (4) minutes
Total: NLT (b) (4)% (Q) released in (b) (4) minutes

Regarding drug product storage conditions, please note that Teva's bulk capsules were stored in Teva's Sellersville warehouse and the RLD capsules were stored in Teva's Pomona facility. The temperature and humidity at which the test and reference products were stored between manufacture of the test procedure (or acquisition of the reference product) and testing in the studies discussed above are as follows:

Sellersville, PA
Temperature: 20°C -25°C, maximum operating range of 17°C - 28°C Relative Humidity: < 60%

Pomona, NY
Temperature: 15°C – 30°C; Relative Humidity: 10 % – 60 %

Reviewer's Comments: The firm's response to the Deficiency #2 is **adequate.**

- In the previous amendment (submission date December 30, 2013), all dissolution data were expressed as the combined release of EPA (g) and DHA (g) divided by 1 g of Omega-3-Acid Ethyl Esters Capsules. The firm was asked to provide the release data for each component rather than for the sum of the two components.

- In the current amendment, the firm submitted the release data for each component using three different QCRT methods. The firm re-calculated the release data based on

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each individual component with its respective amounts (EPA= 465 mg and DHA 375 mg).

APPEARS THIS WAY ON ORIGINAL

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Firm Proposed QCRT method—Tier I

Dissolution Conditions	**Apparatus:**	USP Apparatus 2
	Speed of Rotation:	100 rpm
	Medium:	8% Labrasol in 0.1N HCl (Tier I Dissolution Medium)
	Volume:	900 mL with sinkers ((b) (4) Helix Coil Type)
	Temperature:	37±0.5°C
Firm's Proposed Specifications	NLT (b) (4)% (Q) released in (b) (4) minutes for EPA, DHA, and Total	
Dissolution Testing & Method Validation Site (Name, Address)	Barr Laboratories, 223 Quaker Road, Pomona, NY 10970-0519	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 10	15	30	45	60	90	120
Study Report #: QDP0068622	10/17/13 10/21/13	**Omega-3-Acid Ethyl Ester Capsules USP, 1 gram** Batch # 150000584 Mfg Date: April 2, 2013	1000 mg Capsule	12	**EPA**							
					Mean	5	13	43	74	93	100	100
					Range	(b) (4)						
					%CV	41.3	23.7	37.5	27.5	11.1	2.3	2.5
	10/17/13	**Lovaza** Lot 3ZP1602 Expiration Date: 4/2017	1000 mg Capsule	12	Mean	33	52	80	96	99	99	99
					Range	(b) (4)						
					%CV	51.7	44.6	19.8	5.3	0.0	0.0	0.8
	10/17/13 10/21/13	**Omega-3-Acid Ethyl Ester Capsules USP, 1 gram** Batch # 150000584 Mfg Date: April 2, 2013	1000 mg Capsule	12	**DHA**							
					Mean	5	12	41	74	93	99	100
					Range	(b) (4)						
					%CV	31.5	25.4	41.4	30.5	10.6	1.8	1.6
	10/17/13	**Lovaza** Lot 3ZP1602 Expiration Date: 4/2017	1000 mg Capsule	12	Mean	30	49	75	91	93	93	93
					Range	(b) (4)						
					%CV	54.4	46.5	21.1	5.7	0.0	0.0	0.0
	10/17/13 10/21/13	**Omega-3-Acid Ethyl Ester Capsules USP, 1 gram** Batch # 150000584 Mfg Date: April 2, 2013	1000 mg Capsule	12	**EPA+DHA**							
					Mean	5	13	42	74	93	100	100
					Range	(b) (4)						
					%CV	37.3	28.0	38.4	28.3	11.0	1.2	1.7
	10/17/13	**Lovaza** Lot 3ZP1602 Expiration Date: 4/2017	1000 mg Capsule	12	Mean	31	50	78	93	96	96	96
					Range	(b) (4)						
					%CV	53.0	45.7	20.3	5.6	0.0	0.0	0.4

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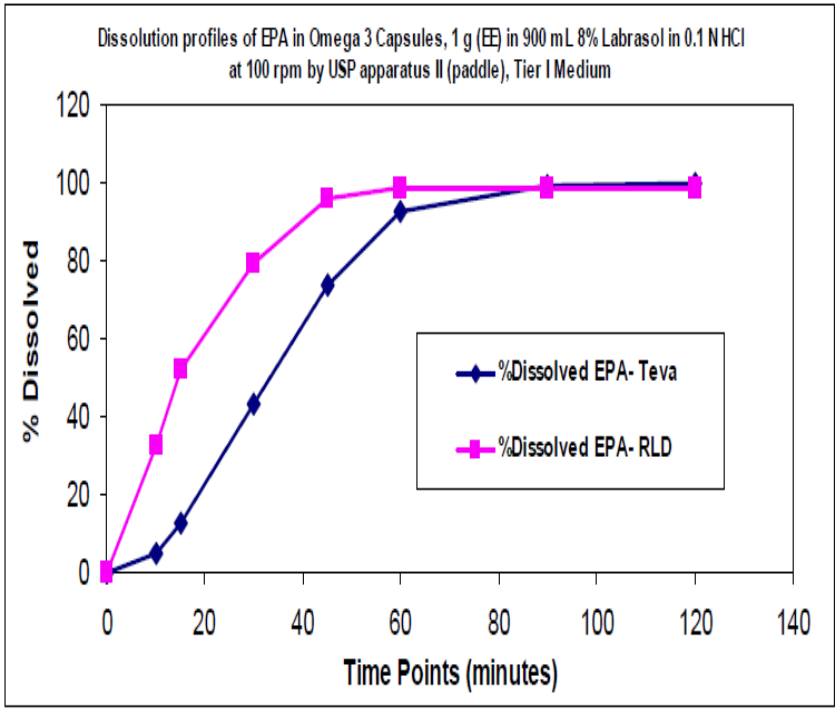
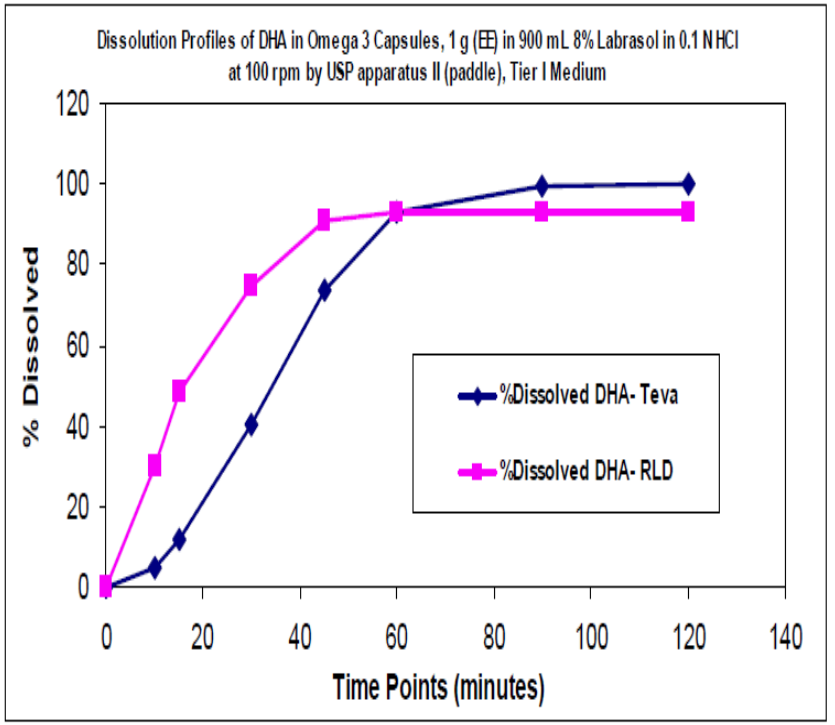
Dissolution Profiles:

Tier I- EPA Component



Tier I- DHA Component



Firm Proposed QCRT method—Tier II

Dissolution Conditions	**Apparatus:**	USP Apparatus 2
	Speed of Rotation:	100 rpm
	Medium:	8% Labrasol in 0.1N HCl with Pepsin (Tier II Dissolution Medium)
	Volume:	900 mL with sinkers ((b) (4) Helix Coil Type)
	Temperature:	37±0.5°C
Firm's Proposed Specifications	NLT (b) (4) % (Q) released in (b) (4) minutes for EPA, DHA, and Total	
Dissolution Testing & Method Validation Site (Name, Address)	Barr Laboratories, 223 Quaker Road, Pomona, NY 10970-0519	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 10	15	30	45	60	90	120
Study Report #: QDP0068624	10/18/13 10/21/13 10/23/13	**Omega-3-Acid Ethyl Ester Capsules USP, 1 gram** Batch # 150000584 Mfg Date: April 2, 2013	1000 mg Capsule	12	**EPA**							
					Mean	12	26	64	87	96	98	99
					Range	(b) (4)						
					%CV	71.6	53.4	38.7	16.5	7.3	2.0	2.0
	10/17/13	**Lovaza** Lot 3ZP1602 Expiration Date: 4/2017	1000 mg Capsule	12	Mean	23	37	55	93	98	101	101
					Range	(b) (4)						
					%CV	28.8	22.5	37.1	13.1	4.7	2.0	1.8
	10/17/13 10/21/13	**Omega-3-Acid Ethyl Ester Capsules USP, 1 gram** Batch # 150000584 Mfg Date: April 2, 2013	1000 mg Capsule	12	**DHA**							
					Mean	12	25	65	88	96	99	99
					Range	(b) (4)						
					%CV	72.2	53.3	40.9	18.1	8.9	1.8	2.2
	10/17/13	**Lovaza** Lot 3ZP1602 Expiration Date: 4/2017	1000 mg Capsule	12	Mean	21	35	51	90	95	97	97
					Range	(b) (4)						
					%CV	29.9	22.6	37.5	13.4	6.5	3.3	3.5
	10/17/13 10/21/13	**Omega-3-Acid Ethyl Ester Capsules USP, 1 gram** Batch # 150000584 Mfg Date: April 2, 2013	1000 mg Capsule	12	**EPA+DHA**							
					Mean	12	26	65	88	96	99	98
					Range	(b) (4)						
					%CV	69.2	53.5	40.0	17.3	7.7	2.1	2.2
	10/17/13	**Lovaza** Lot 3ZP1602 Expiration Date: 4/2017	1000 mg Capsule	12	Mean	22	36	53	91	97	99	99
					Range	(b) (4)						
					%CV	29.1	22.9	37.4	13.0	5.3	0.6	0.8

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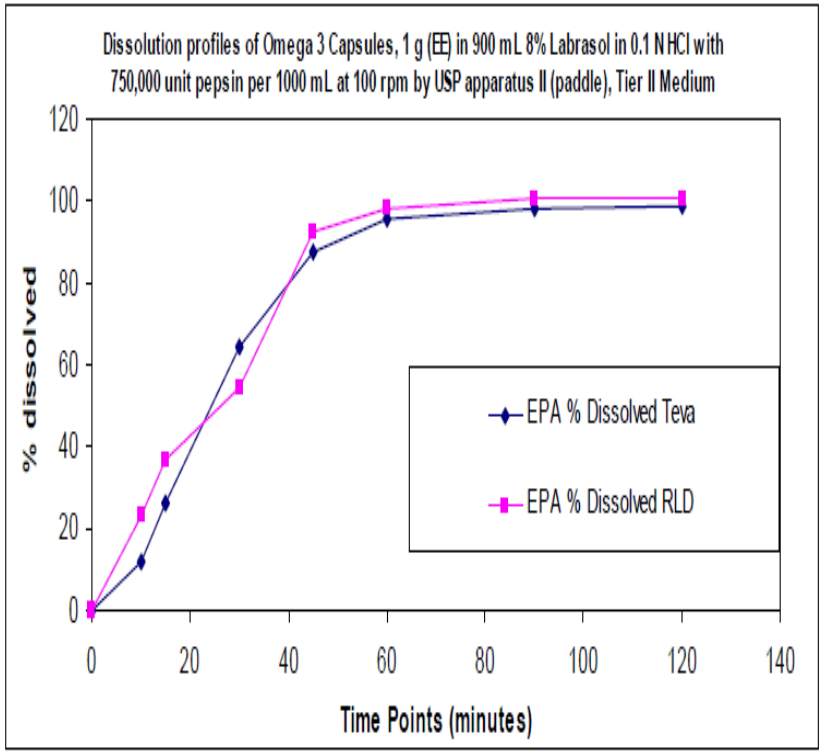
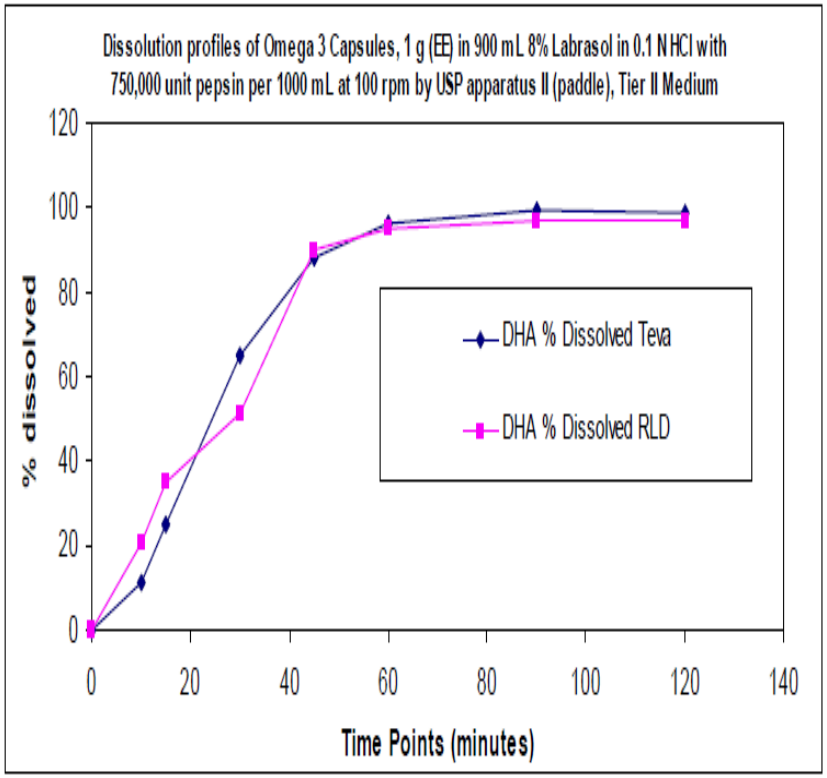
Dissolution Profiles:

Tier II- EPA Component



Tier II- DHA Component



Dissolution Method using [redacted] and Apparatus II

Dissolution Conditions	**Apparatus:**	USP Apparatus 2
	Speed of Rotation:	[redacted]
	Medium:	[redacted]
	Volume:	900 mL with sinkers ([redacted] Helix Coil Type)
	Temperature:	37±0.5°C
Firm's Proposed Specifications		N/A (method not proposed for routine use)
Dissolution Testing & Method Validation Site (Name, Address)		Barr Laboratories, 223 Quaker Road, Pomona, NY 10970-0519

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)						
						15	30	45	60	90	120	135
Study Report #: QDP0060815	03/21/13	**Omega-3-Acid Ethyl Ester Capsules USP, 1 gram** Batch # 30200001A Mfg Date: March 6, 2012	1000 mg Capsule	12	**EPA**							
					Mean	65	81	87	91	94	94	94
					Range	[redacted]						
					%CV	8.0	4.5	4.5	4.2	3.2	3.5	3.0
	03/18/13	**Lovaza** Lot 2ZP1263 Expiration Date: 10/2015	1000 mg Capsule	12	Mean	74	89	95	98	100	101	101
					Range	[redacted]						
					%CV	8.4	5.0	4.0	2.8	1.3	1.3	1.3
	03/21/13	**Omega-3-Acid Ethyl Ester Capsules USP, 1 gram** Batch # 30200001A Mfg Date: March 6, 2012	1000 mg Capsule	12	**DHA**							
					Mean	64	81	87	90	93	94	95
					Range	[redacted]						
					%CV	7.7	5.0	4.5	4.3	3.7	3.4	3.6
	03/18/13	**Lovaza** Lot 2ZP1263 Expiration Date: 10/2015	1000 mg Capsule	12	Mean	69	82	88	91	93	94	94
					Range	[redacted]						
					%CV	8.6	5.7	3.6	2.1	1.5	1.6	1.6
	03/21/13	**Omega-3-Acid Ethyl Ester Capsules USP, 1 gram** Batch # 30200001A Mfg Date: March 6, 2012	1000 mg Capsule	12	**EPA+DHA**							
					Mean	64	81	87	91	93	94	95
					Range	[redacted]						
					%CV	7.8	4.5	4.4	4.0	3.2	3.3	3.1
	03/18/13	**Lovaza** Lot 2ZP1263 Expiration Date: 10/2015	1000 mg Capsule	12	Mean	72	86	92	95	97	98	98
					Range	[redacted]						
					%CV	8.5	5.1	3.5	2.3	1.5	1.3	1.3

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Dissolution Method using [redacted] and Apparatus IV

Dissolution Conditions	**Apparatus:**	USP Apparatus 4
	Flow Rate	[redacted]
	Run Time	
	Medium:	
	Glass Bead Load	
	Temperature:	37±0.5 C
Firm's Proposed Specifications		N/A (method not proposed for routine use)
Dissolution Testing & Method Validation Site (Name, Address)		Barr Laboratories, 223 Quaker Road, Pomona, NY 10970-0519

Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Mfg. Date) (Reference – Exp. Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 10	20	30	40	50	60	90	120
Study Report #: QDP0060815	03/1913 03/21/13	**Omega-3-Acid Ethyl Ester Capsules USP, 1 gm** Batch # 30200001A Mfg. Date:03/06/12	1000 mg Capsule	12		**EPA**							
					Mean	14	62	83	88	90	92	94	94
					Range	[redacted]							
					%CV	66.5	33.8	22.3	15.9	11.7	9.3	6.7	7.0
	03/1913 03/21/13	**Lovaza** Lot 2ZP1263 Expiration Date: 10/2015	1000 mg Capsule	12	Mean	31	72	84	88	91	95	99	99
					Range	[redacted]							
					%CV	62.9	42.6	31.7	24.9	18.7	10.9	3.3	2.7
	03/1913 03/21/13	**Omega-3-Acid Ethyl Ester Capsules USP, 1 gm** Batch # 30200001A Mfg. Date:03/06/12	1000 mg Capsule	12		**DHA**							
					Mean	14	64	85	90	93	94	97	97
					Range	[redacted]							
					%CV	68.0	33.9	22.3	15.7	11.1	8.4	5.3	5.9
	03/1913 03/21/13	**Lovaza** Lot 2ZP1263 Expiration Date: 10/2015	1000 mg Capsule	12	Mean	29	68	80	84	86	90	93	94
					Range	[redacted]							
					%CV	63.6	42.8	32.1	25.1	19.5	11.1	3.0	2.7
	03/1913 03/21/13	**Omega-3-Acid Ethyl Ester Capsules USP, 1 gm** Batch # 30200001A Mfg. Date:03/06/12	1000 mg Capsule	12		**EPA+DHA**							
					Mean	14	63	83	89	91	93	95	96
					Range	[redacted]							
					%CV	68.0	34.1	22.1	15.7	11.4	8.7	5.9	6.3
	03/1913 03/21/13	**Lovaza** Lot 2ZP1263 Expiration Date: 10/2015	1000 mg Capsule	12	Mean	30	70	82	86	88	93	96	93
					Range	[redacted]							
					%CV	63.2	42.6	31.8	25.0	18.9	10.8	2.6	2.0

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- The DBI has recommended the following QCRT methods for two other ANDAs with the same drug product:

  - ANDA 091018 (Par Pharmaceuticals Inc.): The firm acknowledged the DBI recommended method and specification on March 14, 2014[7].

Medium	4.0% Triton X-100 in 0.01 N HCl with pepsin (120k/L)
Volume	900 mL
Temperature	37°C ± 0.5°C
USP Apparatus	I (basket, mesh size 40)
Rotational Speed	100 rpm
Specification	NLT (b)(4)% (Q) of labeled amount of each EPA and DHA in the dosage form is dissolved in 300 minutes (5 hours)

  - ANDA 090973 (Apotex): The firm has not yet acknowledged the DBI recommended method and specification as of March 27, 2014[8].

Apparatus:	USP II (paddle) with sinkers
Speed of Rotation:	50 rpm
Medium:	4% Triton X-100 in 0.05 M Sodium Phosphate Buffer at pH 6.8
Volume:	900 mL
Temperature:	37°C ± 0.5°C
Specifications	NLT (b)(4)% (Q) in 90 minutes for EPA and DHA

- The table below included three QCRT method validation effective dates and dissolution conducted dates:

Method	Validation Dates	Dissolution Conducted Dates
Method 1	December 18, 2013	October 17- 23, 2013
Method 2	April 26, 2013	March 19- 21, 2013
Method 3	April 26, 2013	March 18- 21, 2013

The QCR testing dates were prior to the approved dates for dissolution method validation. Since there are only 1- 2 months apart, the reviewer deems that the firm used the validated conditions in the comparative testing. In future submissions, the firm should be informed that the dissolution validation should be completed prior to comparative QCR testing.

[7] DARRTS ANDA 091018 Jain, Priti R 03/25/2014 N/A 03/25/2014 REV-BIOEQ-02 (Dissolution Review) Archive
[8] DARRTS ANDA 090973 Gong, Li 03/20/2014 N/A 03/20/2014 REV-BIOEQ-02 (Dissolution Review) Archive

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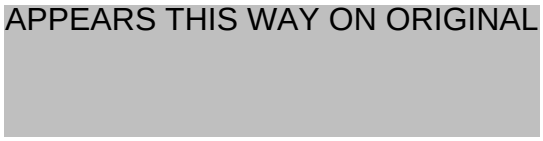
- The data comparisons of the firm's three different QCRT methods are shown in the following table:



Testing Date	Method*	Lot #	10 mins	15 mins	20 mins	30 mins	40 mins	45 mins	50 mins	60 mins	90 mins	120 mins	135 mins
EPA: mean% (%CV)													
10/17-21/2013	Method 1 (Tier I)	T: Bulk # 150000401; package lot #150000584	5 (41.3)	13 (23.7)	--	43 (37.5)	--	74 (27.5)	--	93 (11.1)	100 (2.3)	100 (2.5)	--
10/17/2013		R: 3ZP1602	33 (51.7)	52 (44.6)	--	80 (19.8)	--	96 (5.3)	--	99 (0)	99 (0)	99 (0.8)	--
10/18-23/2013	Method 1 (Tier II)	T: Bulk # 150000401; package lot #150000584	12 (71.6)	26 (53.4)		64 (38.7)		87 (16.5)		96 (7.3)	98 (2.0)	99 (2.0)	--
10/17/2013		R: 3ZP1602	23 (28.8)	37 (22.5)		55 (37.1)		93 (13.1)		98 (4.7)	101 (2.0)	101 (1.8)	--
03/19-21/2013	Method 2	T: Bulk # 150000401; package lot 30200001A	14 (66.5)	--	62 (33.8)	83 (22.3)	88 (15.9)	--	90 (11.7)	92 (9.3)	94 (6.7)	94 (7.0)	--
03/19-21/2013		R: 2ZP1263	31 (62.9)	--	72 (42.6)	84 (31.7)	88 (24.9)	--	91 (18.7)	95 (10.9)	99 (3.3)	99 (2.7)	--
03/21/2013	Method 3	T: Bulk # 150000401; package lot 30200001A	--	65 (8.0)	--	81 (4.5)	--	87 (4.5)	--	91 (4.2)	94 (3.2)	94 (3.5)	94 (3.0)
03/18/2013		R: 2ZP1263	--	74 (8.4)	--	89 (5.0)	--	95 (4.0)	--	98 (2.8)	100 (1.3)	101 (1.3)	101 (1.3)

* Method 1: 900 mL of 8%Labrasol in 0.1 N HCl without enzyme (Tier I) or 8%Labrasol in 0.1 N HCl with pepsin (750,000 units, Tier II) using USP Apparatus II (paddle) with sinkers at 100 rpm;
Method 2: [redacted] (b) (4) using USP Apparatus IV (flow-through cell) [redacted] (b) (4)
Method 3: 900 mL of [redacted] (b) (4) using USP Apparatus II (paddle) at [redacted] (b) (4)

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Notes: Per bio review [DARRTS ANDA 091028 Gong, Li 03/10/2014 N/A 03/10/2014 REV-BIOEQ-21 (Primary Review) Archive], the firm's test API data from its newly manufactured commercial batch (bulk lot #150000401) met the quantitative ranges recommended by the current Guidance. Package lots #30200001A and 150000584 are from the same bulk lot (#150000401)[9].

Testing Date	Method*	Lot #	10 mins	15 mins	20 mins	30 mins	40 mins	45 mins	50 mins	60 mins	90 mins	120 mins	135 mins
DHA: mean% (%CV)													
10/17-21/2013	Method 1 (Tier I)	T: Bulk # 150000401; package lot #150000584	5 (31.5)	12 (25.4)	--	41 (41.4)	--	74 (30.5)	--	93 (10.6)	99 (1.8)	100 (1.6)	--
10/17/2013		R: 3ZP1602	30 (54.4)	49 (46.5)	--	75 (21.1)	--	91 (5.7)	--	93 (0)	93 (0)	93 (0)	--
10/17-21/2013	Method 1 (Tier II)	T: Bulk # 150000401; package lot #150000584	12 (72.2)	25 (53.3)	--	65 (40.9)	--	88 (18.1)	--	96 (8.9)	99 (1.8)	99 (2.2)	--
10/17/2013		R: 3ZP1602	21 (29.9)	35 (22.6)	--	51 (37.5)	--	90 (13.4)	--	95 (6.5)	97 (3.3)	97 (3.50	--
03/19-21/2013	Method 2	T: Bulk # 150000401; package lot 30200001A	14 (68)	--	64 (33.9)	85 (22.3)	90 (15.7)	--	93 (11.1)	94 (8.4)	97 (5.3)	97 (5.9)	--
03/19-21/2013		R: 2ZP1263	29 (63.6)	--	68 (42.8)	80 (32.1)	84 (25.1)	--	86 (19.5)	90 (11.1)	93 (3.0)	94 (2.7)	--
03/21/2013	Method 3	T: Bulk # 150000401; package lot 30200001A	--	64 (7.7)	--	81 (5.0)	--	87 (4.5)	--	90 (4.3)	93 (3.7)	94 (3.4)	95 (3.6)
03/18/2013		R: 2ZP1263	--	69 (8.6)	--	82 (5.7)	--	88 (3.6)	--	91 (2.1)	93 (1.5)	94 (1.6)	94 (1.6)

[9] DARRTS ANDA 091028 Gong, Li 03/10/2014 N/A 03/10/2014 REV-BIOEQ-21 (Primary Review) Archive, page 39 and DARRTS ANDA 091028 Gong, Li 03/06/2014 N/A 03/06/2014 REV-BIOEQ-02 (Dissolution Review) Archive, page 27- 30.

* Method 1: 900 mL of 8%Labrasol in 0.1 N HCl without enzyme (Tier I) or 8%Labrasol in 0.1 N HCl with pepsin (750,000 units, Tier II) using USP Apparatus II (paddle) with sinkers at 100 rpm;
Method 2: [redacted] using USP Apparatus IV (flow-through cell) [redacted]
Method 3: 900 mL of [redacted] using USP Apparatus II (paddle) at [redacted]

Method 1 and Method 2 appear to be more discriminating than Method 3 for both EPA and DHA components.

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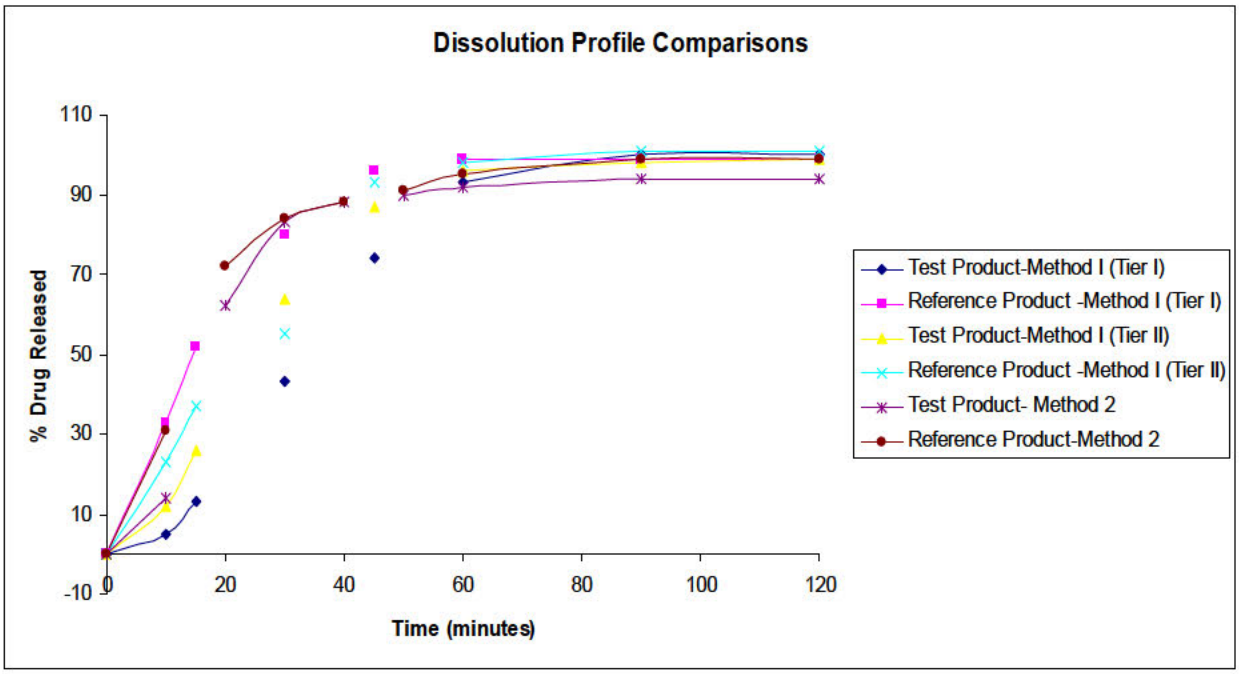
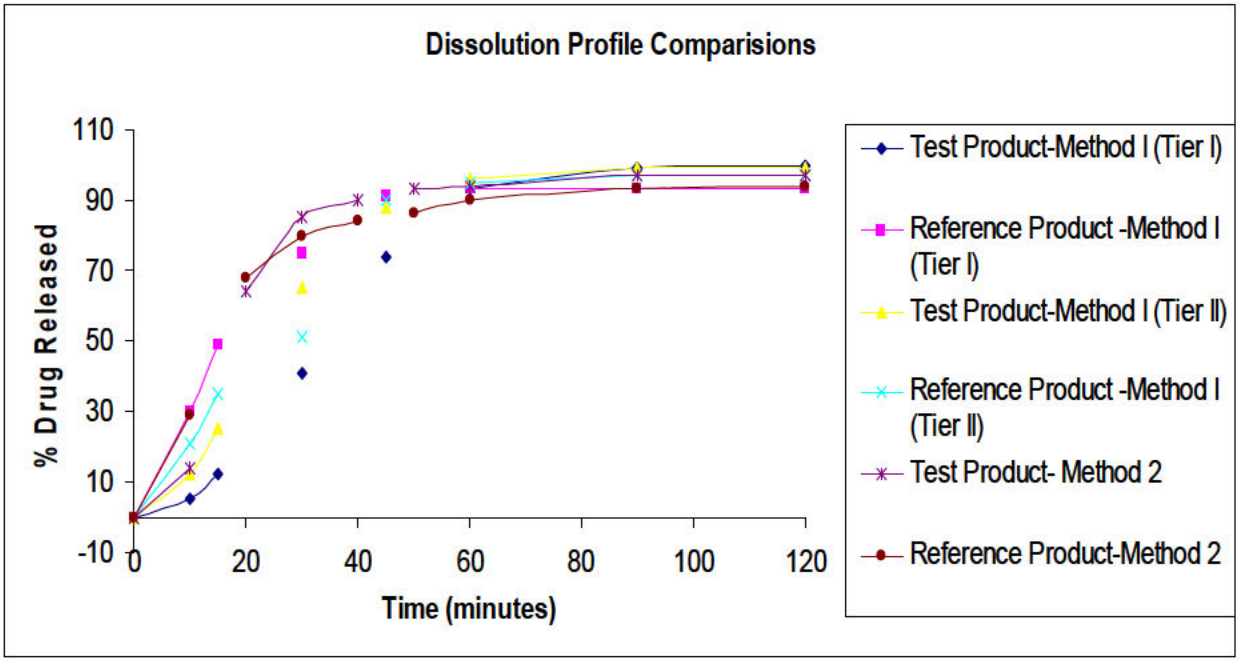
- The QCRT data using Method 1 and Method 2 for the test and reference products are shown in the graphs below:

EPA Component



DHA Component



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- The drug release data with Method 1 (using paddle with sinkers) and Method 2 (using flow-through cell) are comparable for both EPA and DHA components. The variability of the drug release data using both methods is acceptable. Due to the greater complexity of conducting the flow-through cell QCRT testing, the Method 1 (using paddle with sinkers) will be recommended to the firm as regulatory method for release and stability testing of the test product. The firm also proposed Method 1 for both release and stability testing.

- QCRT data at the specification time point of the test product from current application and other two ANDAs are shown in the table below:

ANDA#	Specification Time point
Current Application	Firm proposed specifications: (b)(4)% (Q) at (b)(4) minutes for both components Tier I: EPA: 93 (range: (b)(4)); %CV: 11.1 DHA: 93 (range: (b)(4)); %CV: 10.6 Tier II: EPA: 96 (range: (b)(4)); %CV: 7.3 DHA: 96 (range: (b)(4)); %CV: 8.9
ANDA 090973	DBI recommended specifications: (b)(4)% (Q) at 90 minutes for both components EPA: 85 (range: (b)(4)); %CV: 4.4 DHA: 87 (range: (b)(4)); %CV: 4.6
ANDA 091018	DBI recommended specifications: (b)(4)% (Q) at 300 minutes for both components EPA: 97 (range: (b)(4)); %CV: 3.0 DHA: 98 (range: (b)(4)); %CV: 4.0

- The firm has proposed specifications of NLT (b)(4)% (Q) in (b)(4) minutes for both EPA and DHA components. However, based on the submitted data, unit #8 of the test product failing to meet firm's proposed specifications (i.e., all units should not less than (b)(4)). The dissolution data for unit #8 of the test product are consistently low for both components (EPA and DHA) in Tier I and Tier II testing. At (b)(4) minutes, (b)(4)% of EPA and (b)(4)% of DHA were released for unit #8 of the test product in Tier I testing, respectively. At (b)(4) minutes, (b)(4)% of EPA and (b)(4)% of DHA were released in Tier II testing, respectively (please see the tables below for the individual dissolution data for the test product using Method 1). Therefore, the firm's proposed specifications are not acceptable. Based on the data submitted for Method 1, the DBI recommends appropriate specifications of NLT (b)(4)% (Q) in 90 minutes for both components.

Individual Dissolution Data for the Test Product—Tier I:

EPA Component- Tier I:

Omega-3-acid Ethyl Ester Capsules, 1 gram Manufactured by Banner Pharmacap on behalf of **TEVA Pharmaceuticals, Batch Number 150000584,** Manufacture date: 04/02/2013							
Capsule #	**% Dissolved**						
	10 minutes	**15 minutes**	**30 minutes**	**45 minutes**	**60 minutes**	**90 minutes**	**120 minutes**
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	5	13	43	74	93	100	100
Min	(b) (4)						
Max							
% RSD	41.3	23.7	37.5	27.5	11.1	2.3	2.5
Test Dates	**10/17/2013 and 10/21/2013**						

DHA Component—Tier I:

Omega-3-acid Ethyl Ester Capsules, 1 gram Manufactured by Banner Pharmacap on behalf of **TEVA Pharmaceuticals, Batch Number: 150000584,** Manufacture date: 04/02/2013							
Capsule #	**% Dissolved**						
	10 minutes	**15 minutes**	**30 minutes**	**45 minutes**	**60 minutes**	**90 minutes**	**120 minutes**
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	5	12	41	74	93	99	100
Min	(b) (4)						
Max							
% RSD	31.5	25.4	41.4	30.5	10.6	1.8	1.6
Test Dates	**10/17/2013 and 10/21/2013**						

Reference ID: 3482459

Individual Dissolution Data for the Test Product—Tier II:

EPA Component- Tier II:

Omega-3-acid Ethyl Ester Capsules, 1 gram Manufactured by Banner Pharmacap on behalf of TEVA Pharmaceuticals, Batch Number 150000584, Manufacture date: 04/02/2013							
Capsule #	% Dissolved						
	10 minutes	15 minutes	30 minutes	45 minutes	60 minutes	90 minutes	120 minutes
1							(b) (4)
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	12	26	64	87	96	98	99
Min							(b) (4)
Max							
% RSD	71.6	53.4	38.7	16.5	7.3	2.0	2.0
Test Dates	10/18/2013, 10/21/2013 and 10/23/2013						

DHA Component—Tier II:

Omega-3-acid Ethyl Ester Capsules, 1 gram Manufactured by Banner Pharmacap on behalf of TEVA Pharmaceuticals, Batch Number: 150000584, Manufacture date: 04/02/2013							
Capsule #	% Dissolved						
	10 minutes	15 minutes	30 minutes	45 minutes	60 minutes	90 minutes	120 minutes
1							(b) (4)
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	12	25	65	88	96	99	99
Min							(b) (4)
Max							
% RSD	72.2	53.3	40.9	18.1	8.9	1.8	2.2
Test Dates	10/18/2013, 10/21/2013 and 10/23/2013						

Reference ID: 3482459

- The firm submitted the complete method optimization reports in the previous amendment (submission date December 30, 2013). However, all results were given as combined EPA and DHA measurements. In the current amendment, the firm has submitted addendum of complete method optimization reports, which include the separate EPA and DHA measurements (located at Module 3) and dissolution summary table (located at Module 2).

  - First, per firm's method optimization report, the firm explored QCRT method using USP Apparatus II (paddle) under 12 conductions: different concentrations of Labrasol and different paddle speeds.

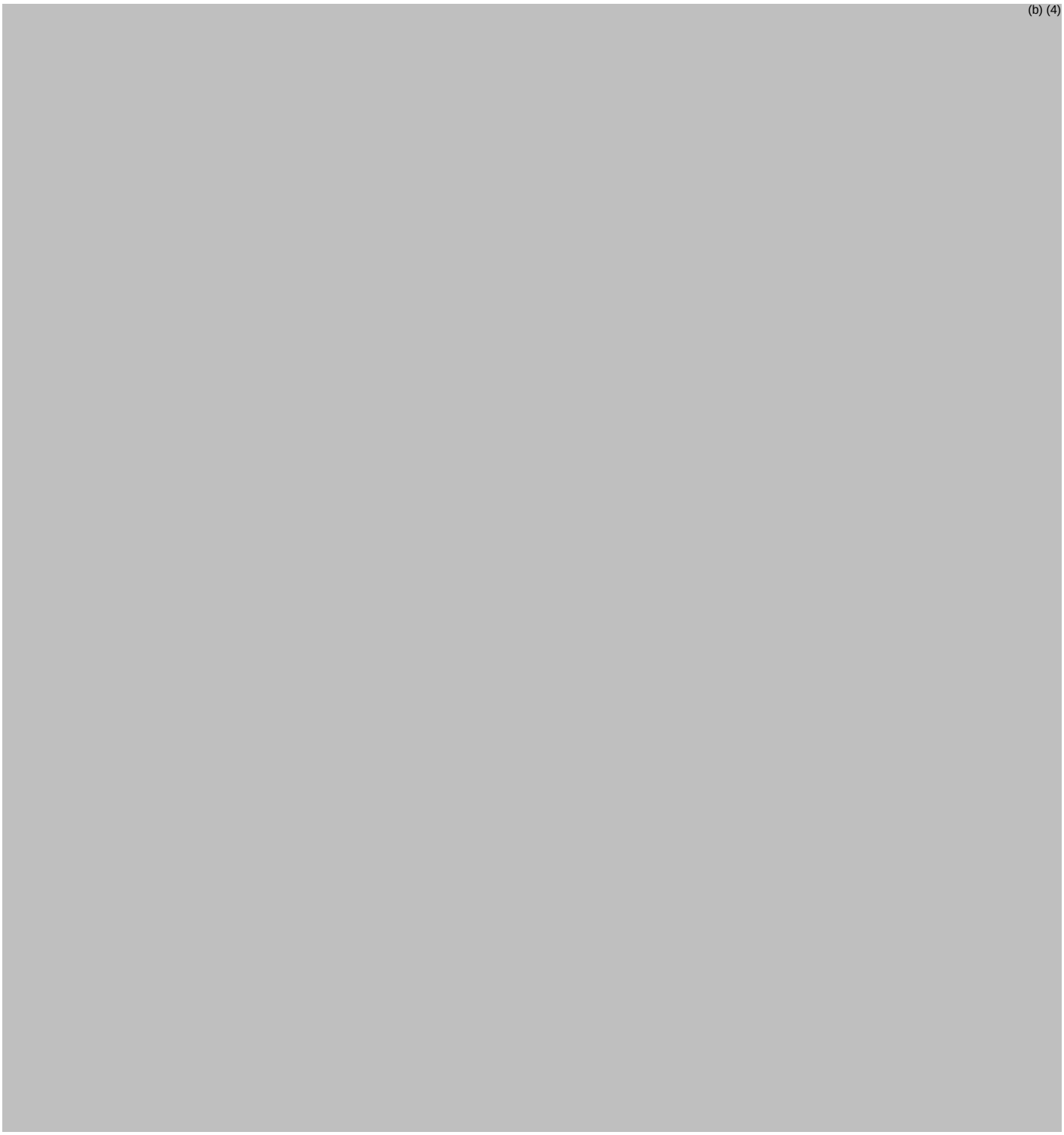
Study #	Paddle Speed (RPM)	Surfactant Level (%)
1	(b) (4)	
2		
3		
4		
5		
6		
7		
8		
9		
10		
11	100	8% Labrasol in 0.1 N HCl with Pepsin (750,000 units/L)
12	100	8% Labrasol in 0.1 N HCl with Pepsin (750,000 units/L), using 17-month-old Test lot (Lot #30200001A)

  - Secondary, the firm explored QCRT method using USP Apparatus II (paddle) (b) (4) different concentrations of (b) (4) different paddle speeds, different pHs in the dissolution medium and volume of the medium and different amounts of enzyme.

(b) (4)

Reference ID: 3482459

Following this page, 3 Pages Withheld in Full as (b)(4)



- Based on firm's method optimization reports mentioned above and QCRT data submitted, the reviewer agrees with the firm's final method conditions, as follows:

QCRT conditions using USP Apparatus II with Labrasol surfactant

Parameters	Condition used after optimization
Medium Surfactant	Labrasol
Surfactant Concentration	8%
Medium	Tier I: 8% Labrasol in 0.1 N HCl Tier II: 8% Labrasol in 0.1 N HCl with Pepsin (750, 000 units)
Paddle Speed	100 RPM
Medium Volume	900 mL
Temperature	37ºC ± 0.5ºC

QCRT conditions using USP Apparatus II with (b) (4) surfactant

Parameters	Condition used after optimization
Medium Surfactant	(b) (4)
Surfactant Concentration	
Medium pH	
Buffer	
Paddle Speed	
Medium Volume	
Enzyme	
Temperature	37ºC ± 0.5ºC

QCRT conditions using USP Apparatus IV with (b) (4) surfactant

Parameters	Condition used after optimization
Medium Surfactant	(b) (4)
Surfactant Concentration	
Medium pH	
Buffer	
Flow Rate	
Volume of Beads	
Glass Bead Size	
Enzyme	
Temperature	37ºC ± 0.5ºC

- The release data contained in the addendum were re-calculated based on each individual component with its respectively amounts (EPA= 465 mg and DHA= 375 mg). In addition, the re-calculated data for the combined release of EPA+DHA was calculated against a theoretical total of omega-3 content of 840 mg (465 mg EPA + 375 mg DHA).

- The individual unit data (located at Module 3) correspond to the data provided in the summary tables (located at Module 2) with respect to the dissolution data, lot numbers and manufacturing/expiration dates of the test product and RLD. The dissolution testing dates of the test and reference products were provided in the individual unit data. These dates match with those provided in the dissolution data summary tables. The information in this bullet point refers to the comparative (test vs. RLD) testing using all three QCRT methods.

- Based on the firm-provided *in vitro* dissolution summary data tables, the QCRT Method 1 were performed about 6 months since manufacture date of the test product, 1 g (lot # 150000584, manufacture in April, 2013; testing performance in October, 2013). The QCRT Method 2 and Method 3 were performed about 12 months since manufacture date of the test product, 1 g (lot # 30200001A, manufacture in March, 2012; testing performance in March, 2013). The reference product, 1 g (lot# 3ZP1602, expire April 2017 and lot #2ZP1263, expire October 2015), used in the QCRT testing were all before the RLD expiration dates

- The firm stored and handled the test and reference product as per the reference label[10] and as per USP recommendations[11] for the comparative (test vs. RLD) testing using all three QCRT methods.

DBI Deficiency Comment #3

You did not provide your Standard Operating Procedures (SOPs) for the QCR testing and in vitro BE studies. Please submit these documents/information.

Firm's Response:

Please refer to our response to bioequivalence comment #1 above. The analytical methods for the QCR testing and *in vitro* BE studies are provided as follows:

- Module 3.2.P.5.2 Analytical Method (QDP0004603)
  USP Apparatus II with the surfactant Labrasol (without enzyme) – Tier I
  USP Apparatus II with the surfactant Labrasol (with enzyme) – Tier II

- Module 3.2.P.5.2 Analytical Method (QDP0074613)

[10] http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=5ada82f0-a5fd-46c9-aecc-f106f614c9f0#nlm34068-7 ; search term: lovaza; last accessed March 30, 2014.
[11] USP: Section 10.30.50 Controlled Room Temperature; last accessed March 30, 2014.

Reference ID: 3482459

USP Apparatus II with the surfactant [redacted]

- Module 3.2.P.5.2 Analytical Method (QDP0074614)
  USP Apparatus IV with the surfactant [redacted]

Reviewer's Comments: Per DBI's request, in the current amendment, the firm provided the dissolution methods for three different QCR testing. The firm's response to the Deficiency #3 is **adequate.**

DBI Deficiency Comment #4

You have used sinkers in study #s QDP0068549, QDP0069171, QDP0068622, QDP0068624, QDP0060815, and study # POPV_0313_0791. Please provide the following information for the sinkers: 1) a detailed description of the sinker used in the dissolution method (including a diagram, dimensions and manufacturing information) and 2) confirmation that the sinker is consistent with those described in USP Chapter <711> with respect to composition and dimensions.

Firm's Response:

The sinker chosen for use in the referenced studies is the [redacted] sinker device manufactured by [redacted] Please find the sinker specifications, including diagram and manufacturing information, in Module 3.2.P.5.6.

This sinker device conforms with the details described in USP Chapter <711> with respect to composition and dimensions. USP <711> states that the use of "a small, loose piece of nonreactive material, such as not more than a few turns of wire helix, may be attached to dosage units that would otherwise float. An alternative sinker device is shown in Figure 2a. Other validated sinker devices may be used."

The USP <711> alternate sinker device was considered, however, it was deemed not appropriate for this product for several reasons. The USP<711> alternate sinker device is intended for use with capsule sizes up to and including size 00 (length: 23.30 mm). [redacted] Teva's Omega-3-Acid Ethyl Ester Capsules USP, 1g [redacted] for use with the USP <711>alternative sinker device.

It is important to note that the USP <711> alternate sinker device is similar to the [redacted] helix coil type sinker device with respect to composition (material and finish), inside diameter, and wire diameter. [redacted]

Reference ID: 3482459

(b) (4) . Please note the (b) (4) sinker has been validated for Teva's Omega-3-Acid Ethyl Esters Capsules USP, 1 gram. The USP <711> and (b) (4) Helix Coil Sinker specifications are summarized as follows:

Sinker Device Comparison

	Alternate USP <711> Basket Requirements	**Capsule Sinker Specifications Helix Coil Type** (b) (4) (b) (4)
Material	316 Stainless Steel	
Finish	Electropolish	
Inside Length	25 – 26 mm	
Inside Diameter	12.0 +/- 0.2 mm	
Wire Diameter	1.0 mm	
Pitch	3.0 – 3.5 mm	
End Mesh Spacing/ End Coil Inside Dia.	3.5 – 4.0 mm	
Maximum Width	About 14.0 mm (inside diameter + 2x wire diameter)*	
Wire Supports	10	
Number of Coils	About 7.1 - 8.7*	
Weight	4.0 gm	
Maximum Capsule Size	00	

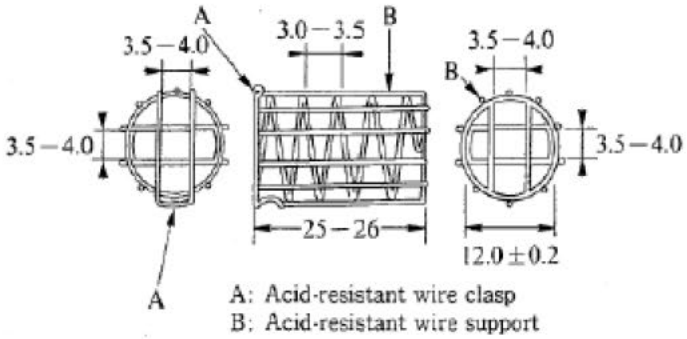
* actual values are calculated based on specifications.

- USP <711> Alternate Sinker Maximum Width = inside diameter + 2x wire diameter = 12.0 mm*2(1.0 mm) = about 14.0 mm
- Helix Coil Type Sinker Maximum Width = inside diameter + 2x wire diameter =11.811 mm*2(1.0922 mm) = 13.9954 mm = about 14.0 mm
- USP <711> Alternate Sinker Number of Coils = inside length/pitch = 25-26 mm/3.0-3.5 mm = 7.142857143 - 8.666666667 = about 7.1 – 8.7 mm

Reviewer's Comments: The reviewer listed the scheme and descriptions of the firm's sinker and the USP's alternative sinker as follows:

Firm's sinkers:

USP's alternative sinker



The firm's response to the Deficiency #4 is **adequate.**

V. DEFICIENCY COMMENTS FOR DISSOLUTION TESTING

1. The firm will be asked to acknowledge the following FDA-recommended QCRT (dissolution) method and specification for the test product:

Apparatus:	USP II (paddle) with (b) (4) Helix Coil sinkers
Speed of Rotation:	100 rpm
Medium:	Tier I: 8% Labrasol in 0.1 N HCl without enzyme Tier II: 8% Labrasol in 0.1 N HCl with pepsin (750, 000 units)
Volume:	900 mL
Temperature:	37°C ± 0.5°C
Specifications	NLT (b) (4)% (Q) in 90 minutes for EPA and DHA

2. The above QCR testing date was prior to the approved date for dissolution method validation (project IDO013; Code: 2000040). In future submissions, the firm should be informed that the dissolution validation should be completed prior to comparative QCR testing.

VI. DISSOLUTION RECOMMENDATIONS

The in vitro dissolution testing conducted by Teva Pharmaceuticals on its test product, Omega-3-Acid Ethyl Esters Capsules, 1g, lot # 150000584, comparing it to Smithkline Beecham's Lovaza® Capsules, 1 g, lot #3ZP1602, is **inadequate** due to the deficiency cited above.

BIOEQUIVALENCE DEFICIENCY TO BE PROVIDED TO THE APPLICANT

ANDA: 091028

APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Omega-3 Acid Ethyl Esters Capsules, 1 gram

The Division of Bioequivalence I (DBI) has completed its review of the drug release testing portion of your submission acknowledged on the cover sheet. The following deficiency has been identified:

1. Your quantitative capsule rupture testing (QCRT) data, using the method stated below, are acceptable. However, your proposed specifications of "NLT (b)(4)% (Q) in (b)(4) minutes" for both Docosahexaenoic Acid (DHA) and Eicosapentaenoic Acid (EPA) components are not acceptable. Based on the submitted data, DBI recommends the specifications below for the test product. Please acknowledge the following QCRT method and specifications for your product:

Apparatus:	USP II (paddle) with (b)(4) Helix Coil sinkers
Speed of Rotation:	100 rpm
Medium:	Tier I: 8% Labrasol in 0.1 N HCl without enzyme Tier II: 8% Labrasol in 0.1 N HCl with pepsin (750000 units/L)
Volume:	900 mL
Temperature:	37°C ± 0.5°C
Specifications	NLT (b)(4)% (Q) in 90 minutes for EPA and DHA

2. The date of the QCRT studies (October 2013) was prior to the approval date for dissolution method validation (project IDO013; Code: 2000040, approval date of December 2013). In future submissions, please be advised that the validation should be completed prior to comparative QCRT studies.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

VII. OUTCOME

ANDA: 091028

Reviewer: Ren, Ke **Date Completed:**

Verifier: **Date Verified:**

Division: Division of Bioequivalence

Description: Omega-3 Acid Ethyl Esters Capsules, 1 gram, Teva Pharmaceuticals USA

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
22200	3/20/2014	Dissolution Data (REGULAR)	Dissolution Amendment	1	1
				Total:	1

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KE REN
04/02/2014

UTPAL M MUNSHI
04/02/2014

HOAINHON N CARAMENICO
04/02/2014

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	091028	
Drug Product Name	Omega-3-Acid Ethyl Esters Capsules	
Strength(s)	1 g	
Applicant Name	Teva Pharmaceuticals USA	
Address	425 Privet Road Horsham, PA 19044	
Applicant's Point of Contact	Scott D. Tomsky VP US Generics Regulatory Affairs	
Contact's Telephone Number	(215) 591-3142; email: scott.tomsky@tevapharm.com	
Contact's Fax Number	(215) 591-8812	
Original Submission Date(s)	November 10, 2008 (Original submission) October 1, 2009 (Dissolution amendment)	
First Generic	No	
Submission Date(s) of Amendment(s) Under Review	December 30, 2013 (Complete response amendment) February 7, 2014 (ECD telephone request)	
Reviewer	Li Gong, Ph.D.	
Study Number (s)	2008-1779	2008-1829
Study Type (s)	Fasting and Fed study (RLD only)	Fed Study (Test and RLD)
Strength (s)	4 X 1 g	4 X 1 g
Clinical Site	Pharma Medica Research Inc.	Allied Research International (Formerly Cetero Research)
Clinical Site Address	4770 Sheppard Avenue East Toronto, Ontario, Canada M1S 3V6	1405 NW 167th Street Miami Gardens, Florida 33169
Analytical Site	(b) (4)	
Analytical Site Address		

OVERALL REVIEW RESULT	**INADEQUATE**		
WAIVER REQUEST RESULT	**N/A**		
OSI REPORT RESULT	**N/A**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1, 8 & 17	**Dissolution**	**1 gram**	**INADEQUATE**
17	***In vitro* BE Study**	**1 gram**	**INADEQUATE**
1	**Pilot Study (fasting and fed)**	**1 gram**	**INADEQUATE**
1	**Pivotal Fed Study**	**1 gram**	**INADEQUATE**

Reference ID: 3468027

Review of an Amendment

I. Executive Summary

On November 10, 2008 Teva Pharmaceuticals USA originally submitted the results of a pilot *in vivo* study (Study No. 2008-1779), a fed pivotal *in vivo* bioequivalence (BE; Study No. 2008-1829) study and an *in vitro* non-quantitative capsule rupture test, comparing its test product, Omega-3-Acid Ethyl Esters Capsules, 1.0 gram, to the corresponding reference listed-drug (RLD) product, GlaxoSmithkline's Lovaza® (Omega-3-Acid Ethyl Esters) Capsules, 1.0 gram, to support its application.[1] However, per the current draft individual drug product Guidance for the Omega-3-Acid Ethyl Esters Capsules,[2] deficiencies were found in both *in vivo* study portion [*In Vivo* Study Option; e.g. pending the firm's submission of new fasting and fed studies) and *in vitro* study portion (*In Vitro* Study Option: e.g. pending the firm's submission of method development report and modification of existing quantitative capsule rupture testing (QCRT)] of the application.[3]

On December 30, 2013, the firm acknowledged its selection of *In Vitro* Study option per the above Guidance to establish the BE between its test and the RLD products in the current amendment submission and responded to the deficiencies identified in the OGD's complete response letter of August 13, 2013. Because the firm's responses to the deficiencies concerning *in vitro* QCRT and *in vitro* BE study are now still found incomplete (see Section D Deficiency Comments of this review for details), therefore, the current submission is considered inadequate.

Thus, the application is still **inadequate** (incomplete) as per the comments above.

[1] DARRTS, ANDA 091028 REV-BIOEQ-01 (General Review); Submit/Final Date 12/14/2012
[2] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM320011.pdf (recommended on September, 2012)
[3] DARRTS, ANDA 091028 COR-ANDAACTION-09(Complete Response); Submit/Final Date 08/13/2013

Reference ID: 3468027

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III. Background Information

1. On November 10, 2008 the firm originally submitted the results of a pilot *in vivo* study (Study No. 2008-1779), a fed pivotal *in vivo* bioequivalence (BE; Study No. 2008-1829) study and an *in vitro* non-quantitative capsule rupture test, comparing its test product, Omega-3-Acid Ethyl Esters Capsules, 1.0 gram, to the corresponding reference listed-drug (RLD) product, GlaxoSmithkline's Lovaza® (Omega-3-Acid Ethyl Esters) Capsules, 1.0 gram, to support its application.

   The results of the original pivotal fed BE study (Study No. 2008-1829) are included below:

Eicosapentaenoic Acid (EPA; Free fatty acids)

Baseline Adjusted **Omega-3-acid ethyl esters Capsules, 4 x 1 g** **Fed Bioequivalence Study No. 2008-1829, N=80 (Male=32 and Female=48)** **Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals**					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	5.14	5.41	0.95	90.25	99.94
Cmax (ng/mL)	0.81	0.87	0.92	84.58	100.67

EPA (Total lipids)

Baseline Adjusted **Omega-3-acid ethyl esters Capsules, 4 x 1 g** **Fed Bioequivalence Study No. 2008-1829, N=80 (Male=32 and Female=48)** **Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals**					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (µg·hr/mL)	947.89	959.67	0.99	94.23	103.53
Cmax (µg /mL)	72.68	75.44	0.96	90.56	102.49

Reference ID: 3468027

Docosahexaenoic Acid (DHA; Free fatty acids)

Baseline Adjusted Omega-3-acid ethyl esters Capsules, 4 x 1 g Fed Bioequivalence Study No. 2008-1829, N=80 (Male=32 and Female=48) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	12.369	12.688	0.97	90.76	104.71
Cmax (ng/mL)	2.364	2.515	0.94	85.27	103.56

DHA (Total lipids)

Baseline Adjusted Omega-3-acid ethyl esters Capsules, 4 x 1 g Fed Bioequivalence Study No. 2008-1829, N=80 (Male=32 and Female=48) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (µg ·hr/mL)	290.59	290.30	1.00	88.92	112.68
Cmax (µg /mL)	44.06	44.86	0.98	89.87	107.36

2. Also, in the same original submission the firm's *in vitro* non-quantitative capsule rupture testing data were generated per USP <2040> Rupture Test for Soft Gelatin Capsules (500 mL of water using Apparatus II (paddle) at 50 rpm, by visual determination of capsule ruptures) and was found inadequate pending its development of a quantitative capsule rupture testing (QCRT) method.[4]

3. On October 1, 2009, the firm submitted a subsequent dissolution amendment[5] in response to the deficiency letter dated May 6, 2009.[6] The firm had provided results of a then newly developed QCRT, which was found non-discriminatory QCRT profiles between the test and reference product. Thus the QCRT was still inadequate pending the firm's modification of the then-current QCRT method.[7]

4. December 30, 2013, the firm submitted the current amendment in response to the Office of Generic Drugs' (OGD's) "Complete Response Letter" of August 13, 2013.[8]

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[4] DARRTS, ANDA 091028, REV-BIOEQ-02(Dissolution Review) Original-1 Archive: Submit/Final Date: 5/4/2009

[5] DARRTS, ANDA 091028, Supporting Document #8 Quality/Quality Information; Bioequivalence/Response to Information Request, Original-1 View EDR; Submit/Final Date: 10/01/2009.

[6] DARRTS, ANDA 091028, COR-ANDAE-01(Bio Incomplete Deficiencies) Original-1 Archive; Submit/Final Date: 5/6/2009.

[7] DARRTS, ANDA 091028, REV-BIOEQ-01(General Review) Original-1 Archive: Submit/Final Date: 12/14/2012

[8] DARRTS, ANDA 091028, COR-ANDAACTION-09(Complete Response) Original-1 Archive; Submit/Final Date: 08/13/2013.

5. However, on February 7, 2014, due to incomplete submission of the QCRT and *in vitro* BE study documentation/data as well as eCTD-formatted data summary tables (see the dissolution amendment review in a separate review document for details), the DBI issued an ECD telephone request to the firm.[9] (Please also refer to Section H Additional Attachments (5) Email Communications among the Bio-, Regulatory Project Managers and Reviewers, of this review for details). The review of the ECD response is included in the current review.

IV. Submission Summary

A. Drug Product Information, PK/PD Information, and Relevant DBE History

For a most recent description of the drug product and PK/PD information (per Drugs@fda and labeling), see DARRTS for ANDA 091028 of Gong, Li 12/14/2012 N/A 12/14/2012 REV-BIOEQ-01 (General Review) Original-1 Archive.[1,10,11]

See above review for Relevant DBE History.

Labeling of this product was revised after the completion of the review listed above (updated 06/26/2013, 09/11/2013 and 11/15/2013). The following labeling changes (added or changed text) were made:[12]

1. **Labeling Revision** (06/26/2013; a revision of the following Section 8.3 Nursing Mothers in the package insert in order to specify the effect of excretion of omega-3-acid ethyl esters in human milk is unknown; thus, caution should be exercised with administration of the drug product to a nursing mother)

   "**8.3 Nursing Mothers**
   Studies with omega-3-acid ethyl esters have demonstrated excretion in human milk. The effect of this excretion on the infant of a nursing mother is unknown; caution should be exercised when LOVAZA is administered to a nursing mother. An animal study in lactating rats given oral gavage ^{14}C-ethyl EPA demonstrated that drug levels were 6 to 14 times higher in milk than in plasma."

2. Manufacturing Change or Addition (09/11/2013): This supplement type does not usually require new labeling.

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[9] DARRTS, ANDA 091028, COR-ECD-01(Easily Correctable Bioequivalence Deficiency) Original-1 Archive; Submit/Final Date: 02/07/2014.

[10] RLD Labeling: http://dailymed nlm nih.gov/dailymed/lookup.cfm?setid=5ada82f0-a5fd-46c9-aecc-f106f614c9f0: 02/14/2014

[11] Clinical Pharmacology Online (2013): http://www.clinicalpharmacology-ip.com/Forms/Monograph/monograph.aspx?cpnum=2722&sec=monphar&t=0; last accessed: 02/14/2014

[12] Drugs@FDA (Keyword Search =Lovaza) Labeling Revision Review (Letters) (http://www.accessdata fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo); last accessed: 02/14/2014

Reference ID: 3468027

3. Manufacturing Change or Addition (11/15/2013): This supplement type does not usually require new labeling.

B. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	-
Single-dose fed	No	-
Steady-state	No	-
In vitro dissolution	No	1 (reviewed in a separate dissolution amendment review document)
Waiver requests	No	-
BCS Waivers	No	-
Vasoconstrictor Studies	No	-
Clinical Endpoints	No	-
Failed Studies	No	-
Amendments	Yes	1

C. Review of Amendment Submissions

Deficiency No. 1: *The DBI has reviewed the test formulation using the criteria on active pharmaceutical ingredient and antioxidant as stated in the draft Individual Product BE Guidance for Omega-3-Acid Ethyl Esters Capsules, posted on September, 2012, (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM320011.pdf), and considers that your test product meets the criteria. The test and reference products are similar and the bioequivalence (BE) may be established based solely on an in vitro method (Quantitative Capsule Rupture Test, also described in the draft guidance).*

Firm's Response to Deficiency #1:

"Teva acknowledges that the Division of Bioequivalence has reviewed our test formulation and considers our test product to meet the criteria established in the draft guidance. As our drug product and the reference products are similar, bioequivalence (BE) may be established solely using an *in vitro* method".

Reviewer's Comments on Firm's Response to Deficiency #1:

- In the prior submission dated 10/28/2011,[13] the firm submitted the active pharmaceutical ingredient (API) data for its test product, Omega-3-Acid Ethyl Esters Capsules, 1 g, and they were found qualitatively and quantitatively (Q1/Q2) equivalent to those of the reference product and were deemed acceptable,[14,15] as per the current draft Guidance for Omega-3-Acid Ethyl Esters Capsules, that is, *"The Omega-3-Acid Ethyl Esters USP monograph defines the active pharmaceutical ingredient (API) as composed of seven individual omega-3-acid ethyl ester components. The Omega-3-Acid Ethyl Esters Capsules USP monograph establishes ranges for the two most abundant components (EPAee and DHAee) of the active pharmaceutical ingredient (API) and ranges for the sum of the two components. The reference product contains lesser quantities of the other five omega-3 acid ethyl esters, although quantitative ranges are not specified in the USP monographs. The Agency has determined the quantitative ranges of the other five omega-3-acid ethyl ester components based on assay of multiple batches of the RLD using the USP monograph analytical method"* and that *"The agency's recommendation for each component of the API varies with its content. API in each batch of a Test product must meet the quantitative ranges for all the seven components"*.[16]

- In the current amendment dated 12/30/2013, the firm acknowledges that it intended to take *In Vitro* method option to establish the bioequivalence (BE) between its test product, Omega-3-Acid Ethyl Esters Capsules, 1 g and the reference listed drug (RLD), GlaxoSmithKline's Lovaza® (omega-3-acid ethyl esters) Capsules, 1 g, per the current Guidance.[16]

- The reviewer noted that the firm has scaled-up its test product and manufactured a new commercial batch (Bulk Batch# 150000401; manufacturing date: 4/3/2012) since the production of the biobatch (Batch# P080602; manufacturing date: 6/24/2008), as shown below, and has used this new batch to conduct the quantitative capsule rupture testing (QCRT) and current *in vitro* BE study (Study# POPV_0313_0791).

Strength	ANDA Batch Size (Batch# P080602)	Proposed Commercial (Batch# 150000401)
Manufacturing Date	6/24/2008	4/3/2012
1 gram strength	(b) (4) capsules	(b) (4) capsules
		(b) (4)

[13] DARRTS, ANDA 091028 Quality/Response To Information Request Original-1 View EDR; Submit/Final Date: 10/28/2011

[14] DARRTS, ANDA 091028, REV-BIOEQ-01(General Review) Original-1 Archive; Submit/Final Date:12/14/2012

[15] DARRTS, ANDA 091028, REV-QUALITY-21(Primary Review) Original-1 Archive; Submit/Final Date:07/30/2013

[16] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM320011.pdf (recommended on September, 2012)

(b) (4)

- In addition, the reviewer summarizes the firm's test API data from its newly manufactured commercial batch (Batch# 150000401) all of which met the quantitative ranges recommended by the current Guidance, as shown in the following table:

Contents	Recommended Quantitative Ranges[16]	Firm's Testing Results[17] (mg/g)	Met/ Failed to meet
Eicosapentaenoic acid ethyl ester (EPAee; C20:5 n-3)	430 - 495 mg/g	(b) (4)	Met
Docosahexaenoic acid ethyl ester (DHAee; C22:6 n-3)	347 - 403 mg/g		Met
Sum of EPAee and DHAee	800 - 880 mg/g		Met
Total omega-3 acid ethyl esters	NLT 90% (w/w)		Met
Moroctic acid ethyl ester (SDAee; C18:4 n-3)	4.0-37.0 mg/g		Met
Heneicosapentaenoic acid ethyl ester (HPAee; C21:5 n-3)	7.9-31.4 mg/g		Met
Docosapentaenoic (Clupanodonic) acid ethyl ester (DPAee; C22:5 n-3)	16.3-50.0 mg/g		Met
Eicosatetraenoic acid ethyl ester (ETAee; C20:4 n-3)	≥1 - <10 mg/g encapsulated oil		Met
Alpha-linolenic acid ethyl ester (ALAee; C18:3 n-3)	below 1 mg/g		Met
*Alpha-tocopherol	4 mg/g encapsulated oil	**4 mg**	Met

(b) (4)

- Although the firm has provided the results of comparative *in vitro* BE studies and *in vitro* QCR testing, along with its pertaining method validation data in the current submission dated 12/30/2014, the dissolution (e.g. QCRT) amendment submission, however, is still considered incomplete due to its unspecified dissolution methods

[17] ***Note:*** Please also refer to Section G Additional Attachments of this review for the test API Certificate of Analysis (COA) for details.
[18] DARRTS, ANDA 091028 REV-QUALITY-21(Primary Review) Original-1 Archive; Submit/Final Date: 02/07/2014.

Reference ID: 3468027

used in its respective method validation and *in vitro* BE studies and QCR testing, and incomplete analytical data submission concerning its *in vitro* BE studies. The firm will be asked to provide the aforementioned clarifications/explanations and additional testing data (please refer to the dissolution amendment review in a separate review document for details). As such, comparisons of the Test and Reference QCRT data will not be made at this time with respect to bioequivalence.

- Hence, the firm's response to Deficiency No. 1 is still considered inadequate.

Deficiency No. 2: *However, per the draft Guidance aforementioned, if you wish to choose In Vivo BE Study Option for your application, please conduct both new fasting and fed BE studies for Omega-3-Acid Ethyl Esters Capsules, 1 g.*

According to that current BE Guidance for Omega-3-Acid Ethyl Esters Capsules posted on September 2012, the 90% confidence intervals (CIs) for the BE fed study are based on: (1) Eicosapentaenoic Acid (EPA) ethyl esters and (2) Docosahexaenoic Acid (DHA) ethyl esters. In addition, a fasting BE study is recommended and its 90% CIs for BE are based on: (1) baseline-adjusted EPA total lipids and (2) baseline-adjusted DHA total lipids.

Firm's Response to Deficiency #2:

"It is our intent to support bioequivalence (BE) by relying on an *in vitro* method".

Reviewer's Comments on Firm's Response to Deficiency #2:

- The firm's response to the above Deficiency No. 2 is also considered acceptable (adequate).

Deficiency No. 3: *Based on your pre-study validation data in your currently submitted fed study (Study No. 2008-1829), the percent of average recovery for the free eicosapentaenoic acid (EPA) (e.g. QC A, B and C: 131.9 % to 140.0 %) and docosahexaenoic acid (DHA) (e.g. QC A, B and C: 130.2 % to 135.8 %) and that of Internal Standard [IS (*(b) (4)*124.1%] are very high. Please provide your explanation(s) about such high values of average recovery of the above mentioned analytes and the internal standard.*

Firm's Response to Deficiency No. 3:

"The contract research organization that performed the bioequivalence study for this ANDA, Pharma Medica Research Inc., has provided a report and supporting data in answer to this question. Please find the report to support the fed study provided in **Module 5.3.1.4**".

The firm's contract research organization (CRO), Pharma Medica Research Inc., answers the above Deficiency No. 3 as follows:

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“Since both EPA and DHA are endogenous components in human plasma, in method PMRI-1026-08, two set of QCs samples at QC-low, QC-middle and QC-high were prepared, respectively: one set of QCs samples (QC-A, QC-B, QC-C) were prepared in surrogate matrix buffer and the 2nd set of QCs samples (QC-E, QC-F, QC-G) were prepared in human plasma.

For EPA, DHA and internal standard (b) (4) recovery experiments reported in PMRI-1026-08, six (6) replicates of each QCs (QC-A, QC-B, QC-C, QC-E, QC-F, QC-G) containing internal standard were extracted and assayed. Six (6) replicates of each of un-extracted QCs (QC-A, QCB, QC-C, QC-E, QC-F, QC-G) containing internal standard were prepared in solvent and assayed. The mean recovery was calculated by comparing the absolute peak area of the extracted samples to the absolute peak area of the un-extracted samples. The un-extracted sample represents 100% recovery.

The recovery of EPA and DHA was reported to be high only in QC samples (QC-A, QC-B and QC-C) that were prepared in surrogate matrix buffer and it is normal in QC samples (QC-E, QCF and QC-G) that were prepared in human plasma. The reason the recovery is high is because QCs (QC-A, QC-B and QC-C) were prepared in surrogate matrix phosphate buffer (see attached Tables 6 and 7).

The Phosphate buffer solution used as surrogate matrix has a pH approximately of 7.5. EPA and DHA as well as the internal standard have a carboxylic acid group and these groups are ionized negatively in the solution. Since the LCMSMS is using negative mode, there is an enhancement of the signal of the analytes including the internal standards response when compared to the unextracted QCs (representing 100% recovery) prepared in the precipitation solvent without phosphate buffer. The result of this enhancement is obvious if the recovery is calculated based on the absolute area of each analyte but is compensated for when using the ratio of analyte and internal standard since both the analyte and internal standard signal are enhanced. In reality recovery is very similar in the surrogate buffer and the plasma except the signal in the surrogate buffer is higher for same concentration and translates to higher recovery for the analytes and the internal standard when using absolute area.

When calculating the EPA/DHA recovery using the peak area ratio of analyte to internal standard, the recovery data obtained in samples QC-A, QC-B, and QC-C is found to be within the range of 92.0 to 96.9% for EPA and 90.6% to 94.1% for DHA. This data is consistent and reproducible with the recovery data of QC-E, QC-F and QC-G that is in the range of 94.2 to 101.2% for EPA and 82.5 to 98.8% for DHA (see attached Tables 6A & 7A).

When calculating the internal standard recovery using the peak area ratio of IS to Analyte, the recovery data obtained in samples QC-A, QC-B and QC-C is found to be within the range of 103.1% to 108.7% for EPA and 106.3% to 110.2% for DHA. This data is consistent and reproducible with the recovery data of QC-E, QC-F and QC-G that is within

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the range of 98.8% to 106.4% for EPA and 101.6% to 110.8% for DHA (see attached Tables 8, 8A1-12, 8B1-12).

The recovery of EPA, DHA and internal standard [redacted] (b) (4) in both human plasma and in surrogate buffer is consistent and reproducible based on the ratio of analyte to internal standard.

Please refer to files:
Table 6 and 6A Recovery-EPA-DL.pdf
Table 7 and 7A Recovery-DHA-DL.pdf
Table 8 IS Recovery-DL.pdf
Table 8A 1-12 IS Recovery-DL.pdf
Table 8B 1-12 IS Recovery-DL.pdf'

Reviewer's Comments on firm's response to Deficiency No. 3

- In the original submission dated 11/10/2008, the firm submitted the results of a pilot study (under fasting and fed states; Study No. 2008-1779) and a fed bioequivalence (BE) study (pivotal study; Study No. 2008-1829) comparing its test product, Omega-3-Acid Ethyl Esters Capsules, 1 g, to the corresponding RLD, Lovaza® (omega-3-acid ethyl esters) Capsules, 1 g, before the posting date of the most current draft Guidance[16]. The above Deficiency No. 3 was related to the pre-study method validation with regard to the firm's fed BE study (Study No. 2008-1829). Per the current Guidance, the firm intends to take the *in vitro* method option to establish the BE between its test and the RLD products (please see reviewer's comments on firm's response to Deficiency No. 1 above). Thus, this aforementioned deficiency is not of concern this time in terms of *in vivo* BE study on the test product.

- However, the reviewer did verify the pre-study method validation data originally submitted, with the supporting data/documents provided by the firm in the current submission dated 12/30/2013 (please also refer to Section H Additional Attachments (3) for details), and tended to agree with the firm's explanation of using the peak area ratio to calculate EPA/DHA recovery due to the unwanted, masked signal enhancement interference from LC/MS/MS. Indeed, the reviewer verified that the aforementioned peak area ratio calculations did give rise to acceptable ranges of recovery being (a) Samples: QC-A, QC-B, and QC-C found to be within the range of 92.0 to 96.9% for EPA and 90.6% to 94.1% for DHA; and QC-E, QC-F and QC-G in the range of 94.2 to 101.2% for EPA and 82.5 to 98.8% for DHA, and (b) Internal Standard (IS): QC-A, QC-B and QC-C found to be within the range of 103.1% to 108.7% for EPA and 106.3% to 110.2% for DHA; and QC-E, QC-F and QC-G in the range of 94.2 to 101.2% for EPA and 82.5 to 98.8% for DHA.

- Therefore, the firm's response to Deficiency No. 3 is acceptable.

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Deficiency No. 4: *For your future submissions, please be advised of the following:*

*Please submit complete (100%) raw numerical data of **all** assay and reassay runs for **all subjects**, including the data of peak area/height for the drug, peak area/height for the internal standard, ratio of the peak area/height for the drug to the peak area/height for the internal standard, dilution factor (if any), and the corresponding concentration for each assayed and reassayed sample of all subject samples, calibration standard concentration samples, and quality control samples for each of your BE study. For your pilot study (Study No. 2008-1779) and fed study (Study No. 2008-1829) currently submitted, you only submitted the raw numerical data of **approximately 50% and 22.5%** of the subjects, respectively.*

Firm's Response to Deficiency No. 4:

"Teva acknowledges that for future submissions, complete (100%) raw numerical data is to be submitted as indicated.".

Reviewer's Comments on Firm's Response to Deficiency No. 4:

- The firm's response to Deficiency No. 4 is acceptable.

Deficiency No. 5: *Regarding Compliance with Section 508 of the Rehabilitation Act of 1973: The images included in your submission do not contain alternate text and are therefore unsearchable and not in compliance with Section 508 of the Rehabilitation Act of 1973, which requires that Federal agencies' electronic and information technology is accessible to people with disabilities. Please ensure that future submissions are in compliance with Section 508 and contain images with alternate text so that the images are searchable. Instructions for adding alternate text should be provided in the software used to construct/view the PDF file. Please refer to the website http://www.section508.gov for further information.*

Firm's Response to Deficiency No. 5:

"Teva acknowledges that future submissions are required to be in compliance with Section 508 of the Rehabilitation Act of 1973."

Reviewer's Comments on Firm's Response to Deficiency No. 5:

- The firm's response to Deficiency No. 5 is acceptable.

Deficiency No. 6: See the dissolution (e.g. QCRT) amendment review in a separate Bio dissolution review document for details.

Firm's Response to Deficiency No. 6: See the dissolution (e.g. QCRT) amendment review in a separate Bio dissolution review document.

Reviewer's Comments on Firm's Response to Deficiency No. 6:

- The overall review status of the firm's quantitative capsule rupture testing (dissolution) is **inadequate** (refer to the above same Bio dissolution review document for details).

Deficiency No. 7: See the dissolution (e.g. QCRT) amendment review in a separate Bio dissolution review document.

Firm's Response to Deficiency No. 7: See the dissolution (e.g. QCRT) amendment review in a separate Bio dissolution review document.

Reviewer's Comments on Firm's Response to Deficiency No. 7:

- The overall review status of the firm's quantitative capsule rupture testing (dissolution) is **inadequate** (refer to the above same Bio dissolution review document for details).

Deficiency No. 8: *Please provide the quantitative amount of each component of your Soft Gelatin Capsule Shell and White Printing Ink* (b) (4) *per capsule in your test formulation.*

Firm's Response to Deficiency No. 8:

"Banner Pharmacaps Inc., the DMF holder for the (b) (4), has responded to all deficiencies for DMF 14194. Please find in Module 1.4.1, a copy of the August 30, 2013 **cover letter** and a copy of **Banner's DMF letter of authorization** that accompanied Banner's DMF amendment. The quantitative amount of each component of the Soft Gelatin Capsule Shell and White Printing Ink can be found in DMF 14194".

Reviewer's Comments on Firm's Response to Deficiency No. 8:

- Same as with the original submission dated 11/10/2008, the firm currently still referred the quantitative composition for its Soft Gelatin Capsule Shell and White Printing Ink (b) (4) to the DMF #14194 [please refer to Section H Additional Attachments (4) of this review for detailed authorization letter from Banner Pharmacaps, Inc]. After an extensive search for the above mentioned DMF, this reviewer now is able to locate the test product-specific quantitative composition related to the DMF aforementioned.

- In addition, as per the firm's batch formula[19] submitted as follows, this reviewer can at this time further evaluate the test formulation and determine if it is acceptable from the bioequivalence standpoint.

[19] DARRTS, ANDA 091028 REV- QUALITY-21(Primary Review) Original-1 Archive; Submit/Final Date: 2/7/2014.

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Reference ID: 3468027

(b) (4)

- Per the comments above, the firm's test formulation is now considered acceptable (complete).

- Therefore, the firm's response to Deficiency No. 8 is acceptable (adequate).

D. Deficiency Comments

The following deficiencies has been communicating to the firm in the DBI's deficiency comments for drug release testing review (please see DARRTS, ANDA 091028 REV-BIOEQ-02(Dissolution Review) Original-1 Archive; Submit/Final Date: 3/6/2014, for details)

1. With respect to the Quantitative Capsule Rupture Testing (QCRT) and in vitro bioequivalence (BE) studies submitted on December 30, 2013, the firm has referenced two different analytical methods. Specifically, the analytical method used in its method validation (Project ID O013; Code: 2000040) differs from that used in the QCRT [Report No. QDP0060815] and in the *in vitro* BE testing (POPV_0313_0791, POPV_0313_0852, POPV_0313_0853, POPV_0313_0892, POPV_0313_0891), as follows:

   Analytical method used in the firm's method validation (Project ID O013; Code: 2000040):

   Column:

   Detection:
   Flow Rate:
   Injection Volume:
   Column Temperature:
   Run Time:

   (b) (4)

   Analytical method used in the firm's quantitative capsule rupture testing (QCRT) using USP Apparatus II (paddles) or USP apparatus IV [Report No. QDP0060815] and in the *in vitro* bioequivalence (BE) testing (POPV_0313_0791, POPV_0313_0852, POPV_0313_0853, POPV_0313_0892, POPV_0313_0891):

   Column:

   (b) (4)

Detection:	(b) (4)
Flow Rate:	
Injection Volume:	
Column Temperature:	
Auto sampler Temperature:	
Run Time (Apparatus II):	
Run Time (Apparatus IV):	

The firm is advised to clearly identify which instrument conditions were used during the QCRT testing [Report No. QDP0060815] and the in vitro BE testing (POPV_0313_0791). If the method used in these studies differs from that already validated, then the firm is asked to provide additional validation as necessary. Also, the firm is asked to provide its Standard Operating Procedure (SOP) for each of the above methods as well as for the method validation procedure.

2. In the firm's QCRT testing [Report No. QDP0060815] and *In vitro* BE testing (POPV_0313_0791) submitted December 30, 2013, it submitted data reflecting the sum of Eicosapentaenoic Acid (EPA) + Docosahexaenoic Acid (DHA) release. The firm is asked to submit the release data from the referenced studies for each individual component rather than for the sum of the two components. The firm is also asked to submit the data from 12 individual dosage units of the Test and Reference products from the referenced studies. In addition, the firm is asked to submit all mean data, range, %CV, and the dates of these studies in eCTD format (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120957.pdf). Finally, the firm is asked to submit the temperature and humidity at which the test and reference product lots were stored between manufacture of the test product (or acquisition of the reference product) and the time of the aforementioned studies.

3. The firm did not provide its Standard Operating Procedures (SOPs) for its QCR testing and in vitro BE studies. The firm is asked to submit the above documents/information.

4. The firm has used sinkers in its study #s QDP0068549, QDP0069171, QDP0068622, QDP0068624, QDP0060815, and study # POPV_0313_0791. The firm is asked to provide the following information for the sinkers: 1) a detailed description of the sinker used in the dissolution method (including a diagram, dimensions and manufacturing information) and 2) confirmation that the sinker is consistent with those described in USP Chapter <711> with respect to composition and dimensions.

E. Recommendations

1. Per the current draft Individual Product BE Guidance for Omega-3-Acid Ethyl Esters Capsules, recommended on September 2012, the Division of Bioequivalence I (DBI)

acknowledges that the firm, Teva Pharmaceuticals USA, intends to take *In Vitro* method option to establish the bioequivalence (BE) between the test product, Omega-3-Acid Ethyl Esters Capsules, 1 g (Lot# 150000401), and the RLD, GlaxoSmithKline's Lovaza® (omega-3-acid ethyl esters) Capsules, 1 g (Lot# 2ZP1263).

2. The firm's *in vitro* drug release testing (QCRT) for the purpose of BE determination is still considered **incomplete** (inadequate) due to the above deficiency comments. As a result, the firm's *in vitro* BE study is inadequate at this time.

As per comments above, the application is **inadequate** (incomplete).

F. Comments for Other OGD Disciplines

Discipline	Comment
None	--

G. Pending Consults (Clinical, Statistical, Science Staff, Chemistry etc.)

Discipline	Comment
None	--

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Reference ID: 3468027

5) Email Communications among the Bio-, Regulatory Project Managers and Reviewers

(NOT TO BE RELEASED UNDER FOIA)

From: Yoon, Martin
Sent: Friday, February 21, 2014 1:05 PM
To: Nguyen, Hoainhon T; Munshi, Utpal; Gong, Li
Cc: Yoon, Martin
Subject: FW: ANDA 091028 - Omega-3-Acid Ethyl Esters Capsules USP, 1 gram - clarification requested on ECD

Hello All,

The firm has not responded back to Bio ECD within the 10 business days. Bio ECD was submitted 2/7/2014 and today is the 11th business day.

Li: Please proceed with completing your review so the Office can issue a CR.

Hoai: Please let us know if you have any questions or comments.

Thank you,
Martin

From: Olele, Chinyelum
Sent: Friday, February 21, 2014 11:41 AM
To: Yoon, Martin
Subject: RE: ANDA 091028 - Omega-3-Acid Ethyl Esters Capsules USP, 1 gram - clarification requested on ECD

Hi Martin,

No I did not, we have contacted the firm and told them not to respond to the ECD since it has passed the 10 days and instead we will issue a CR letter

Regards,

Chinyelum (Chi-Chi) Olele, PharmD
LCDR, United States Public Health Service
FDA, Office of Generic Drugs
Ph: 240-276-9778

From: Yoon, Martin
Sent: Friday, February 21, 2014 8:07 AM
To: Olele, Chinyelum
Subject: RE: ANDA 091028 - Omega-3-Acid Ethyl Esters Capsules USP, 1 gram - clarification requested on ECD

Hi Chi-Chi,

Reference ID: 3468027

Did you hear anything back from the firm on Bio ECD?

Thank you,
Martin

From: Nguyen, Hoainhon T
Sent: Friday, February 14, 2014 8:38 AM
To: Yoon, Martin; Munshi, Utpal; Gong, Li
Cc: Nguyen, Hoainhon T
Subject: RE: ANDA 091028 - Omega-3-Acid Ethyl Esters Capsules USP, 1 gram - clarification requested on ECD

Martin,
We would like the firm to submit release data for each component, EPA and DHA, separately as opposed to the sum of the components, for **all** DOE experiments of report QDP0060815 AND other reports provided in the ANDA 12/30/2013 amendment.
Thanks,
Hoai

From: Yoon, Martin
Sent: Friday, February 14, 2014 8:25 AM
To: Nguyen, Hoainhon T; Munshi, Utpal; Gong, Li
Cc: Yoon, Martin
Subject: FW: ANDA 091028 - Omega-3-Acid Ethyl Esters Capsules USP, 1 gram - clarification requested on ECD

Hello All,

The RPM has forward an inquiry from Teva requesting clarification regarding question 2 on Bio ECD submitted 2/7/2014.

Please advise how bio will like to respond.

Thank you,
Martin

From: Olele, Chinyelum
Sent: Thursday, February 13, 2014 10:20 AM
To: Yoon, Martin
Cc: Gaines, Robert
Subject: FW: ANDA 091028 - Omega-3-Acid Ethyl Esters Capsules USP, 1 gram - clarification requested on ECD

Hi Martin,
Can you please forward this to your reviewer. The firm is seeking a response to clarify the ECD that they were issued. Thanks

Regards,

Reference ID: 3468027

Chinyelum (Chi-Chi) Olele, PharmD
LCDR, United States Public Health Service
FDA, Office of Generic Drugs
Ph: 240-276-9778

From: Rich Leone [mailto:Rich.Leone@tevapharm.com]
Sent: Wednesday, February 12, 2014 10:55 AM
To: Olele, Chinyelum
Cc: Rich Leone; Jill Pastore; Scott Tomsky; Gaines, Robert
Subject: ANDA 091028 - Omega-3-Acid Ethyl Esters Capsules USP, 1 gram - clarification requested on ECD

Good Morning Dr. Olele,

Teva recently received an Easily Correctable Deficiency Letter for our pending ANDA 091028 - Omega-3-Acid Ethyl Esters Capsules USP, 1 gram (letter attached for your easy reference). We are seeking clarity from the Agency as we are processing the information request in order to submit a timely response. Specifically, question 2 requests that Teva provide release data for each component, EPA and DHA, separately as opposed to the sum of the components as had been submitted previously. We are seeking clarification to understand if the Agency is requesting information from the 2 reports (QDP0060815) containing the final sets of DOE experiments, i.e. the 12 unit data for both the test and reference products (Reference: POPV_0313_0791). Or is the Agency requesting the release data for each component, EPA and DHA, from all DOE experiments of report QDP0060815 AND other reports provided in our 12/30/2013 amendment. Please see the below list of reports that we have provided in our earlier amendment.

Reports Pertaining to Dissolution Submitted in Amendment Dated 12/30/2013:
QDP0060815: Summary of In Vitro Evaluation of Teva's Omega-3-Acid Ethyl Esters Capsules and RLD, LOVAZA® Capsules for Establishing Bioequivalence details the use of USP apparatus 4 and USP apparatus 2 using (b) (4) as surfactant.
QDP0069171: Special Study Dissolution Profile Report for Omega-3 Ethyl Esters Capsules 1 g
QDP0068549: Analytical Method Validation Report for Dissolution Test (Apparatus II) for Omega-3-Acid Ethyl Ester Capsules, 1 gram
QDP0068622: Omega-3-Acid Ethyl Ester Capsules, 1 gram Comparative Dissolution Profile (Tier I Dissolution Medium)
QDP0068624: Omega-3-Acid Ethyl Ester Capsules, 1 gram Comparative Dissolution Profile (Tier II Dissolution Medium)

Please contact me if you have any questions. We appreciate your timely feedback so we can adequately address the Agency's questions. Thank you.

Best regards,
Rich

Rich Leone Senior Director, Generics Regulatory Affairs
Tel: +1-201-930-2161 Cell: (b) (6) Fax: +1-201-489-1350
Rich.Leone@tevapharm.com sip:Rich.Leone@tevapharm.com www.tevapharm.com

Reference ID: 3468027

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA:	091028
APPLICANT:	Teva Pharmaceuticals USA
DRUG PRODUCT:	Omega-3-Acid Ethyl Esters Capsules, 1 g

The Division of Bioequivalence I (DBI) has completed its review of your submission(s) acknowledged on the cover sheet and has identified the following deficiencies.

The *in vitro* quantitative capsule rupture testing (QCRT) method used for the purpose of confirming bioequivalence (BE) of the test product is inadequate for the reasons listed below. Please note that these deficiencies are the same as those identified for the QCRT method used for the regulatory release and stability testing purpose, as the two methods are identical for the current ANDA.

1. With respect to the Quantitative Capsule Rupture Testing (QCRT) and *in vitro* bioequivalence (BE) studies submitted on December 30, 2013, you have referenced two different analytical methods. Specifically, the analytical method used in your method validation (Project ID O013; Code: 2000040) differs from that used in the QCRT [Report No. QDP0060815] and in the *in vitro* BE testing (POPV_0313_0791, POPV_0313_0852, POPV_0313_0853, POPV_0313_0892, POPV_0313_0891), as follows:

   Analytical method used in your method validation (Project ID O013; Code: 2000040):

   Column:

   Detection:
   Flow Rate:
   Injection Volume:
   Column Temperature:
   Run Time:

   (b) (4)

   Analytical method used in your quantitative capsule rupture testing (QCRT) using USP Apparatus II (paddles) or USP apparatus IV [Report No. QDP0060815] and in the *in vitro* bioequivalence (BE) testing (POPV_0313_0791, POPV_0313_0852, POPV_0313_0853, POPV_0313_0892, POPV_0313_0891):

Column:

(b) (4)

Detection:
Flow Rate:
Injection Volume:
Column Temperature:
Auto sampler Temperature:
Run Time (Apparatus II):
Run Time (Apparatus IV):

Please clearly identify which instrument conditions were used during the QCRT testing [Report No. QDP0060815] and the *in vitro* BE testing. If the method used in these studies differs from that already validated, then please provide additional validation as necessary. Also, please provide your Standard Operating Procedure (SOP) for each of the above methods as well as for the method validation procedure.

2. In your QCRT testing [Report No. QDP0060815] and In vitro BE testing submitted December 30, 2013, you submitted data reflecting the sum of Eicosapentaenoic Acid Ethyl Ester (EPA) + Docosahexaenoic Acid Ethyl Ester (DHA) release. Please submit the release data from the referenced studies for each individual component rather than for the sum of the two components. Please submit the data from 12 individual dosage units of the Test and Reference products from the referenced studies. In addition, please submit all mean data, range, %CV, and the dates of these studies in eCTD format (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120957.pdf). Finally, please submit the temperature and humidity at which the test and reference product lots were stored between manufacture of the test product (or acquisition of the reference product) and the time of the aforementioned studies.

3. You did not provide your Standard Operating Procedures (SOPs) for the QCR testing and *in vitro* BE studies. Please submit these documents/information.

4. You have used sinkers in study #s QDP0068549, QDP0069171, QDP0068622, QDP0068624, QDP0060815, and study # POPV_0313_0791. Please provide the following information for the sinkers: 1) a detailed description of the sinker used in the dissolution method (including a diagram, dimensions and manufacturing information) and 2) confirmation that the sinker is consistent with those described in USP Chapter <711> with respect to composition and dimensions.

Please note that Deficiency #s 1 and 2 above have been changed from those issued in the Easily Correctible Deficiency (ECD) letter dated 2/7/2014. In addition, please note that Deficiency #s 3 and 4 are new deficiencies that were not issued in the above-mentioned ECD letter. We communicate the above deficiencies in the current letter since you did not respond to the 2/7/2014 ECD letter within 10 business days.

Please also note that the bioequivalence comments provided in this communication are comprehensive as of issuance. These comments are subject to revision if additional concerns by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

I. Outcome Page

ANDA: 091028

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
21797	12/30/2013	Other	Study Amendment	1	1
				Bean Total:	1

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LI GONG
03/10/2014

UTPAL M MUNSHI
03/10/2014

HOAINHON N CARAMENICO
03/10/2014

DALE P CONNER
03/10/2014

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	091028
Drug Product Name	Omega-3-Acid Ethyl Esters Capsules
Strength (s)	1 g
Applicant Name	Teva Pharmaceuticals USA
Applicant Address	425 Privet Road Horsham, PA 19044
US Agent Name and the mailing address	Scott D. Tomsky VP US Generics Regulatory Affairs
US Agent's Telephone Number	(215) 591-3142; email: scott.tomsky@tevapharm.com
US Agent's Fax Number	(215) 591-8812
Original Submission Date(s)	November 10, 2008
Submission Date(s) of Amendment(s) Under Review	December 30, 2013 (Dissolution amendment) February 7, 2014 (ECD telephone request)
First Generic	No
Reviewer	Li Gong, Ph.D.
OVERALL DISSOLUTION REVIEW RESULT	**INADEQUATE**

Study Site(s) Information

Study Number (s)	**2008-1779**	**2008-1829**
Study Type (s)	Fasting and Fed Studies (RLD only)	Fed Study (Test and RLD)
Strength(s)	1 g	1 g
Clinical Site	Pharma Medica Research Inc.	Allied Research International (Formerly Cetero Research)
Clinical Site Address	4770 Sheppard Avenue East Toronto, Ontario, Canada M1S 3V6	1405 NW 167th Street Miami Gardens, Florida 33169
OSI Inspection Status of Clinical Site	**N/A** (*In vitro* BE study option only)	
Analytical Site	(b) (4)	
Analytical Address		
OSI Inspection Status of Analytical Site	**N/A** (*In vitro* BE study option only)	

I. EXECUTIVE SUMMARY

The Division of Bioequivalence 1 (DBI) previously reviewed the dissolution testing data [see DARRTS for ANDA 091028 of GONG, LI 12/14/2013 N/A 12/14/2013 REV-BIOEQ-21(Primary Review) Original-1 Archive]. Two deficiencies were identified and issued to the firm:

- Based on the quantitative capsule rupture testing (QCRT) data previously submitted, the firm was advised to modify its proposed dissolution method by using (b) (4) paddle speeds and/or lower surfactant (e.g. Labrasol) concentration, with USP Apparatus Type 2 or alternatively Type 4, and submit its new testing data to be evaluated.

- The DBI will evaluate the method development and optimization data as well as the complete data of the test and reference products obtained for 12 units per product, based on the most appropriate procedure, and determine the most suitable QCRT method and specification for its test product.

In the current amendment, the firm submitted its response to the above deficiencies for its proposed test drug product, Omega-3-Acid Ethyl Esters Capsules, 1.0 gram. The firm provided results of currently modified *in vitro* QCRT, along with its details of the method development report which included the data for method optimization. However, the firm's responses to the deficiencies are considered **incomplete** (inadequate) and an Easily-Correctable-Deficiency (ECD) telephone request[1] was issued to the firm for the related items specified as follows:

- The firm was asked to provide clarifications about two different analytical instrumental conditions used in the respective QCRT and bioequivalence (BE) testing.
- In addition, the firm was asked to submit results of individual component of Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) release for the above-mentioned testing, rather than providing sum of EPA + DHA data.
- The firm was also advised to submit eCTD-formatted dissolution data summary tables for the above studies, and provide the temperature and humidity at which the test and reference product lots were stored.

Since the firm has not responded to the above deficiency comments in the DBI's ECD request within 10 business days, these aforementioned bio deficiencies will be incorporated into the Office of Generic Drugs' (OGD's) COMPLETE RESPONSE LETTER to be communicated to the firm (please refer to Section V Appendix V.1 Email Communications among the Bio-, Regulatory Project Managers and Reviewers, of this review for details). Based on this and an additional deficiency regarding the sinkers used in the testing, the firm's *in vitro* quantitative capsule rupture testing is still considered **inadequate**.

[1] DARRTS for ANDA 091028 COR-ECD-01(Easily Correctable Bioequivalence Deficiency) Original-1 Archive; Final/Submit Date: 02/07/2014.

Reference ID: 3465662

The DBI will review the firm's fasting and fed study amendment in a separate bioequivalence review document.

II. BACKGROUND INFORMATION

On November 10, 2008, the firm conducted a comparative non-quantitative capsule rupture testing on its test product, Omega-3-Acid Ethyl Esters Capsules, 1.0 gram, and the reference-listed drug (RLD), GlaxoSmithkline's Lovaza® (Omega-3-Acid Ethyl Esters) Capsules, 1.0 gram, respectively. The data were generated per USP <2040> Rupture Test for Soft Gelatin Capsules (500 mL of water using Apparatus II (paddle) at 50 rpm, by visual determination of capsule ruptures). The *in vitro* testing was found **i**ncomplete. The DBI sent two deficiencies to the firm as follows:

1) Development of its own quantitative capsule rupture method which should be discriminating to detect potential differences between the test and the reference products;[2] and 2) Submission of long term storage stability (LTSS) data of free eicosapentaenoic acid and free docosahexaenoic acid in frozen plasma to cover the maximum storage time of the study samples for free eicosapentaenoic acid and free docosahexaenoic acid assay.

On October 1, 2009, the firm submitted a subsequent dissolution amendment[3] in response to the deficiency letter dated May 6, 2009. The firm had provided results of a then newly developed QCRT, which was found non-discriminatory QCRT profiles between the test and reference product, pending the firm's modification of the then-current QCRT method.[4]

December 30, 2013, the firm submitted the latest amendment in response to the Office of Generic Drugs' (OGD's) "Complete Response Letter" of August 13, 2013, which included QCRT deficiencies.[5] The firm addressed these deficiencies identified by the DBI.

However, on February 7, 2014, due to incomplete submission of the QCRT and *in vitro* BE study documentation/data as well as eCTD-formatted data summary tables (see

[2] DARRTS, ANDA 091028, COR-ANDADE-01(Bio Incomplete Deficiencies) Original-1 Archive; Submit/Final Date: 05/06/2009.
[3] DARRTS, ANDA 091028, Supporting Document #8 Quality/Quality Information; Bioequivalence/Response to Information Request, Original-1 View EDR; Submit/Final Date: 10/01/2009.
[4] DARRTS, ANDA 091028, REV-BIOEQ-01(General Review) Original-1 Archive; Submit/Final Date: 12/14/2012.
[5] DARRTS, ANDA 091028, COR-ANDAACTION-09(Complete Response) Original-1 Archive; Submit/Final Date: 08/13/2013.

Reference ID: 3465662

comments in Section I Executive Summary of this review for details), the DBI issued an ECD telephone request to the firm.[6]

APPEARS THIS WAY ON ORIGINAL

[6] DARRTS, ANDA 091028, COR-ECD-01(Easily Correctable Bioequivalence Deficiency) Original-1 Archive; Submit/Final Date: 02/07/2014.

Reference ID: 3465662

II. TABLE CONTENTS

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Reference ID: 3465662

III. DISSOLUTION AMENDMENT REVIEW

A. Checklist

Information	YES	NO	N/A
Is there a posted dissolution method on the FDA website?	☐	☒	☐
Did the firm use the above method?	☐	☐	☒
Is there a USP dissolution method?	☐	☒	☐
Did the firm use the USP dissolution method?	☐	☐	☒
Did the firm use 12 units of both test and reference in dissolution testing?	☒	☐	☐
***Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)?**	☒	☐	☐
Did the firm conduct dissolution testing with its own proposed method?	☒	☐	☐

**Note*: The firm did not submit data on Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) as each individual % drug release, and instead, the combined sum of EPA + DHA data were provided. The firm will be asked to resubmit the respective EPA and DHA data rather than that of sum of values of % drug release.

B. Additional Information

Dissolution Method #	Dissolution Method Number not provided
Deaeration/ degassing of the medium (Yes/No,)	No
Filter Description (if used in dissolution testing)	None
Sinker Description (if used in dissolution testing)	(b) (4) Helix Coil Type or equivalent which can hold the capsule freely.
Mesh Size Description (if basket used in dissolution testing)	N/A
Sampling (manual/Auto/fiber optics)	Not provided
CoA of Test Product (location in the submission)	Module 3.2.P.5.4
CoA of Reference Product (location in the submission)	Not provided (only batch expiration dates included)

C. Dissolution Method As Posted on the FDA Website (if any)

N/A

D. USP Method (if any)

N/A

E. Validation of Analytical Method Used in the Dissolution Studies:

Reference ID: 3465662

Analytical Method: HPLC

HPLC Parameters Used in Firm's Method Validation using 8% Labrasol as medium with USP Apparatus II*	
Mobile phase:	(b) (4)
Column:	
Flow rate:	
Wavelength:	
Injection volume:	
Column temperature:	
Run time:	

HPLC Parameters Used in Firm's QCRT Quantitation Method using (b) (4) as medium with USP Apparatus II*	
Mobile phase:	(b) (4)
Column:	
Flow rate:	
Wavelength:	
Injection volume:	
Column temperature:	
Auto sampler temperature	
Run time:	

Note: there are some slight differences between the above two analytical methods and the firm will be asked to provide clarification(s) for these differences and submit all relevant data as well as supporting documents if necessary in response to DBI's Easily Correctable Deficiency (ECD) Telephone Request.[5]

Reviewer's Note: The information in the table below has been verified by the reviewer based on the results presented in the method validation report [also please refer to Section V Appendix (4) of this review for details). The firm has validated the QCRT method of "8% Labrasol as medium with USP Apparatus II", as follows:

Analytical Method Validation Report # and Date	Project ID O013; Code: 2000040 [Date not provided; also please refer to Section V Appendix (4) of this review for details]
Submission of SOP for Method Validation (Yes/No, Effective Date)	SOP not provided
Address of Method Validation Site	Teva Pharmaceuticals USA Pharmaceutical Research & Development 223 Quaker Road, Box 2900 Pomona, NY 10970
Address of Dissolution Testing Site	Same as above

Reference ID: 3465662

Submission of Dissolution Method Transfer Report (if the dissolution testing site is different from the method validation site) (Yes/No, Location of the Report)	N/A (dissolution testing and method validation were conducted at the same site; for detailed address, also refer to Module 3, Section 3.2.P.5 Control of Drug Product; page 221)
Analytes	Eicosapentaenoic Acid Ethyl Ester (EPA) Docosahexaenoic Acid Ethyl Ester (DHA)
Method Description	HPLC

(b) (4)

[redacted]

Reference ID: 3465662

Following this page, 3 Pages Withheld in Full as (b)(4)

Additional analytical method validation for modified release dosage forms (for multimedia or biphasic dissolution testing). N/A

F. Review of Dissolution (QCRT) Amendment

Deficiency No. 01 (Bio Deficiency No. 6 in OGD's Complete Response Letter):
The quantitative capsule rupture (QCR) testing conducted using your proposed method, in 900 mL of 10% Labrasol in 0.1N HCl using USP Apparatus 2 (Paddle) with (b) (4) *rpm at 37°C ± 0.5°C, is not sufficiently discriminatory, based on the release profile submitted for your test product, Omega-3-Acid Ethyl Esters Capsules, 1 g, comparing it with the reference product, GlaxoSmithKline's Lovaza® Capsules, 1 g.*
Based on the QCR data submitted by you for your test product, the DBI suggests you modify your proposed method by using (b) (4) *paddle speeds such as 50 rpm, 75 rpm and 100 rpm, and/or lower Labrasol concentration, as follows:*

Medium:	*Labrasol in 0.1N HCl at 1%, 2%, 5%, 8%, 10% etc.*
Apparatus:	*USP Apparatus 2 (Paddle)*
Speed:	***50**, **75** and **100** rpm*
Volume:	*900 mL*
Temperature:	*37°C ± 0.5°C*
Sampling times:	*5, 10, 15, 30, 45, and 60 minutes until at least 80% of the drug is released from the dosage form.*

Please be advised that for USP Apparatus 2, when used for this dosage form, the sampling probes should remain immersed in the dissolution medium throughout the duration of testing in order to obtain reproducible results. The use of a sinker with USP Apparatus 2 may be considered in preventing the capsules from floating to the top.

Alternatively, you may consider using different surfactants and/or the USP Apparatus 4 (flow-through cell) as suggested in the draft guidance.

Firm's Response to Deficiency No. 01:
"As requested, further analytical work was performed on the proposed quantitative rupture test method. The following reports detail the studies that were performed:

- Module 3.2.P.5.6 Special Study Dissolution Profile Report for Omega-3 Ethyl Esters Capsules 1 g (QDP0069171) details the *in vitro* performance of the drug product in the dissolution conditions suggested by the Agency. Various paddle speeds and surfactant concentrations were evaluated using a design of experiments (DOE). Outcomes of the study are summarized below:

a) In general, low surfactant concentrations and low paddle speeds resulted in high variability and low release from the drug product. These conditions were therefore deemed inappropriate for Omega- 3 Acid Ethyl Esters Capsules.

b) Based on the data, *8% Labrasol in 0.1N HCl at 100 rpm* was considered to be the most discriminative for a quantitative rupture test for Teva's product.

Reference ID: 3465662

c) Since this is a soft gel product and subject to cross-linking, the selected media (8% Labrasol in 0.1N HCl) at 100 rpm was further evaluated in the presence of enzyme, Pepsin, with maximum allowable quantity, 750,000 Units/L. Similar results were obtained for both Teva's product and RLD for this Tier II method.

d) The dissolution test using 8% Labrasol in 0.1N HCl at 100 rpm provided consistent results for the capsules tested and more than (b) (4)% release was observed for all capsules within (b) (4) minutes.

- Module 3.2.P.5.3 Analytical Method Validation Report for Dissolution Test (Apparatus II) for Omega-3-Acid Ethyl Ester Capsules, 1 gram (QDP0068549) details the validation of the proposed Tier I and Tier II dissolution methods using the Dissolution Medium 8% Labrasol in 0.1 N HCl at 100 rpm utilizing Apparatus II, as discussed in (QDP0069171).

- Module 3.2.P.5.6 Omega-3-Acid Ethyl Ester Capsules, 1 gram Comparative Dissolution Profile (Tier I Dissolution Medium) (QDP0068622) details the comparative dissolution profile of the test product and RLD in Tier 1 dissolution conditions without enzyme (pepsin).

- Module 3.2.P.5.6 Omega-3-Acid Ethyl Ester Capsules, 1 gram Comparative Dissolution Profile (Tier II Dissolution Medium) (QDP0068624) details the comparative dissolution profile of the test product and RLD in Tier 2 dissolution conditions with enzyme (pepsin).

- Module 3.2.P.5.6 Summary of *In Vitro* Evaluation of Teva's Omega-3-Acid Ethyl Esters Capsules and RLD, LOVAZA® Capsules for Establishing Bioequivalence (QDP0060815) details the use of USP apparatus 4 and USP apparatus 2 using (b) (4) (b) (4) as surfactant.

In summary, we believe we have developed a discriminating method for evaluating Teva's product against the RLD, and that this method demonstrates that the test product is equivalent to the RLD. It is our recommendation that the USP apparatus 2 method with Labrasol (as discussed in QDP0069171) be deemed appropriate for performing the Quantitative Capsule Rupture test, however we await DBIs final determination.

Reviewer's Comments on the Firm's Response to Deficiency No. 01

- In previous submission dated October 1, 2009, the firm had developed its own QCRT method [900 mL of 10% Labrasol in 0.1N HCl using USP Apparatus 2 (paddle) with rotation speed of (b) (4) rpm at 37°C ± 0.5°C] and also provided results of then developed QCRT. The DBI found these drug release results not sufficiently discriminatory. The firm was advised then to continue to modify its own QCRT method using (b) (4) paddle speeds (e.g. 50 rpm, 75 rpm and 100 rpm), and/or lower surfactant (e.g. Labrasol in 0.1 N HCl at 1%, 2%, 5%, 8% and 10% of concentrations)

per the current individual drug product draft Guidance for Omega-3-Acid Ethyl Esters Capsules.[7]

- In the current amendment, as recommended by the DBI, the firm has continued to explore and modified the existing QCRT. The firm evaluated three different QCRT methods: USP II using Labrasol as surfactant, USP IV using (b) (4) as surfactant, and USP II using (b) (4) as surfactant. The complete method optimization reports are found in Module 3.2.P.5 of the firm's submission dated 12/30/2013.

- First, the firm used varying concentrations of surfactant, Labrasol (e.g. 1% to 10% of Labrasol) and rotation speeds of Apparatus II (e.g. 50 to 100 rpm) in order to optimize the then current QCRT per DBI's recommendation, based on the following 12 experiments:

Study #	**Paddle Speed (RPM)**	**Surfactant Level (%)**
1	(b) (4)	
2		
3		
4		
5		
6		
7		
8		
9		
10		
11	100	8% Labrasol in 0.1 N HCl with Pepsin (750,000 units/L)
12	100	8% Labrasol in 0.1 N HCl with Pepsin (750,000 units/L), using 17-month-old Test lot (Lot #30200001A)

The firm concluded that inclusion of 8% Labrasol, speed of 100 rpm and two tiers of testing (e.g. in the presence and absence of an enzyme, Pepsin) would be the optimum method studied settings, with the results as follows **(all data are expressed as the combined release of EPA(g) and DHA(g) divided by 1 g of omega-3 x 100):**

[7] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM320011.pdf; recommended September 2012.

Results of the Dissolution Profile for Teva's Omega-3-acid Ethyl Ester Capsules, 1 gram, using 8% Labrasol and USP Apparatus II without Pepsin

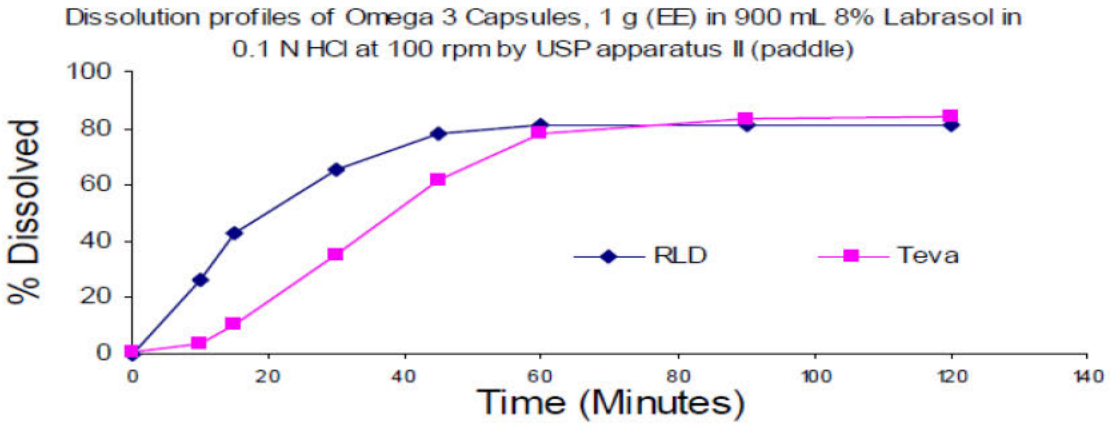
Omega-3-acid Ethyl Ester Capsules, 1 gram Batch Number 150000584 Manufactured by Banner Pharmacap on behalf of TEVA Pharmaceuticals							
Tablet #	% Dissolved						
	10 minutes	15 minutes	30 minutes	45 minutes	60 minutes	90 minutes	120 minutes
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	4	11	35	62	78	84	84
Min	(b) (4)						
Max							
% RSD	38.4	26.6	38.5	28.5	10.8	1.5	1.8
Dates of testing	10/17/2013 and 10/21/2013						

Results of the Dissolution Profile for Lovaza® (Omega-3-acid Ethyl Ester) Capsules, 1 gram, using 8% Labrasol and USP Apparatus II without Pepsin

Lovaza® (Omega-3-acid Ethyl Esters) Capsules, 1 gram LOT 3ZP1602, EXP 4/2017 manufactured by Catalent Pharma Solutions and marketed by GlaxoSmithKline							
Tablet #	% Dissolved						
	10 minutes	15 minutes	30 minutes	45 minutes	60 minutes	90 minutes	120 minutes
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							

Mean	**27**	**43**	**65**	**79**	**81**	**81**	**81**
Min	(b) (4)						
Max							
% RSD	**52.7**	**45.5**	**20.4**	**5.6**	**0.0**	**0.0**	**0.5**
Dates of testing	**10/17/2013**						

Figure 1. Dissolution Profile of Batch Number 150000584 Manufactured by Banner Pharmacap on behalf of TEVA Pharmaceuticals VS Lovaza® (Omega-3-acid Ethyl Esters) Capsules, 1 gram LOT 3ZP1602, EXP 4/2017 manufactured by Catalent Pharma Solutions and marketed by GlaxoSmithKline



Reference: POPV_1013_4449, Title: Teva-RLD_NoPepsin8%labrasol in 0.1 N HCl_PV_Comparative_102813.xls

Results of the Dissolution Profile for Teva's Omega-3-acid Ethyl Ester Capsules, 1 gram, using 8% Labrasol and USP Apparatus II with Pepsin

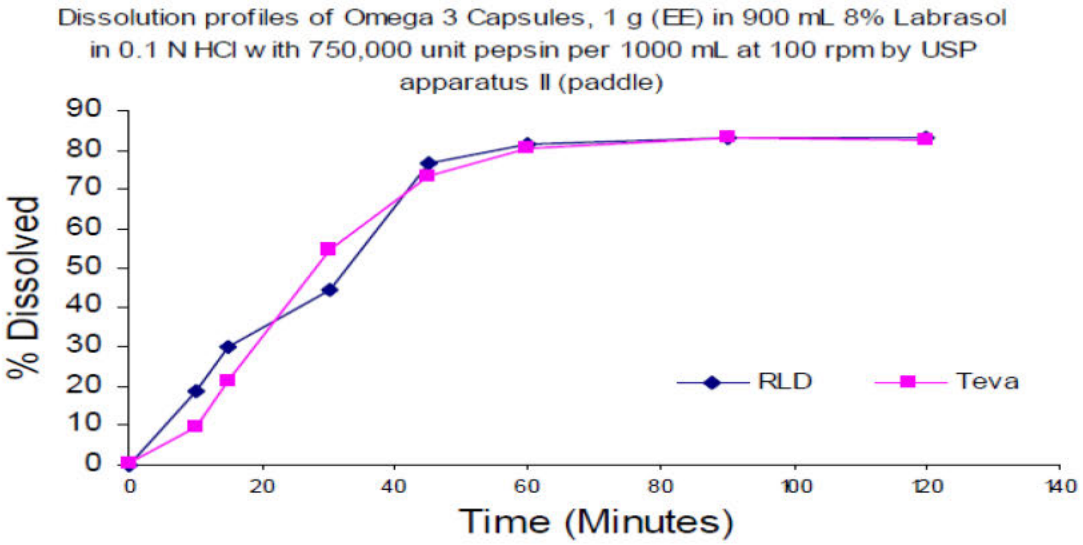
Omega-3-acid Ethyl Ester Capsules, 1 gram Batch Number 150000584 Manufactured by Banner Pharmacap on behalf of **TEVA Pharmaceuticals**							
Tablet #	**% Dissolved**						
	10 minutes	**15 minutes**	**30 minutes**	**45 minutes**	**60 minutes**	**90 minutes**	**120 minutes**
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							

12	(b) (4)						
Mean	**10**	**21**	**55**	**74**	**81**	**83**	**83**
Min	(b) (4)						
Max							
% RSD	**70.4**	**53.8**	**39.9**	**17.2**	**7.8**	**2.1**	**2.1**
Dates of testing	**10/18/2013, 10/21/2013 and 10/23/2013**						

Results of the Dissolution Profile for Lovaza® (Omega-3-acid Ethyl Ester) Capsules, 1 gram, using 8% Labrasol and USP Apparatus II with Pepsin

Lovaza® (Omega-3-acid Ethyl Esters) Capsules, 1 gram LOT 3ZP1602, EXP 4/2017 manufactured by Catalent Pharma Solutions and marketed by GlaxoSmithKline							
Tablet #	**% Dissolved**						
	10 minutes	**15 minutes**	**30 minutes**	**45 minutes**	**60 minutes**	**90 minutes**	**120 minutes**
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	**19**	**30**	**45**	**77**	**81**	**83**	**83**
Min	(b) (4)						
Max							
% RSD	**29.3**	**22.5**	**37.3**	**13.1**	**5.2**	**0.7**	**1.0**
Dates of testing	**10/18/2013**						

Figure 1. Dissolution Profile of Batch Number 150000584 Manufactured by Banner Pharmacap on behalf of TEVA Pharmaceuticals VS Lovaza® (Omega-3-acid Ethyl Esters) Capsules, 1 gram LOT 3ZP1602, EXP 4/2017 manufactured by Catalent Pharma Solutions and marketed by GlaxoSmithKline



Reference: POPV_1013_4488, Title: Teva_RLD_Pepsin8%labrasol in 0.1 N HCl_PV_Comparative_102813.xls

- Second, the firm further explored lower concentrations of another surfactant, (b) (4) (b) (4) paddle speeds of 50, 75, and 100 rpm, respectively, different pHs in the dissolution medium, lower volume of the medium (e.g. 500 mL) as well as (b) (4) using USP Apparatus II (paddle) per the Guidance above, based on the following 14 experiments (please also refer to Module 3.2.P.5 of the firm's submission dated 12/30/2013, for details):

(b) (4)

(b) (4)

- After optimization of the dissolution conditions, the firm submitted the new results of the above mentioned QCRT using USP Type II (paddle) Apparatus, for the test and reference products as shown in the following tables, with the conclusion, that is, *"Teva has conducted a thorough investigation into possible variations of Quantitative rupture tests using both USP Apparatus IV* (see reviewer's comment below) *and USP Apparatus II. Suitable methods on each apparatus were developed and optimized. The resultant dissolution data presented herein from the various studies demonstrates that a method using USP Apparatus II* (b) (4)

Reference ID: 3465662

Following this page, 7 Pages Withheld in Full as (b)(4)

Firm's In Vitro BE study Data Summary Table, using 8% Labrasol and USP Apparatus II (paddles) in the absence of Pepsin (constructed by this reviewer):

(All data are expressed as the combined release of EPA(g) and DHA(g) divided by 1 g of omega-3 x 100):

Dissolution Conditions	**Apparatus:**	II (Paddle)
	Speed of Rotation:	100 rpm
	Medium:	8% Labrasol in 0.1 N HCl
	Volume:	900 mL
	Temperature:	37 ± 0.5 °C
Firm's Proposed Specification	None	
Dissolution Testing Site (Name, Address)	Teva Pharmaceuticals USA Pharmaceutical Research & Development, 223 Quaker Road, Box 2900, Pomona, NY 10970	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**							**Study Report Location**
						10	**15**	**30**	**45**	**60**	**90**	**120**	
POPV_10 13_4449	10/17/2013 & 10/21/2013	Test Product: Omega-3-Acid Ethyl Esters Capsules Bulk Lot# 150000401 Packaging Lot # 150000584 (Mfg. 04/03/2012)	1 g Capsule	12	Mean	4	11	35	62	78	84	84	See Omega-3-Acid Ethyl Ester Capsules, 1 gram Comparative Dissolution Profile (Tier I Dissolution Medium)
					Range	(b) (4)							
					% CV	38.4	26.6	38.5	28.5	10.8	1.5	1.8	
POPV_10 13_4449	10/17/2013	Reference Product: LOVAZA® Capsules Lot # 3ZP1602 (Exp.04/2017)	1 g Capsule	12	Mean	27	43	65	79	81	81	81	
					Range	(b) (4)							
					% CV	8.6	5.3	3.6	2.5	0.0	0.0	0.5	

Firm's In Vitro BE study Data Summary Table, using 8% Labrasol and USP Apparatus II (paddles) in the presence of Pepsin (constructed by this reviewer):

Dissolution Conditions	**Apparatus:**	II (Paddle)
	Speed of Rotation:	100 rpm
	Medium:	8% Labrasol in 0.1 N HCl in the presence of Pepsin with maximum allowable quantity, 750,000 Units/L
	Volume:	900 mL
	Temperature:	37 ± 0.5 °C
Firm's Proposed Specification	None	
Dissolution Testing Site (Name, Address)	Teva Pharmaceuticals USA Pharmaceutical Research & Development, 223 Quaker Road, Box 2900, Pomona, NY 10970	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**							**Study Report Location**
						10	**15**	**30**	**45**	**60**	**90**	**120**	
POPV_1013_4488	10/18/2013; 10/21/2013 & 10/23/2013	Test Product: Omega-3-Acid Ethyl Esters Capsules Bulk Lot# 150000401 Packaging Lot # 150000584 (Mfg. 04/03/2012)	1 g Capsule	12	Mean	10	21	55	74	81	83	83	See Omega-3-Acid Ethyl Ester Capsules, 1 gram Comparative Dissolution Profile (Tier II Dissolution Medium)
					Range	(b) (4)							
					% CV	70.4	53.8	39.9	17.2	7.8	2.1	2.1	
POPV_1013_4488	10/18/2013	Reference Product: LOVAZA® Capsules Lot # 3ZP1602 (Exp.04/2017)	1 g Capsule	12	Mean	19	30	45	77	81	83	83	
					Range	(b) (4)							
					% CV	29.3	22.5	37.3	13.1	5.2	0.7	1.0	

Reference ID: 3465662

Firm's In Vitro BE study Data Summary Table, using [redacted] and USP Apparatus II (paddles) (constructed by this reviewer):

Dissolution Conditions	**Apparatus:**	II (Paddle)
	Speed of Rotation:	[redacted]
	Medium:	[redacted]
	Volume:	900 mL
	Temperature:	37 ± 0.5 °C
Firm's Proposed Specification	None	
Dissolution Testing Site (Name, Address)	Teva Pharmaceuticals USA Pharmaceutical Research & Development, 223 Quaker Road, Box 2900, Pomona, NY 10970	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**							**Study Report Location**
						15	**30**	**45**	**60**	**90**	**120**	**135**	
POPV_0313_0791	Not provided	Test Product: Omega-3-Acid Ethyl Esters Capsules Bulk Lot# 150000401 Packaging Lot # 30200001A (Mfg. 04/03/2012)	1 g Capsule	12	Mean	54	68	73	76	79	79	79	See Summary of In-Vitro Evaluation Bio-Equivalency Report QDP0060815s
					Range	[redacted]							
					% CV	7.7	4.7	4.5	4.1	3.2	3.2	3.0	
POPV_0313_0791	Not provided	Reference Product: LOVAZA® Capsules Lot # 2ZP1263 (Exp.10/2015)	1 g Capsule	12	Mean	60	72	77	80	82	83	83	
					Range	[redacted]							
					% CV	8.6	5.3	3.6	2.5	1.2	1.1	1.1	

Reference ID: 3465662

Firm's In Vitro BE study Data Summary Table, using [redacted] (b) (4) and USP Apparatus IV (flow-through cell)
(constructed by this reviewer):

Dissolution Conditions	**Apparatus:**	IV (Flow-through cell)
	Flow rate:	[redacted] (b) (4)
	Medium:	[redacted] (b) (4)
	Volume:	900 mL
	Temperature:	37 ± 0.5 °C
Firm's Proposed Specification	None	
Dissolution Testing Site (Name, Address)	Teva Pharmaceuticals USA Pharmaceutical Research & Development, 223 Quaker Road, Box 2900, Pomona, NY 10970	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference –**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**								**Study Report Location**
						10	**20**	**30**	**40**	**50**	**60**	**90**	**120**	
POPV_0313_0852 ; POPV_0313_0891	Not provided	Test Product: Omega-3-Acid Ethyl Esters Capsules Bulk Lot# 150000401 Packaging Lot # 30200001A (Mfg. 04/03/2012)	1 g Capsule	12	Mean	12	53	70	75	77	78	80	80	See Summary of In-Vitro Evaluation Bio-Equivalency Report QDP2.00060815
					Range	[redacted] (b) (4)								
					% CV	67.0	33.7	22.2	15.7	11.3	8.8	5.9	6.3	
POPV_0313_0853 ; POPV_0313_0892	Not provided	Reference Product: LOVAZA® Capsules Lot # 2ZP1263 (Exp.10/2015)	1 g Capsule	12	Mean	25	59	69	72	74	78	81	81	
					Range	[redacted] (b) (4)								
					% CV	63.2	42.6	31.8	25.0	18.9	10.8	2.6	2.0	

Reference ID: 3465662

- The DBI has recommended similar dissolution (QCRT) methods for two other ANDAs[8,9] with the same drug product, as shown in the following:

  Method #1 under ANDA 091018 (the firm then acknowledged the DBI-recommended method but later reformulated its test product):

  1) Medium: Water + 5% Triton X-100 with 1% pancreatin
     Apparatus; USP apparatus 2 (paddle)
     Speed: 75 rpm
     Volume: 900 mL
     Temperature: 37°C ± 0.5°C
     Specification: NLT (b)(4)% (Q) of EPA and DHA is dissolved in 60 minutes.

  Method #2 under ANDA (b) (4) :

  2) (b) (4)

  (b) (4) compared to the current proposed test method using USP Apparatus II (paddles) under the ANDA 091028.

- Despite the extensive development work conducted by the firm using three different types of methods, the ultimate acceptability of the firm's optimization studies and the selection of a quality control QCRT method is pending the firm's submission of data for EPA and DHA separately. (See email communications among the firm, regulatory and bio-project managers and the reviewers in Section V of this review for details).

- As per the comments above, the firm's response to Deficiency No. 1 is considered inadequate.

Deficiency No. 02 (Bio Deficiency No. 7 in OGD's Complete Response Letter):
The DBI will evaluate the method development and optimization data as well as the complete data of the test and reference products obtained for 12 units per product, based

[8] DARRTS for ANDA 091018, REV-BIOEQ-02(Dissolution Review); Submit/Final Date: 08/11/2010.
[9] (b) (4)

on the most appropriate procedure, and determine the most suitable QCR method and specification for your test product.

Firm's Response to Deficiency No. 02:
"As indicated in Bio response # 1, summary reports of the analytical work performed have been provided for your evaluation, and we acknowledge that DBI will determine the method that is most suitable."

Reviewer's Comments on Firm's Response to Deficiency No. 02:

- As per comments above, although the firm has submitted the new results of the currently modified QCRT testing and *in vitro* BE study, along with its method development reports using the respective USP apparatus II (paddle) and IV (flow-through cell) per the current Guidance[10], the new results were not given as separate EPA and DHA measurements. The DBI will evaluate the complete data and make recommendations on the most suitable QCRT method and specification for the test product upon the receipt of the firm's responses to the aforementioned ECD request, originally dated 2/7/2014. As of 2/28/2014, the DBI has not received firm's responses to the aforementioned deficiency comments in the ECD request (longer than 10 business days). Therefore, these deficiencies will be incorporated into the OGD's COMPLETE RESPONSE LETTER to be communicated to the firm at a later date.

- As a result, the firm's response to Deficiency No. 2 is also inadequate.

G. Deficiency Comments for Dissolution (QCRT) Testing

1. With respect to the Quantitative Capsule Rupture Testing (QCRT) and in vitro bioequivalence (BE) studies submitted on December 30, 2013, the firm has referenced two different analytical methods. Specifically, the analytical method used in its method validation (Project ID O013; Code: 2000040) differs from that used in the QCRT [Report No. QDP0060815] and in the in vitro BE testing (POPV_0313_0791), as follows:

   Analytical method used in the firm's method validation (Project ID O013; Code: 2000040):

   Detection:
   Flow Rate:
   Injection Volume:
   Column Temperature:
   Run Time:

   (b) (4)

[10] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM320011.pdf; recommended September 2012.

Reference ID: 3465662

Analytical method used in the firm's quantitative capsule rupture testing (QCRT) using USP Apparatus II (paddles) [Report No. QDP0060815] and in the in vitro bioequivalence (BE) testing (POPV_0313_0791):

Detection:	(b) (4)
Flow Rate:	
Injection Volume:	
Column Temperature:	
Auto sampler Temperature:	
Run Time:	

The firm is advised to clearly identify which instrument conditions were used during the QCRT testing [Report No. QDP0060815] and the in vitro BE testing (POPV_0313_0791). If the method used in these studies differs from that already validated, then the firm is asked to provide additional validation as necessary. Also, the firm is asked to provide its Standard Operating Procedure (SOP) for each of the above methods as well as for the method validation procedure.

2. In the firm's QCRT testing [Report No. QDP0060815] and *In vitro* BE testing (POPV_0313_0791)_submitted December 30, 2013, it submitted data reflecting the sum of Eicosapentaenoic Acid (EPA) + Docosahexaenoic Acid (DHA) release. The firm is asked to submit the release data from the referenced studies for each individual component rather than for the sum of the two components. The firm is also asked to submit the data from 12 individual dosage units of the Test and Reference products from the referenced studies. In addition, the firm is asked to submit all mean data, range, %CV, and the dates of these studies in eCTD format (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120957.pdf). Finally, the firm is asked to submit the temperature and humidity at which the test and reference product lots were stored between manufacture of the test product (or acquisition of the reference product) and the time of the aforementioned studies.

3. The firm did not provide the Standard Operating Procedures (SOPs) for its QCRT and *in vitro* BE studies. The firm will be asked to submit the necessary documentation of its methods.

4. The firm has used sinkers in its QCRT (with USP apparatus II) and in the *in vitro* BE testing (with USP apparatus II). The firm should provide the following information for the sinkers: 1) a detailed description of the sinker used in the dissolution method (including a diagram, dimensions and manufacturing information) and 2) confirmation that the sinker is consistent with those described in USP Chapter <711> with respect to composition and dimensions.

H. Dissolution Recommendations

The *in vitro* quantitative capsule rupture testing (dissolution testing) is **incomplete** (inadequate), due to the deficiency comments specified above.

IV. OSI INSPECTION STATUS

A. Clinical Site

Summarization of the OSI Inspection of Clinical Site							
Clinical Site Address:	N/A (*In Vitro* BE option)						
Application	**Inspected BE Study Type (In Vivo, In Vitro)**	**OSI Inspection date (EIR date)**	**Inspection Outcome (NAI, VAI, OAI)***	**Current ANDA clinical dates**	**Dates of clinical portion of inspected studies**	**Were the Current ANDA studies conducted within 2 years of the studies under/pending the OSI inspection?**	**Conclusion (Relevant, Irrelevant)**
N/A	-	-	-	-	-	-	-

*NAI: No Action Indicated; VAI: Voluntary Action Indicated; OAI: Official Action Indicated

B. Analytical Site

Summarization of the OSI Inspection of Analytical Site							
Analytical Site Address:	N/A (*In Vitro* BE option)						
Application	**Inspected BE Study Type (In Vivo, In Vitro)**	**OSI Inspection date (EIR date)**	**Inspection Outcome (NAI, VAI, OAI)***	**Current ANDA analytical dates**	**Dates of analytical portion of inspected studies**	**Were the Current ANDA studies conducted within 2 years of the studies under/pending the OSI inspection?**	**Conclusion (Relevant, Irrelevant)**
N/A	-	-	-	-	-	-	-

*NAI: No Action Indicated; VAI: Voluntary Action Indicated; OAI: Official Action Indicated

Reviewer's Comment:

The firm has chosen the *In Vitro* BE study option per the current Guidance for Omega-3-Acid Ethyl Ester Capsules[10]. Therefore, OSI inspections of the study sites for the in vivo BE studies submitted under the current ANDA 091028 are considered not necessary (please refer to Bio amendment review for details in a separate review document).

Clinical Site:

See comment above

Analytical Site:
See comment above

Reference ID: 3465662

V APPENDIX

V.1. DBI's Easily Correctable Deficiency (ECD) Telephone Request[11]

On February 7, 2014, DBI sent an ECD telephone request to the firm. The content of the ECD request is below. The email communication related to this request is also attached. The firm informed the RPM that it could not provide the requested information within 10 business days allowed for an ECD response. Therefore, DBI will communicate the same request, with an additional deficiency comment requesting clarification of the sinker used in the proposed method, in the deficiency letter of the current review.

(a) ECD Comments Sent on February 7, 2014:

1. With respect to the Quantitative Capsule Rupture Testing (QCRT) and in vitro bioequivalence (BE) studies submitted on December 30, 2013, you have referenced two different analytical methods. Specifically, the analytical method used in your method validation (Project ID O013; Code: 2000040) differs from that used in the QCRT [Report No. QDP0060815] and in the in vitro BE testing (POPV_0313_0791), as follows:

   Analytical method used in your method validation (Project ID O013; Code: 2000040):

   Detection:
   Flow Rate:
   Injection Volume:
   Column Temperature:
   Run Time:

   (b) (4)

   Analytical method used in your quantitative capsule rupture testing (QCRT) using USP Apparatus II (paddles) [Report No. QDP0060815] and in the in vitro bioequivalence (BE) testing (POPV_0313_0791):

   Detection:
   Flow Rate:
   Injection Volume:
   Column Temperature:
   Auto sampler Temperature:
   Run Time:

   (b) (4)

   Please clearly identify which instrument conditions were used during the QCRT testing [Report No. QDP0060815] and the in vitro BE testing (POPV_0313_0791).

[11] DARRTS for ANDA 091028 COR-ECD-01(Easily Correctable Bioequivalence Deficiency) Original-1 Archive; Final/Submit Date: 02/07/2014.

Reference ID: 3465662

If the method used in these studies differs from that already validated, then please provide additional validation as necessary. Also, please provide your Standard Operating Procedure (SOP) for each of the above methods as well as for the method validation procedure.

2. In your QCRT testing [Report No. QDP0060815] and In vitro BE testing (POPV_0313_0791) submitted December 30, 2013, you submitted data reflecting the sum of Eicosapentaenoic Acid (EPA) + Docosahexaenoic Acid (DHA) release. Please submit the release data from the referenced studies for each individual component rather than for the sum of the two components. Please submit the data from 12 individual dosage units of the Test and Reference products from the referenced studies. In addition, please submit all mean data, range, %CV, and the dates of these studies in eCTD format (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120957.pdf). Finally, please submit the temperature and humidity at which the test and reference product lots were stored between manufacture of the test product (or acquisition of the reference product) and the time of the aforementioned studies.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

(b) Email Communication Between Bio-PM, RPM, and DBI Related to the ECD Request:

(NOT TO BE RELEASED UNDER FOIA)

From: Yoon, Martin
Sent: Friday, February 21, 2014 1:05 PM
To: Nguyen, Hoainhon T; Munshi, Utpal; Gong, Li
Cc: Yoon, Martin
Subject: FW: ANDA 091028 - Omega-3-Acid Ethyl Esters Capsules USP, 1 gram - clarification requested on ECD

Hello All,

The firm has not responded back to Bio ECD within the 10 business days. Bio ECD was submitted 2/7/2014 and today is the 11th business day.

Li: Please proceed with completing your review so the Office can issue a CR.

Hoai: Please let us know if you have any questions or comments.

Thank you,
Martin

From: Olele, Chinyelum
Sent: Friday, February 21, 2014 11:41 AM
To: Yoon, Martin
Subject: RE: ANDA 091028 - Omega-3-Acid Ethyl Esters Capsules USP, 1 gram - clarification requested on ECD

Hi Martin,

No I did not, we have contacted the firm and told them not to respond to the ECD since it has passed the 10 days and instead we will issue a CR letter

Regards,

Chinyelum (Chi-Chi) Olele, PharmD
LCDR, United States Public Health Service
FDA, Office of Generic Drugs
Ph: 240-276-9778

From: Yoon, Martin
Sent: Friday, February 21, 2014 8:07 AM
To: Olele, Chinyelum
Subject: RE: ANDA 091028 - Omega-3-Acid Ethyl Esters Capsules USP, 1 gram - clarification requested on ECD

Reference ID: 3465662

Hi Chi-Chi,

Did you hear anything back from the firm on Bio ECD?

Thank you,
Martin

From: Nguyen, Hoainhon T
Sent: Friday, February 14, 2014 8:38 AM
To: Yoon, Martin; Munshi, Utpal; Gong, Li
Cc: Nguyen, Hoainhon T
Subject: RE: ANDA 091028 - Omega-3-Acid Ethyl Esters Capsules USP, 1 gram - clarification requested on ECD

Martin,
We would like the firm to submit release data for each component, EPA and DHA, separately as opposed to the sum of the components, for **all** DOE experiments of report QDP0060815 AND other reports provided in the ANDA 12/30/2013 amendment.
Thanks,
Hoai

From: Yoon, Martin
Sent: Friday, February 14, 2014 8:25 AM
To: Nguyen, Hoainhon T; Munshi, Utpal; Gong, Li
Cc: Yoon, Martin
Subject: FW: ANDA 091028 - Omega-3-Acid Ethyl Esters Capsules USP, 1 gram - clarification requested on ECD

Hello All,

The RPM has forward an inquiry from Teva requesting clarification regarding question 2 on Bio ECD submitted 2/7/2014.

Please advise how bio will like to respond.

Thank you,
Martin

From: Olele, Chinyelum
Sent: Thursday, February 13, 2014 10:20 AM
To: Yoon, Martin
Cc: Gaines, Robert
Subject: FW: ANDA 091028 - Omega-3-Acid Ethyl Esters Capsules USP, 1 gram - clarification requested on ECD

Hi Martin,

Reference ID: 3465662

Can you please forward this to your reviewer. The firm is seeking a response to clarify the ECD that they were issued. Thanks

Regards,

Chinyelum (Chi-Chi) Olele, PharmD
LCDR, United States Public Health Service
FDA, Office of Generic Drugs
Ph: 240-276-9778

From: Rich Leone [mailto:Rich.Leone@tevapharm.com]
Sent: Wednesday, February 12, 2014 10:55 AM
To: Olele, Chinyelum
Cc: Rich Leone; Jill Pastore; Scott Tomsky; Gaines, Robert
Subject: ANDA 091028 - Omega-3-Acid Ethyl Esters Capsules USP, 1 gram - clarification requested on ECD

Good Morning Dr. Olele,

Teva recently received an Easily Correctable Deficiency Letter for our pending ANDA 091028 - Omega-3-Acid Ethyl Esters Capsules USP, 1 gram (letter attached for your easy reference). We are seeking clarity from the Agency as we are processing the information request in order to submit a timely response. Specifically, question 2 requests that Teva provide release data for each component, EPA and DHA, separately as opposed to the sum of the components as had been submitted previously. We are seeking clarification to understand if the Agency is requesting information from the 2 reports (QDP0060815) containing the final sets of DOE experiments, i.e. the 12 unit data for both the test and reference products (Reference: POPV_0313_0791). Or is the Agency requesting the release data for each component, EPA and DHA, from all DOE experiments of report QDP0060815 AND other reports provided in our 12/30/2013 amendment. Please see the below list of reports that we have provided in our earlier amendment.

Reports Pertaining to Dissolution Submitted in Amendment Dated 12/30/2013:
QDP0060815: Summary of In Vitro Evaluation of Teva's Omega-3-Acid Ethyl Esters Capsules and RLD, LOVAZA® Capsules for Establishing Bioequivalence details the use of USP apparatus 4 and USP apparatus 2 using (b) (4) as surfactant.
QDP0069171: Special Study Dissolution Profile Report for Omega-3 Ethyl Esters Capsules 1 g
QDP0068549: Analytical Method Validation Report for Dissolution Test (Apparatus II) for Omega-3-Acid Ethyl Ester Capsules, 1 gram
QDP0068622: Omega-3-Acid Ethyl Ester Capsules, 1 gram Comparative Dissolution Profile (Tier I Dissolution Medium)
QDP0068624: Omega-3-Acid Ethyl Ester Capsules, 1 gram Comparative Dissolution Profile (Tier II Dissolution Medium)

Please contact me if you have any questions. We appreciate your timely feedback so we can adequately address the Agency's questions. Thank you.

Best regards,
Rich

Rich Leone Senior Director, Generics Regulatory Affairs
Tel: +1-201-930-2161 Cell: (b) (6) Fax: +1-201-489-1350
Rich.Leone@tevapharm.com sip:Rich.Leone@tevapharm.com www.tevapharm.com

DISSOLUTION DEFICIENCIES TO BE PROVIDED TO THE APPLICANT (BY BIO-PM)

ANDA:	091028
APPLICANT:	Teva Pharmaceuticals USA
DRUG PRODUCT:	Omega-3-Acid Ethyl Esters Capsules, 1 g

The Division of Bioequivalence I (DBI) has completed its review of the drug release testing portion of your submission acknowledged on the cover sheet. The following deficiencies have been identified:

1. With respect to the Quantitative Capsule Rupture Testing (QCRT) and *in vitro* bioequivalence (BE) studies submitted on December 30, 2013, you have referenced two different analytical methods. Specifically, the analytical method used in your method validation (Project ID O013; Code: 2000040) differs from that used in the QCRT [Report No. QDP0060815] and in the *in vitro* BE testing (POPV_0313_0791, POPV_0313_0852, POPV_0313_0853, POPV_0313_0892, POPV_0313_0891), as follows:

   Analytical method used in your method validation (Project ID O013; Code: 2000040):

   Column:

   Detection:
   Flow Rate:
   Injection Volume:
   Column Temperature:
   Run Time:

   (b) (4)

   Analytical method used in your quantitative capsule rupture testing (QCRT) using USP Apparatus II (paddles) or USP apparatus IV [Report No. QDP0060815] and in the *in vitro* bioequivalence (BE) testing (POPV_0313_0791, POPV_0313_0852, POPV_0313_0853, POPV_0313_0892, POPV_0313_0891):

   Column:

   Detection:
   Flow Rate:

   (b) (4)

Injection Volume:	(b) (4)
Column Temperature:	
Auto sampler Temperature:	
Run Time (Apparatus II):	
Run Time (Apparatus IV):	

Please clearly identify which instrument conditions were used during the QCRT testing [Report No. QDP0060815] and the *in vitro* BE testing. If the method used in these studies differs from that already validated, then please provide additional validation as necessary. Also, please provide your Standard Operating Procedure (SOP) for each of the above methods as well as for the method validation procedure.

2. In your QCRT testing [Report No. QDP0060815] and *in vitro* BE testing submitted December 30, 2013, you submitted data reflecting the sum of Eicosapentaenoic Acid Ethyl Ester (EPA) + Docosahexaenoic Acid Ethyl Ester (DHA) release. Please submit the release data from the referenced studies for each individual component rather than for the sum of the two components. Please submit the data from 12 individual dosage units of the Test and Reference products from the referenced studies. In addition, please submit all mean data, range, %CV, and the dates of these studies in eCTD format (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120957.pdf). Finally, please submit the temperature and humidity at which the test and reference product lots were stored between manufacture of the test product (or acquisition of the reference product) and the time of the aforementioned studies.

3. You did not provide your Standard Operating Procedures (SOPs) for the QCR methods and *in vitro* BE studies. Please submit the necessary documentation of your methods.

4. You have used sinkers in study #s QDP0068549, QDP0069171, QDP0068622, QDP0068624, QDP0060815, and study # POPV_0313_0791. Please provide the following information for the sinkers: 1) a detailed description of the sinker used in the dissolution method (including a diagram, dimensions and manufacturing information) and 2) confirmation that the sinker is consistent with those described in USP Chapter <711> with respect to composition and dimensions.

Please note that Deficiency #s 1 and 2 above have been changed from those issued in the Easily Correctible Deficiency (ECD) letter dated 2/7/2014. In addition, please note that Deficiency #s 3 and 4 are new deficiencies that were not issued in the above-mentioned ECD letter. We communicate the above deficiencies in the current letter since you did not respond to the 2/7/2014 ECD letter within 10 business days.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

VI. OUTCOME

ANDA: 091028

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
21765	12/30/2013	Dissolution Data (REGULAR)	Dissolution Amendment	1	1
				Bean Total:	1

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LI GONG
03/05/2014

UTPAL M MUNSHI
03/05/2014

HOAINHON N CARAMENICO
03/06/2014

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	091028	
Drug Product Name	Omega-3-Acid Ethyl Esters Capsules	
Strength(s)	1 g	
Applicant Name	Teva Pharmaceuticals USA	
Address	1090 Horsham Road PO BOX 1090 North Wales, PA 19454	
Applicant's Point of Contact	Jean W. Zwicker Senior Director Regulatory Affairs	
Contact's Telephone Number	(215) 591-8725	
Contact's Fax Number	(215) 591-8812	
Original Submission Date(s)	November 10, 2008	
First Generic	Yes	
Submission Date(s) of Amendment(s) Under Review	October 02, 2009 (Dissolution Amendment)	
Reviewer	Li Gong, Ph.D.	
Study Number (s)	2008-1779	2008-1829
Study Type (s)	Fasting and Fed study (RLD only)	Fed Study (Test and RLD)
Strength (s)	4 X 1 g	4 X 1 g
Clinical Site	Pharma Medica Research Inc.	Allied Research International (Formerly Cetero Research)
Clinical Site Address	4770 Sheppard Avenue East Toronto, Ontario, Canada M1S 3V6	1405 NW 167th Street Miami Gardens, Florida 33169
Analytical Site	(b) (4)	
Analytical Site Address		

OVERALL REVIEW RESULT	**INADEQUATE**		
WAIVER REQUEST RESULT	**N/A**		
OSI REPORT RESULT	**N/A**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1 & 8	**DISSOLUTION**	**1 gram**	**INADEQUATE**
1	**PILOT STUDY (FASTING AND FED)**	**1 gram**	**INADEQUATE**
1	**FED STUDY**	**1 gram**	**INADEQUATE**

Reference ID: 3227106

1 EXECUTIVE SUMMARY

This is a review of Teva Pharmaceuticals USA's Omega-3-Acid Ethyl Esters Capsules, 1 g, comparing it to the corresponding reference listed drug (RLD), Lovaza® (omega-3-acid ethyl esters) Capsules, 1 g. As per the current draft Individual Product Bioequivalence (BE) Guidance for Omega-3-Acid Ethyl Esters Capsules (recommended on September 2012, which is currently available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM320011.pdf), there are two bioequivalence (BE) study options:

- *In Vitro* Study Option
- *In Vivo* Study Option

In the original submission dated November 10, 2008, the firm submitted *in vitro* and *in vivo* study data in order to support its application.

***In Vitro* Study Option**

This "In Vitro Study Option" is based on the following two portions:

1. Whether the test product can be considered qualitatively (Q1) and quantitatively (Q2) the same as the RLD.

The firm submitted the data for the active pharmaceutical ingredient (API) of the test product per the current Guidance.[1] The Division of Bioequivalence I (DBI) considers that the firm's test product meets the criteria on the API and antioxidant as stated in the Guidance (please see Sections 4.3 & 4.7 of this review for details).

2. Whether the firm's *in vitro* dissolution testing is adequate.

The firm originally conducted a non-quantitative comparative capsule rupture testing using USP method for disintegration testing [see DARRTS for ANDA 091028 of REN, KE 05/04/2009 N/A 05/04/2009 REV-BIOEQ-02(Dissolution Review) Original-1 Archive] but the disintegration testing is not the current Division of Bioequivalence I (DBI)-recommended method. The DBI recommended the firm to develop a quantitative capsule rupture test to evaluate its *in vitro* performance of Omega-3-acid Ethyl Esters Capsules. As per the dissolution amendment dated 10/02/2009 (currently under review), the firm developed its own quantitative capsule rupture testing (dissolution testing) for the test product. However, the firm's dissolution testing data was not sufficiently discriminatory for its test product and thus the DBI will ask the firm to continue to develop dissolution testing method per the current Guidance. The DBI will evaluate and determine the most suitable dissolution method for the firm's test product and the

[1] DARRTS, ANDA 091028 Quality/Response To Information Request Original-1 View EDR; Submit/Final Date: 10/28/2011

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dissolution specification will be recommended upon reviewing its resubmitted complete dissolution testing data. Thus, the firm's *in vitro* dissolution testing is still **incomplete** (inadequate).

Therefore, the above "In Vitro Study Option" of the application is **inadequate** (incomplete).

In addition, the firm will be asked to provide its quantitative amount of each component of the Soft Gelatin Capsule Shell and White Printing Ink (b) (4) (b) (4) per capsule in the test formulation.

In Vivo Study Option

This "In Vivo Study Option" recommends a **fasting** and a **fed** BE study.

This application originally contains the results of a pilot study (under fasting and fed states) and a fed bioequivalence (BE) study (pivotal study) comparing a test product, Omega-3-Acid Ethyl Esters Capsules, 1 g, to the corresponding reference listed drug (RLD), Lovaza® (omega-3-acid ethyl esters) Capsules, 1 g. Each of these studies was designed as a single-dose, two-way crossover study in healthy male and female subjects. The results of the firm's fed BE study (pivotal study) are summarized in the tables below.

Eicosapentaenoic Acid (EPA; Free fatty acids)

Baseline Adjusted **Omega-3-acid ethyl esters Capsules, 4 x 1 g** **Fed Bioequivalence Study No. 2008-1829, N=80 (Male=32 and Female=48)** **Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals**					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	5.14	5.41	0.95	90.25	99.94
Cmax (ng/mL)	0.81	0.87	0.92	84.58	100.67

EPA (Total lipids)

Baseline Adjusted **Omega-3-acid ethyl esters Capsules, 4 x 1 g** **Fed Bioequivalence Study No. 2008-1829, N=80 (Male=32 and Female=48)** **Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals**					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (µg·hr/mL)	947.89	959.67	0.99	94.23	103.53
Cmax (µg /mL)	72.68	75.44	0.96	90.56	102.49

Docosahexaenoic Acid (DHA; Free fatty acids)

Baseline Adjusted Omega-3-acid ethyl esters Capsules, 4 x 1 g Fed Bioequivalence Study No. 2008-1829, N=80 (Male=32 and Female=48) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	12.369	12.688	0.97	90.76	104.71
Cmax (ng/mL)	2.364	2.515	0.94	85.27	103.56

DHA (Total lipids)

Baseline Adjusted Omega-3-acid ethyl esters Capsules, 4 x 1 g Fed Bioequivalence Study No. 2008-1829, N=80 (Male=32 and Female=48) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (µg ·hr/mL)	290.59	290.30	1.00	88.92	112.68
Cmax (µg /mL)	44.06	44.86	0.98	89.87	107.36

However, the firm's pilot and pivotal fed BE studies are **not acceptable** (inadequate) per the current Guidance. According to the current BE guidance for Omega-3-Acid Ethyl Esters Capsules posted on September 2012, the 90% confidence intervals (CIs) for bioequivalence (BE) of fed study are based on: (1) EPA ethyl esters and (2) DHA ethyl esters. In addition, a fasting BE study is recommended and its 90% CIs for BE are based on: (1) baseline-adjusted EPA total lipids and (2) baseline-adjusted DHA total lipids. Hence, the firm will be asked to conduct both new fasting and fed BE studies if they wish to pursue the *in vivo* study option per the Guidance.

Therefore, the above "In Vivo BE Study Option" of the application is also **inadequate** (incomplete).

No Office of Scientific Investigations (OSI) inspections are pending or necessary.

Thus, the application is **inadequate** (incomplete) with deficiencies.

Note: The Regulatory Project Manager should be informed that the deficiencies to be issues to the firm are located on pages 292-294 of this review.

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3 SUBMISSION SUMMARY

3.1 Drug Product Information[2]

Test Product	Omega-3-Acid Ethyl Esters Capsules, 1g
Reference Product	Lovaza® (Omega-3-Acid Ethyl Esters) Capsules, 1 g
RLD Manufacturer	GlaxoSmithKline
NDA No.	021654
RLD Approval Date	November 10, 2004
Indication	Lovaza® (omega-3-acid ethyl esters), a lipid-regulating agent, is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia.

3.2 PK/PD Information[3,7]

Bioavailability	Omega-3 fatty acids appear to be well-absorbed from the oral route whether they are administered from dietary fish, capsule supplements, or in microencapsulated fish-oil-enriched foods. In healthy volunteers and in patients with hypertriglyceridemia, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) were absorbed when administered as ethyl esters orally. Omega-3-acids administered as ethyl esters (LOVAZA) induced significant, dose-dependent increases in serum phospholipid EPA content, though increases in DHA content were less marked and not dose-dependent when administered as ethyl esters.
Food Effect	Omega-3 fatty acids may be taken with or without food.[4]
Tmax	Data not available
Metabolism[7]	The metabolic fate of Omega-3 fatty acids after oral absorption includes formation into eicosanoids (prostaglandins, leukotrienes, lipoxins, etc.), esterification and hydrolysis from tissue glycerolipids, and elongation and desaturation to a variety of polyunsaturated fatty acids (PUFAs).
Excretion[7]	Fatty acids are eliminated primarily by oxidative catabolism to carbon dioxide and water; small quantities are lost when skin and digestive cells are sloughed.
Half-life	Data not available
Drug Specific Issues (if any)	**Usage Considerations:** Patients should be placed on an appropriate lipid-lowering diet before receiving Lovaza® and should continue this diet during treatment with Lovaza®.

[2] Orange Book Online (2012): http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=021654&TABLE1=OB_Rx; last accessed date: 11/21/2012.

[3] Lovaza® label: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=413f4274-9ccf-4708-9be8-9435e7a19a60; last accessed date: 11/21/2012.

[4] Clinical Pharmacology Online: http://www.clinicalpharmacology-ip.com/Forms/Monograph/monograph.aspx?cpnum=2722&sec=monphar; last accessed date: 11/21/2012.

	Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal before instituting Lovaza® therapy. Every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (such as beta blockers, thiazides, estrogens) should be discontinued or changed if possible prior to consideration of triglyceride-lowering drug therapy. **Limitations of Use:** The effect of Lovaza® on cardiovascular mortality and morbidity in patients with elevated triglycerides has not been determined.

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	One, *In Vitro* Study or two, *In Vivo* Studies (fasting and fed)

In Vitro Study Option

1.	**Type of study:**	In vitro
	Design:	In vitro quantitative capsule rupture test
	Strength:	1 g
	Subjects:	N/A
	Additional Comments:	Providing the recommendations on active pharmaceutical ingredient (API) in Appendix 1 and the recommendations on antioxidant in Appendix 2 are both met (refer to Section 4.8 Additional Attachments of this review for details), the capsule fills of the Test and Reference drug products are considered very similar, and BE may be established based solely on an in vitro method (Quantitative Capsule Rupture Test described below) that assures equivalent release of API from the capsules. **Quantitative Capsule Rupture Test** A quantitative capsule rupture test method should measure the release of eicosapentaenoic acid ethyl ester (EPAee) and docosahexaenoic acid ethyl ester (DHAee) in an aqueous testing medium. In order to obtain an accurate release profile, the test samples should be taken at early times (e.g., 5, 10, 15, 20, 25 minutes) and as frequently as possible, until at least 80% of the drugs are released from the capsules. The method should demonstrate sufficient discrimination for detection of potential differences between formulations, with acceptable variability. Based on the information available to the Agency, as well as the recommendation given in the USP Pharm Forum[5], USP Apparatus 4

[5] Marques MRC, Cole E et al., Stimuli to the Revision Process: Liquid-filled Gelatin Capsules. *USP Pharm Forum 2009;35(4, July-Aug)1029-41.*

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		(flow-through cell) has been shown to be the most appropriate apparatus for drugs with poor solubility, compared with the conventional USP Apparatus 1 (basket) and Apparatus 2 (paddle). In addition, the use of surfactant is also critical in the *in vitro* drug release method development for an Omega-3-Acid Ethyl Esters Capsule drug product. The firm should develop the *in vitro* drug release method for the drug product using USP Apparatus 4 (flow-through cell). A second method using USP Apparatus 2 (paddle) may be developed in conjunction with the method using USP Apparatus 4 for comparison, if desired. The data from USP Apparatus 4, and from USP Apparatus 2 (if conducted), should be submitted to the Division of Bioequivalence for evaluation and for determination of the most suitable method. The firm should provide all dissolution method development data showing that the dissolution method(s) studied have been systematically optimized for (but not limited to) the following parameters: 1. Dissolution medium and volume 2. Surfactant and concentration 3. Filter type and size for sample collection and preparation, where applicable 4. Enzyme and concentration, where applicable 5. Rotation speed (USP Apparatus 2 (paddle)) 6. Flow rate (USP Apparatus 4 (flow-through cell) Other parameters for USP Apparatus 4: 7. System mode (closed versus open) 8. Type of cell (size in mm) 9. Glass beads (size in mm) 10. Glass bead loading (weight in gm) 11. Sample load (volume in mL) 12. Split ratio (%) 13. Size of sample tube (volume in mL) For each parameter, at least 5 values, in addition to zero value, around the selected final value should be tested in the optimization. The optimization data should demonstrate that the selected value is optimal and appropriate. For example, in order to select the final drug release medium of 0.5% Sodium Lauryl Sulfate (SLS), data from testing using the media of 0%, 0.25%, 0.35%, 0.65% and 0.75% SLS should also be submitted for comparison. In addition, other scientific justifications and evidence may be submitted to support the choices of the final parameter values. Optimizing testing should employ 6 dosage units for each determination. For final testing using the optimized method, 12 dosage units each of the test and reference products should be employed.

[6] USP *Revision Bulletin* Official August 1, 2011 <2040> Disintegration and Dissolution of Dietary Supplements.

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		NOTE: It is critical that for USP Apparatus 4, when used for lipid-filled soft gelatin capsule (SGC) dosage forms, a modified flow-through cell designed for SGC[6] be used in the testing. For USP Apparatus 2, when used for this dosage form, the sampling probes should remain immersed in the dissolution medium throughout the duration of testing in order to obtain reproducible results. The use of a sinker with USP Apparatus 2 may be considered in preventing the capsules from floating to the top.

In Vivo Study Option

1.	**Type of study:**	Fasting
	Design:	Single-dose, partial or fully replicated crossover *in-vivo*
	Strength:	1 g [contains at least 900 mg of the ethyl esters of Omega-3 fatty acids (Dose: 4×1 gram capsules)
	Subjects:	Healthy males and nonpregnant females, general population
	Additional Comments:	(1) In using the reference-scaled average bioequivalence approach for Omega-3-Acid Ethyl Esters capsules, please provide evidence of high variability in the bioequivalence parameters of AUC and/or Cmax (i.e., within-subject variability ≥ 30%). For details on the method for statistical analysis using the reference-scaled average bioequivalence approach, please refer to the draft Progesterone Oral Capsule Guidance at http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM320011.pdf. (2) We recommend that the applicant control the subjects' diet from at least 48 hr prior to till at least 36 hr after drug administration. We recommend EPA and DHA limited meals throughout the diet control period. (3) We recommend that baseline measures be calculated from an average of three or more (>3) samples collected between 24 and 0 hours (inclusive) prior to dosing.

2.	**Type of study:**	Fed
	Design:	Single-dose, partial or fully replicated crossover *in-vivo*
	Strength:	1 g [contains at least 900 mg of the ethyl esters of Omega-3 fatty acids (Dose: 4×1 gram capsules)]
	Subjects:	Healthy males and nonpregnant females, general population
	Additional Comments:	We recommend a high-fat, high-calorie, EPA and DHA-limited test meal for fed BE study. Please also see comments in the study above.

Analytes to measure (in plasma/serum/blood):	**Fasting study:** (1) EPA total lipids in plasma (2) Baseline-adjusted EPA total lipids in plasma (3) DHA total lipids in plasma (4) Baseline-adjusted DHA total lipids in plasma (5) EPA free fatty acids in plasma (6) Baseline-adjusted EPA free fatty acids in plasma (7) DHA free fatty acids in plasma (8) Baseline-adjusted DHA free fatty acids in plasma **Fed study:** (1) EPA ethyl esters in plasma (2) DHA ethyl esters in plasma (3) EPA total lipids in plasma (4) Baseline-adjusted EPA total lipids in plasma (5) DHA total lipids in plasma (6) Baseline-adjusted DHA total lipids in plasma (7) EPA free fatty acids in plasma (8) Baseline-adjusted EPA free fatty acids in plasma (9) DHA free fatty acids in plasma (10) Baseline-adjusted DHA free fatty acids in plasma
Bioequivalence based on:	**Fasting study (90%CI):** (1) Baseline-adjusted EPA total lipids (2) Baseline-adjusted DHA total lipids Please submit the data of baseline-adjusted EPA and DHA free fatty acids and the statistical analysis using the reference-scaled average bioequivalence approach as supportive evidence. **Fed study (90%CI):** (1) EPA ethyl esters (2) DHA ethyl esters Please submit the data of baseline-adjusted EPA and DHA total lipids and baseline-adjusted EPA and DHA free fatty acids, and the statistical analysis using the reference-scaled bioequivalence approach as supportive evidence.
Waiver request of in-vivo testing:	N/A

Source of most recent recommendations:	Please see Draft Guidance for Omega-3-Acid Ethyl Esters Capsules in the following FDA website (recommended on September, 2012): http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM320011.pdf
Summary of OGD or DBE History (for details, see Appendix Error! Reference source not found.**):**	**ANDAs:** According to the Electronic Orange Book there is no approved ANDA for this particular drug product on the market.[7] **Controls:** There were several control documents for this particular product including "Open" or "Closed" status. Please see the following site for details: Internal Control Correspondence Database: (b) (4) Last accessed: 11/21/2012. **Protocols:** Four protocols were found (b) (4); last accessed: 11/21/2012) as follows: Protocol # 11-039 (b) (4) Protocol # 10-059 Protocol # 10-056 Protocol # 08-063

[7] Online-Orange Book (2012): http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm; Search Term: Ethyl Esters; last accessed: 10/19/2012.

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3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting & fed (Pilot)	Yes	1
Single-dose fed (Pivotal)	Yes	1
Steady-state	No	--
In vitro dissolution	Yes	1 (reviewed in a previous dissolution review)
Waiver requests	No	--
BCS Waivers	No	--
Clinical Endpoints	No	--
Failed Studies	No	--
Amendments	Yes	1 (dissolution amendment)

3.5 Pre-Study Bioanalytical Method Validation

Free eicosapentaenoic acid and free docosahexaenoic acid

Information Requested	Data
Bioanalytical method validation report location	Pages 1-220
Analytes	Free eicosapentaenoic acid and free docosahexaenoic acid
Internal standard (IS)	(b) (4)
Method description	Protein precipitation; liquid chromatographic (LC) tandem mass spectrometric detection (MSMS) method
Limit of quantitation	10.0 ng/mL
Average recovery of Free EPA (%) QC A, QC B and QC C:	131.9 % to 140.0 %
Average recovery of Free EPA (%) QC E, QC F and QC G:	96.3 % to 107.4 %
Average recovery of Free DHA (%) QC A, QC B and QC C:	130.2 % to 135.8 %
Average recovery of Free DHA (%) QC E, QC F and QC G:	95.4 % to 103.3 %
Average recovery of IS (%)	124.1 %
Standard curve concentrations (units/mL)	10.00, 20.00, 50.00, 125.0, 350.0, 750.0, 1500, 3000 and 5000 ng/mL
QC concentrations (units/mL)	30.00 ng/mL (QC A), 400.0 ng/mL (QC B), 4000 ng/mL (QC C) for both EPA and DHA. 175 (QC E), 1952 ng/mL (QC F) and 3583 ng/mL (QC G) for EPA 669 (QC E), 1816 ng/mL (QC F) and 3668 ng/mL (QC G) for DHA
QC Intraday precision range (%)	2.5 to 8.1 % for EPA
QC Intraday accuracy range (%)	86.9 to 111.5 % for EPA
QC Intraday precision range (%)	2.5 to 8.7 % for DHA
QC Intraday accuracy range (%)	94.2 to 111.6 % for DHA
QC Interday precision range (%)	2.1 to 5.7 % for EPA
QC Interday accuracy range (%)	98.9 to 106.5 %. for EPA
QC Interday precision range (%)	2.4 to 6.0 % for DHA
QC Interday accuracy range (%)	100.3 to 106.5 % for DHA
Bench-top stability (hrs)	6.25 hours @ room temperature
Stock stability (days)	123 days @ -25°C± 10°C for both free eicosapentaenoic acid and free docosahexaenoic acid
Processed stability (hrs)	56.50 hours @ approximately 5°C
Freeze-thaw stability (cycles)	6 cycles @ -70°C± 10°C
Long-term storage stability (days)	183 days @ -70°C± 10°C for both free eicosapentaenoic acid and free docosahexaenoic acid
Dilution integrity	Concentration diluted 2-fold and 5-fold
Selectivity	Selectivity was not established due to endogenous levels.

Reference ID: 3227106

Eicosapentaenoic acid and docosahexaenoic acid (Total lipids)

Information Requested	Data
Bioanalytical method validation report location	Pages 1-220
Analytes	Eicosapentaenoic acid and docosahexaenoic acid
Internal standard (IS)	(b) (4)
Method description	Protein precipitation; liquid chromatographic (LC) tandem mass spectrometric detection (MSMS) method
Limit of quantitation	1.00 µg/mL
Average recovery of EPA (%)	102.8 % to 116.1 %
Average recovery of DHA (%)	91.4 % to 111.0 %
Average recovery of IS (%)	92.5 %
Standard curve concentrations (units/mL)	1.00, 2.00, 5.00, 10.0, 25.0, 50.0, 100 and 150 µg/mL
QC concentrations (units/mL)	3.00 µg/mL (QC A), 20.0 µg/mL (QC B), 120 µg/mL (QC C) for both EPA and DHA. 6.12 µg/mL (QC E), 63.1 µg/mL (QC F) and 99.3 µg/mL (QC G) for EPA 25.8 µg/mL (QC E), 56.7 µg/mL (QC F) and 91.9 µg/mL (QC G) for DHA
QC Intraday precision range (%)	3.5 to 5.8 % for EPA
QC Intraday accuracy range (%)	90.6 to 107.5 % for EPA
QC Intraday precision range (%)	3.3 to 5.6 % for DHA
QC Intraday accuracy range (%)	90.1 to 107.5 % for DHA
QC Interday precision range (%)	2.7 to 4.2 % for EPA
QC Interday accuracy range (%)	96.5 to 104.2 %. for EPA
QC Interday precision range (%)	2.9 to 4.9 % for DHA
QC Interday accuracy range (%)	98.1 to 103.3 % for DHA
Bench-top stability (hrs)	5.00 hours @ room temperature
Stock stability (days)	123 days @ -25°C± 10°C for both eicosapentaenoic acid and docosahexaenoic acid
Processed stability (hrs)	57.00 hours @ approximately 5°C
Freeze-thaw stability (cycles)	5 cycles @ -70°C± 10°C
Long-term storage stability (days)	183 days @ -70°C± 10°C for both eicosapentaenoic acid and docosahexaenoic acid
Dilution integrity	Concentration diluted 2-fold and 5-fold
Selectivity	Selectivity was not established due to endogenous levels.

SOPs submitted	YES
Was the % recovery consistent across QC concentrations?	YES
Is the same anticoagulant used in the pre-method validation study used in the sample assay?	YES (K_2EDTA)
If not, was cross validation study conducted?	N/A
Was the dilution factor adequate for the current study sample analysis?	YES
Was the same dilution medium (plasma/solvent) used during validation and sample analysis?	YES

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Does the duration of the each of the stability parameters support the sample preparation and assay dates	YES
Was the pre-study validation of the bioanalytical method used for the pivotal bioequivalence studies acceptable?	YES

Comments on the Pre-Study Method Validation:

- The firm submitted the long-term storage stability (LTSS) data of free eicosapentaenoic acid (EPA), free docoshexaenoic acid (DHA), total EPA and total DHA in human plasma containing ethylenediaminetetraacetic acid dipotassium salt (K_2EDTA) as the anticoagulant, in a dissolution amendment dated October 01, 2009 [see DARRTS for ANDA 091028 Supporting Document #8 Bioequivalence/Responses to Information Request; Submit/Final Date:10/01/2009). The data demonstrated that free and total EPAs and DHAs, are stable after storage at -70°C ±10°C for 183 days.

- The LTSS data of 183 days for the respective free EPA & DHA and total EPA & DHA exceeds the maximum duration of storage of the pilot (104 days for free EPA & DHA and 80 days for total lipid EPA & DHA, respectively) and fed (56 days for free EPA & DHA and 42 days for total lipid EPA & DHA, respectively) BE study samples.

- The anticoagulant used in the pre-study validation was K_2EDTA salt form, and was the same as used in within study sample analysis.

- According to the firm's pre-study validation, the average recovery for the free EPA (QC A, B and C: 131.9 % to 140.0 %) and DHA (QC A, B and C: 130.2 % to 135.8 %) and that of Internal Standard [IS (b) (4) 124.1%] are very high. The firm will be asked to provide explanation(s) about such high values of average recovery of the analyte and its internal standard.

- Therefore, the pre-study validation data are **incomplete**.

3.6 In Vivo Studies

Table 1.1 Summary of all in vivo Pilot Study

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (CV%)			Study Report Location
					Cmax (µg/mL)	Tmax (hr)	AUC0-t (µg*h/mL)	
Eicosapentaenolic acid (free fatty acids)								
2008-1779	A Single-Dose, Pharmacokinetic Study of Lovaza™ 1000 mg Capsules Under Fasting and Fed Conditions	Randomized single-dose crossover	Lovaza™, 1000 mg, Capsules p.o. [Lot # 7HG0158]	6 completing (3M/3F) Healthy subjects 41 (29-47)	0.096 (72) 1.235 (32)	3.00 (1.00-9.00) 5.00 (4.00-8.00) Median (Range)	0.501 (85) 6.393 (41)	M5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fasting-fed-study-2008-1779\synopsis.pdf
Docosahexaenoic acid (free fatty acids)								
2008-1779	A Single-Dose, Pharmacokinetic Study of Lovaza™ 1000 mg Capsules Under Fasting and Fed Conditions	Randomized single-dose crossover	Lovaza™, 1000 mg, Capsules p.o. [Lot # 7HG0158]	6 completing (3M/3F) Healthy subjects 41 (29-47)	0.550 (42) 4.266 (35)	3.00 (1.00-9.00) 5.00 (4.00-8.00) Median (Range)	2.530 (66) 13.927 (40)	M5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fasting-fed-study-2008-1779\synopsis.pdf

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Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (CV%)			Study Report Location
					Cmax (µg/mL)	Tmax (hr)	AUC0-t (µg*h/mL)	
Eicosapentaenolic acid (total lipids)								
2008-1779	A Single-Dose, Pharmacokinetic Study of Lovaza™ 1000 mg Capsules Under Fasting and Fed Conditions	Randomized single-dose crossover	Lovaza™, 1000 mg, Capsules p.o. [Lot # 7HG0158]	6 completing (3M/3F) Healthy subjects 41 (29-47)	5.22 (59) 73.64 (11)	8.50 (7.00-36.00) 7.00 (4.00-10.00) Median (Range)	73.27 (104) 1022.86 (34)	M5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fasting-fed-study-2008-1779\synopsis.pdf
Docosahexaenoic acid (total lipids)								
2008-1779	A Single-Dose, Pharmacokinetic Study of Lovaza™ 1000 mg Capsules Under Fasting and Fed Conditions	Randomized single-dose crossover	Lovaza™, 1000 mg, Capsules p.o. [Lot # 7HG0158]	6 completing (3M/3F) Healthy subjects 41 (29-47)	8.46 (43) 50.53 (12)	6.50 (3.00-10.00) 6.50 (4.00-10.00) Median (Range)	65.67 (91) 348.99 (33)	M5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fasting-fed-study-2008-1779\synopsis.pdf

Table 1.2 Summary of all in vivo Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (CV%)			Study Report Location
					Cmax (µg/mL)	Tmax (hr)	AUC0-t (µg*h/mL)	
Eicosapentaenoic acid (free fatty acids)								
2008-1829/ M1FX08001	A Relative Bioavailability Study of 1000 mg Omega-3-Acid Ethyl Esters Capsules Versus 1000 mg Lovaza™ Capsules Under Fed Conditions	Randomized single-dose crossover	Omega-3 Acid Ethyl Esters, 1000 mg, Capsules p.o. [Lot # P080602–B2] Lovaza™, 1000 mg, Capsules p.o. [Lot # 7HH0014]	80 completing (32=M/48=F) Healthy subjects mean age (range)=46	0.896 (41) 0.940 (39)	6.00 (3.00-12.12) 6.00 (3.00-12.00) Median (Range)	5.438 (30) 5.589 (25)	M5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fed-study-2008-1829\ synopsis.pdf
Docosahexaenoic acid (free fatty acids)								
2008-1829/ M1FX08001	A Relative Bioavailability Study of 1000 mg Omega-3-Acid Ethyl Esters Capsules Versus 1000 mg Lovaza™ Capsules Under Fed Conditions	Randomized single-dose crossover	Omega-3 Acid Ethyl Esters, 1000 mg, Capsules p.o. [Lot # P080602–B2] Lovaza™, 1000 mg, Capsules p.o. [Lot # 7HH0014]	80 completing (32=M/48=F) Healthy subjects mean age (range)=46	2.659 (41) 2.686 (35)	6.00 (0.00-12.12) 6.00 (4.00-10.00) Median (Range)	13.375 (33) 13.193 (27)	M5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fed-study-2008-1829\ synopsis.pdf

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Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (CV%)			Study Report Location
					Cmax (µg/mL)	Tmax (hr)	AUC0-t (µg*h/mL)	
Eicosapentaenoic acid (total lipids)								
2008-1829/ M1FX08001	A Relative Bioavailability Study of 1000 mg Omega-3-Acid Ethyl Esters Capsules Versus 1000 mg Lovaza™ Capsules Under Fed Conditions	Randomized single-dose crossover	Omega-3 Acid Ethyl Esters, 1000 mg, Capsules p.o. [Lot # P080602–B2] Lovaza™, 1000 mg, Capsules p.o. [Lot # 7HH0014]	80 completing (32=M/48=F) Healthy subjects mean age (range)=46	80.07 (50) 81.70 (41)	6.00 (3.00-14.00) 6.00 (5.00-12.00) Median (Range)	1001.79 (39) 1006.43 (38)	M5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fed-study-2008-1829\ synopsis.pdf
Docosahexaenoic acid (total lipids)								
2008-1829/ M1FX08001	A Relative Bioavailability Study of 1000 mg Omega-3-Acid Ethyl Esters Capsules Versus 1000 mg Lovaza™ Capsules Under Fed Conditions	Randomized single-dose crossover	Omega-3 Acid Ethyl Esters, 1000 mg, Capsules p.o. [Lot # P080602–B2] Lovaza™, 1000 mg, Capsules p.o. [Lot # 7HH0014]	80 completing (32=M/48=F) Healthy subjects mean age (range)=46	54.10 (66) 52.28 (54)	5.00 (3.00-14.00) 5.54 (5.00-12.00) Median (Range)	389.37 (81) 363.78 (77)	M5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fed-study-2008-1829\ synopsis.pdf

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Baseline Adjusted **Omega-3-acid ethyl esters Capsules, 4 x 1 g** **Fed Bioequivalence Study No. 2008-1829, N=80 (Male=32 and Female=48)** **Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals**					
Eicosapentaenoic acid (free fatty acids)					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	5.14	5.41	0.95	90.25	99.94
Cmax (ng/mL)	0.81	0.87	0.92	84.58	100.67

Baseline Adjusted **Omega-3-acid ethyl esters Capsules, 4 x 1 g** **Fed Bioequivalence Study No. 2008-1829, N=80 (Male=32 and Female=48)** **Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals**					
Eicosapentaenoic acid (total lipids)					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (µg·hr/mL)	947.89	959.67	0.99	94.23	103.53
Cmax (µg /mL)	72.68	75.44	0.96	90.56	102.49

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Baseline Adjusted
Omega-3-acid ethyl esters Capsules, 4 x 1 g
Fed Bioequivalence Study No. 2008-1829, N=80 (Male=32 and Female=48)
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals

Docosahexaenoic acid (free fatty acids)					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	12.369	12.688	0.97	90.76	104.71
Cmax (ng/mL)	2.364	2.515	0.94	85.27	103.56

Baseline Adjusted
Omega-3-acid ethyl esters Capsules, 4 x 1 g
Fed Bioequivalence Study No. 2008-1829, N=80 (Male=32 and Female=48)
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals

Docosahexaenoic acid (total lipids)					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (µg·hr/mL)	290.59	290.30	1.00	88.92	112.68
Cmax (µg /mL)	44.06	44.86	0.98	89.87	107.36

Table 3. Reanalysis of Study Samples

Pilot Study (Study No. 2008-1779)

Study No. 2008-1779 Additional information, 16.5 Analytical Report Pages 23-33								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Docosahexaenoic Acid (Total Lipids)								
Pharmacokinetic[1]	0	0	0	0	0	0	0	0
AULOQ	0	4	0	3.17	0	4	0	3.17
Total	**0**	**4**	**0**	**3.17**	**0**	**4**	**0**	**3.17**
Docosahexaenoic Acid (Free Fatty Acids)								
Pharmacokinetic[1]	0	0	0	0	0	0	0	0
AULOQ	0	4	0	3.17	0	4	0	3.17
UISR	0	1	0	0.79	0	1	0	0.79
Total	**0**	**5**	**0**	**3.97**	**0**	**5**	**0**	**3.97**

1 - If no repeats were performed for pharmacokinetic reasons, insert "0.0."
AULOQ: Above the Upper Limit of Quantitation
UISR: Unacceptable Internal Standard Response.
Note: there were no study sample repeats for free Study No. 2008-1779).

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Fed BE Study (Study No. 2008-1829)

Study No. 2008-1829 Additional information, 16.5 Analytical Report Pages 47-119								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Eicosapentaenoic Acid (Total Lipids)								
Pharmacokinetic[1]	4	5	0.15	0.18	0	1	0	0.04
AULOQ	16	11	0.59	0.40	16	11	0.59	0.40
EE	3	2	0.11	0.07	3	2	0.11	0.07
UISR	41	27	1.51	0.99	41	27	1.51	0.99
Total	**64**	**45**	**2.35**	**1.65**	**60**	**41**	**2.21**	**1.51**
Docosahexaenoic Acid (Total Lipids)								
Pharmacokinetic[1]	7	3	0.26	0.11	2	1	0.07	0.04
AULOQ	30	23	1.10	0.85	30	23	1.10	0.85
EE	3	2	0.11	0.07	3	2	0.11	0.07
UISR	41	27	1.51	0.99	41	27	1.51	0.99
Total	**81**	**55**	**2.98**	**2.02**	**76**	**53**	**2.79**	**1.95**
Eicosapentaenoic Acid (Free Fatty Acids)								
Pharmacokinetic[1]	1	1	0.04	0.04	1	1	0.04	0.04
UISR	28	26	1.03	0.96	28	26	1.03	0.96
Total	**29**	**27**	**1.07**	**0.99**	**29**	**27**	**1.07**	**0.99**
Docosahexaenoic Acid (Free Fatty Acids)								
Pharmacokinetic[1]	2	2	0.07	0.07	1	0	0.04	0
AULOQ	6	4	0.22	0.15	6	4	0.22	0.15
EE	2	1	0.07	0.04	2	1	0.07	0.04
IE	2	1	0.07	0.04	2	1	0.07	0.04
UISR	60	45	2.21	1.65	60	45	2.21	1.65
Total	**72**	**53**	**2.65**	**1.95**	**71**	**51**	**2.61**	**1.88**

1 - If no repeats were performed for pharmacokinetic reasons, insert "0.0."
AULOQ: Above the Upper Limit of Quantitation
EE: Extraction Error
IE: Injection Error
UISR: Unacceptable Internal Standard Response.

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Table 4. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
LAB 105.05	Nov 16, 2007	Repeat Sample Analysis Procedure and Acceptance Criteria

Did use of recalculated plasma concentration data change study outcome? No

Comments from the Reviewer:

- The firm reassayed some pilot and fed BE study samples for the following reasons, as per its objective reassay SOP (Repeat Sample Analysis Procedure and Acceptance Criteria; effective date: 11/16/2007):
  (1) Pharmacokinetic repeats: *"Aberrant concentration values or concentration –time profiles can be encountered in the pharmacokinetic analysis of data generated in Phase I-II or comparative bioavailability studies for several reasons, including (a) a sample switch during the clinical or analytical phase (b) sample contamination during the collection, handling or analytical phase and (c) unknown errors that exceed the tolerance level".*
  (2) Above the upper limit of quantitation: *"An analytical repeat is performed in single, using the same or different aliquot due to concentration above the upper limit of quantitation".*
  (3) Extraction error: *"One of the analytical repeats is performed in single, using the same or different aliquot".*
  (4) Injection error; *"One of the analytical repeats is performed in single, using the same or different aliquot".*
  (5) Unacceptable internal standard response: *"The acceptable range for the internal standard (ISTD) response is ±20% of the average ISTD response for each analytical batch"; "Samples with internal standard response outside the acceptable ISTD response range are repeated due to UISR".*

- However, the firm submitted the analytical raw data from the study runs of approximately 50% of the subjects of the pilot study and approximately 22.5% of subjects of the fed BE study. The firm should submit complete raw data of all sample analysis and reanalysis for the pilot (study no. 2008-1779) and fed (study no. 2008-1829) studies including the peak area for the drug, peak area for the internal standard, the ratio of the peak area for the drug to the peak area for the internal standard, dilution factor (if any), and the corresponding concentration for each assayed and/or reassayed sample for all subject samples, calibration standard concentration samples, and quality control samples.

- As a result, the re-analysis of samples for firm's fasting and fed study is **incomplete** (inadequate).

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3.7 Formulation

Location in appendix	Section 4.2, Formulation Data
If a tablet, is the RLD scored?	No
If a tablet, is the test product biobatch scored	No
Is the formulation acceptable?	**FORMULATION INCOMPLETE**
If not acceptable, why?	Pending firm's submission of quantitative composition of soft gelatin capsule shell and white printing ink in the formulation. Also pending the Chemistry Division III's evaluation of the test API to be pharmaceutically equivalent to the RLD's.

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	DARRTS ANDA 091028 REN, KE REV-BIOEQ-02(Dissolution Review), 05/04/2009 and current review
Source of Method (USP, FDA or Firm)	Firm
Medium	10% Labrasol in 0.1N HCl
Volume (mL)	900
USP Apparatus type	2 (Paddle)
Rotation (rpm)	(b) (4)
DBE-recommended specifications	Pending firm's additional dissolution testing data
If a modified-release tablet, was testing done on ½ tablets?	NA
F2 metric calculated?	Pending firm's additional dissolution testing data
If no, reason why F2 not calculated	N/A
Is method acceptable?	**Incomplete**
If not then why?	Pending firm's additional dissolution testing data

3.9 Waiver Request(s)

None.

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3.10 Deficiency Comments

Deficiencies Related to the BE studies:

1. The DBI has reviewed the test formulation using the criteria on active pharmaceutical ingredient and antioxidant as stated in the draft Individual Product BE Guidance for Omega-3-Acid Ethyl Esters Capsules, recommended on September,2012 (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM320011.pdf), and considers that the firm's test product meets the criteria. The test and reference products are similar and the bioequivalence (BE) may be established based solely on an *in vitro* method (Quantitative Capsule Rupture Test, also described in the draft guidance).

2. However, per the Guidance aforementioned, if the firm wishes to choose *In Vivo* BE Study Option for its application, the firm will be asked to conduct both new fasting and fed BE studies for Omega-3-Acid Ethyl Esters Capsules, 1 g.

   According to that current BE Guidance for Omega-3-Acid Ethyl Esters Capsules recommended on September 2012, the 90% confidence intervals (CIs) for bioequivalence (BE) of fed study are based on**:** (1) Eicosapentaenoic Acid (EPA) ethyl esters and (2) Docosahexaenoic Acid (DHA) ethyl esters. In addition, a fasting BE study is recommended and its 90% CIs for BE are based on: (1) baseline-adjusted EPA total lipids and (2) baseline-adjusted DHA total lipids.

3. Based on its pre-study validation data in firm's currently submitted fed study (Study No. 2008-1829), the percent of average recovery for the free eicosapentaenoic acid (EPA) (e.g. QC A, B and C: 131.9 % to 140.0 %) and docosahexaenoic acid (DHA) (e.g. QC A, B and C: 130.2 % to 135.8 %) and that of Internal Standard [IS (b) (4): 124.1%] are very high. The firm is advised to provide its explanation(s) about such high values of average recovery of the above mentioned analytes and the internal standard.

4. In addition, for its future submissions, the firm is asked to submit complete (100%) raw numerical data of **all** assay and reassay runs for **all subjects**, including the data of peak area/height for the drug, peak area/height for the internal standard, ratio of the peak area/height for the drug to the peak area/height for the internal standard, dilution factor (if any), and the corresponding concentration for each assayed and reassayed sample of all subject samples, calibration standard concentration samples, and quality control samples for its pilot study (Study No. 2008-1779) and fed study (Study No. 2008-1829). The firm has submitted the raw numerical data of **approximately 50% and 22.5%** of the subjects, respectively. Submission of additional chromatograms is not necessary.

5. Regarding Compliance with Section 508 of the Rehabilitation Act of 1973: The images included in firm's submission do not contain alternate text and are

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therefore unsearchable and not in compliance with Section 508 of the Rehabilitation Act of 1973, which requires that Federal agencies' electronic and information technology is accessible to people with disabilities. The firm is advised for its future submissions to ensure that future submissions are in compliance with Section 508 and contain images with alternate text so that the images are searchable. Instructions for adding alternate text should be provided in the software used to construct/view the PDF file. The firm is asked to refer to the website http://www.section508.gov for further information.

Deficiency Related to the *In Vitro* Drug Release Testing:

6. The quantitative capsule rupture (QCR) testing conducted using firm's proposed method, in 900 mL of 10% Labrasol in 0.1N HCl using USP Apparatus 2 (Paddle) with (b) (4) rpm at 37°C ± 0.5°C, is not sufficiently discriminatory, based on the release profile submitted for its test product, Omega-3-Acid Ethyl Esters Capsules, 1 g, comparing it with the reference product, GlaxoSmithKline's Lovaza® Capsules, 1 g.

   Based on the QCR data submitted by the firm for its test product, the DBI suggests the firm modify its proposed method by using (b) (4) paddle speeds such as 50 rpm, 75 rpm and 100 rpm, and/or lower Labrasol concentration, as follows:

Medium:	Labrasol in 0.1N HCl at 1%, 2%, 5%, 8%, 10% etc.
Apparatus:	USP Apparatus 2 (Paddle)
Speed:	**50**, **75** and **100** rpm
Volume:	900 mL
Temperature:	37°C ± 0.5°C
Sampling times:	5, 10, 15, 30, 45, and 60 minutes until at least 80% of the drug is released from the dosage form.

   The firm is advised that for USP Apparatus 2, when used for this dosage form, the sampling probes should remain immersed in the dissolution medium throughout the duration of testing in order to obtain reproducible results. The use of a sinker with USP Apparatus 2 may be considered in preventing the capsules from floating to the top.

   Alternatively, the firm may consider using different surfactants and/or the USP Apparatus 4 (flow-through cell) as suggested in the draft guidance.

7. The DBI will evaluate the method development and optimization data as well as the complete data of the test and reference products obtained for 12 units per product, based on the most appropriate procedure, and determine the most suitable QCR method and specification for firm's test product.

Deficiency Related to the Test Product Formulation

8. In addition, the firm is asked to provide the quantitative amount of each component of its Soft Gelatin Capsule Shell and White Printing Ink (b) (4) (b) (4) per capsule in its formulation.

3.11 Recommendations

1. The Division of Bioequivalence I (DBI) finds the pilot BE study (2008-1779) **inadequate** (incomplete) due to the above deficiency comments #2 - #4 and #7. Teva Pharmaceuticals USA conducted the pilot BE study on the reference listed drug (RLD), Lovaza® (omega-3-acid ethyl esters) Capsules, 1 g, lot #7HG0158, manufactured by GlaxoSmithKline, under the fasting and fed conditions.

2. The DBI finds the fed BE study (2008-1829) **inadequate** (incomplete) due the above deficiency comments #2 - #4 and #7. Teva Pharmaceutical USA conducted the fed BE study on its Omega-3-Acid Ethyl Esters Capsules, 1 g, lot # P080602, comparing it to GlaxoSmithKline's Lovaza® (omega-3-acid ethyl esters) Capsules, 1 g, lot #7HH0014.

3. Per the current draft Individual Product BE Guidance for Omega-3-Acid Ethyl Esters Capsules, recommended on September, 2012, the Division of Bioequivalence I (DBI) defers to the Office of Generic Drugs's (OGD's) Division of Chemistry III for the evaluations and recommendations of the test product to be pharmaceutically equivalent to the RLD product.

4. The dissolution testing conducted is **incomplete**. The firm is advised to continue to develop its dissolution testing method for the test product per the current Guidance The DBI will evaluate and determine the most suitable dissolution method for firm's test product and the dissolution specification will be recommended upon reviewing its complete dissolution testing data.

5. Per the BE Guidance aforementioned, if the firm wishes to choose *In Vivo* BE study option, the DBI recommends that the firm conduct new fasting and fed BE studies for Omega-3-Acid Ethyl Esters Capsules, 1 g.

The application is **incomplete** (inadequate).

The firm should be informed of the above deficiency comments and recommendations.

3.12 Comments for Other OGD Disciplines

Discipline	Comment
Division of Chemistry III (DCIII)	Pending DCIII's review of the test product to be pharmaceutically equivalent to the RLD.

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4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Pilot Study

4.1.1.1 Study Design

Table 5 Study Information

Study Number	2008-1779
Study Title	A Single-Dose, Pharmacokinetic Study of Lovaza™ 1000 mg Capsules Under Fasting and Fed Conditions
Clinical Site (Name, Address, Phone #)	Pharma Medica Research Inc. 4770 Sheppard Avenue East Toronto, Ontario, Canada M1S 3V6 Phone: (416) 759-4111
Principal Investigator	Xueyu (Eric) Chen, M.D., Ph.D., FRCP (C)
Dosing Dates	Period I: July 12, 2008 Period II: July 19, 2008
Analytical Site (Name, Address, Phone #)	(b) (4)
Analysis Dates	July 26, 2008 to October 24, 2008 for Free Eicosapentaenoic acid and July 26, 2008 to October 22, 2008 for Free Docosahexaenoic acid. September 22, 2008 and September 23, 2008 for Eicosapentaenoic acid and between September 22, 2008 and September 29, 2008 for Docosahexaenoic acid
Analytical Director	(b) (6) M.Sc.
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	One hundred and four (104) days (July 11, 2008 – October 23, 2008) for Free Eicosapentaenoic acid and Free Docosahexaenoic acid. Eighty (80) days (July 11, 2008 – September 29, 2008) for Eicosapentaenoic acid and Docosahexaenoic acid

Table 6. Product information

Product	Fasting	Fed
Treatment ID	A	B
Product Name	Lovaza Capsules, 1 g	Lovaza Capsules, 1 g
Manufacturer	Reliant Pharmaceuticals, Inc., USA	Reliant Pharmaceuticals, Inc., USA
Batch/Lot No.	7HG0158	7HG0158
Manufacture Date	N/A	N/A
Expiration Date	March 2010	March 2010
Strength	1 g	1 g
Dosage Form	Capsule	Capsule

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Bio-batch Size	N/A	N/A
Production Batch Size	N/A	N/A
Potency	103.4%	103.4%
Content Uniformity (mean, %RSD, Acceptance Value)	N/A	N/A
Dose Administered	4 x 1 g capsule	4 x 1 gram capsule
Route of Administration	Oral	Oral

Table 7. Study Design, Single-Dose Pilot Bioequivalence Study

Number of Subjects	Enrolled: 6 Dosed: 6 Completed: 6 Samples Analyzed: 6 Data Analyzed: 6
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	Fasting→Fed: 2, 3 and 6 Fed→Fasting: 1, 4 and 5
Blood Sampling Times	Baseline at -24 (x 2), -21, -18, -15, -12 and -1 hours pre-dose, and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 30 and 36 hours post-dose.
Blood Volume Collected/Sample	10 mL
Blood Sample Processing/Storage	Blood samples were collected using a syringe through an indwelling intravenous cannula placed in the forearm vein of the subjects and then transferred into pre-labeled vacutainers containing K_2EDTA as the anticoagulant. After collection from subjects, blood samples were centrifuged at approximately 4 ^{0}C with 3500 rpm for 8 minutes to separate plasma from whole blood. Three aliquots were transferred to pre-labeled fresh polypropylene tubes and stored in a freezer at -70 ^{0}C or colder until shipment to an analytical facility.
IRB Approval	Yes (June 5, 2008)
Informed Consent	Yes (June 5, 2008)
Length of Fasting	**Fasting group:** At least 10 hours overnight fast prior to dosing. Subject fasted for at least four hours after dosing. **Fed group:** At least 10 hours overnight fast and then a high-fat, high calorie breakfast was given to the subjects 30 minutes prior to dosing..
Length of Confinement	Approximately 34.5 hours prior to drug administration per study period until 36 hours postdose.

Reference ID: 3227106

Safety Monitoring	Clinical laboratory tests were performed for each subject at the time of check-in and post-study procedures including urinalysis, serum chemistry, hematology and pregnancy (female subjects) clinical lab tests. Body temperature and physical examinations were performed at the time of each study period. Subjects were questioned regarding their health status throughout study. Medical investigator was present or on-call throughout the study.

Standard FDA Meal Used?	Yes

Comments on Study Design:

The study design is acceptable.

4.1.1.2 Clinical Results

Table 8. Demographics Profile of Subjects Completing the Pilot BE Study

Pilot Study No 2008-1779		
		Treatment Groups
		Reference Product N =6
Age (years)	Mean ± SD	41 ± 7
	Range	29 - 47
Age Groups	< 18	0 (0%)
	18 – 40	2 (33.3%)
	41 – 64	4 (66.7%)
	65 – 75	0 (0%)
	> 75	0 (0%)
Sex	Male	3 (50.0%)
	Female	3 (50.0%)
Race	Asian	0 (0%)
	American Indian or Alaska Native	0 (0%)
	Black or African American	1 (16.7%)
	Caucasian	3 (50.0%)
	Hispanic/Latino	2 (33.3%)
BMI (kg/m^2)	Mean ± SD	28.3 ± 2.1
	Range	24.6 – 29.9
Other	N/A	None

Reference ID: 3227106

Table 9. Dropout Information, Pilot Bioequivalence Study

Study No. 2008-1779				
Subject No	**Reason for dropout/replacement**	**Period**	**Replaced?**	**Replaced with**
None	--	--	--	--

Table 10. Study Adverse Events, Fasting Bioequivalence Study

System Organ Class Term (Preferred Term)	**Reported Incidence by Treatment Groups**	
	Bioequivalence Study Study No: 2008-1779	
	Test A (Fasting) N = 6	**Test B (Fed)** N = 6
Investigations		
Bacteria urine identified	1 (16.7%)	0 (0%)
Blood creatinine increased	1 (16.7%)	2 (33.3%)
Blood urine present	1 (16.7%)	0 (0%)
Haemoglobin decreased	1 (16.7%)	0 (0%)
Red cell distribution width increased	1 (16.7%)	0 (0%)
Musculoskeletal and connective tissue disorders		
Back pain	0 (0%)	1 (16.7%)
Total	**5 (83.5%)**	**3 (50.0%)**

Subjects Experiencing Emesis (Include in eCTD)

Subject Number	**Test/Reference**	**Period**	**Time Post-Dose**	**Duration Between Dosing and Emesis (hrs)**
--	-	--	--	--

Do any of the adverse events require statistical analysis consideration (e.g. vomiting)? No.

If yes, does the time exceed the Tmax limit according to the *Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products*? N/A

Was the adverse event profile observed during the pilot bioequivalence study the same for the test and reference product? No, this study was designed as a single-Dose, two-way, crossover study using the RLD, Lovaza® (omega-3-acid ethyl esters) Capsules, 1 g, under fasting and fed conditions. Although there is a slight difference in the number of adverse events (AEs) between the fasting and fed states, it is not expected to impact and/or should not raise additional clinical questions on the outcome of the pilot study.

Reference ID: 3227106

Table 11. Protocol Deviations, Pilot Bioequivalence Study

Study No. 2008-1779		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
Section 12.12 of the protocol states: "*After being centrifuged, 3 mL of the plasma will be transferred into 3 labeled polypropylene tubes (3 x 1 mL); each of the 3 tubes will contain 50 µL of sodium fluoride solution. The plasma will be mixed with the solution. These tubes will be flash frozen as soon as possible after separation.*" 50 µL of sodium fluoride solution was not added and the impact was not evaluated during the analysis.	N/A	N/A
Section 9.3 of the protocol states: "*Screening procedures will include the following: medical history, vital signs (blood pressure, pulse rate, respiration, and temperature), demographic data collection and measurements of height, weight, and elbow breadth, electrocardiogram, physical examination.*" Elbow breadth measurement for Subject 03 was not performed. This deviation did not comprise subject safety or the subject's eligibility into the study.	N/A	N/A

Comments on Dropouts/Adverse Events/Protocol Deviations:

Dropouts:
There were 6 subjects enrolled in the pilot study, all subjects completed the study and were determined for PK parameters for statistical analysis. No subjects were withdrawn from the pilot study

Adverse Events:
No serious adverse drug event occurred. According to the case report forms, four adverse events (AEs) were related to the renal and urinary tract system (e.g. increase in blood creatinine level, blood in urine and bacteria in urine), one was a decrease in hemoglobin and the other back pain. The intensity of all these AEs was graded as mild. No vomiting event was reported in the pilot study.

Protocol Deviations:
There were some blood sampling time deviations reported during the pilot bioequivalence study which occurred in less than 5% of the nominal time points, and thus considered to be insignificant. The firm used actual sampling times for its PK calculation and the reviewer used nominal times for its PK calculation. Based on the results which are similar for both time deviations should not have an impact on the outcome of the study.

Therefore, the "Dropouts/Adverse Events/Protocol Deviations" are **acceptable.**

Reference ID: 3227106

4.1.1.3 Bioanalytical Results

Table 12. Assay Validation – During the Pilot Study

Free Eicosapentaenoic Acid

Bioequivalence Study No. 2008-1779 Free Eicosapentaenoic Acid									
Parameter	**Standard Curve Samples**								
Concentration (ng/mL)	10.0	20.0	50.0	125	350	750	1500	3000	5000
Inter day Precision (%CV)	2.9	6.5	3.5	6.0	1.3	2.3	0.8	2.9	1.7
Inter day Accuracy (%Actual)	99.1	102.5	99.4	100.8	96.6	100.1	100.9	103.1	98.2
Linearity	0.9980-0.9997								
Linearity Range (ng/mL)	10.0 -5000 ng/mL								
Sensitivity/LOQ (ng/mL)	10.0 ng/mL								

Bioequivalence Study No. 2008-1779 Free Eicosapentaenoic Acid						
Parameter	**Quality Control Samples**					
Concentration (ng/mL)	30.0	400	4000	175	1950	3580
Inter day Precision (%CV)	3.7	2.8	4.8	3.6	2.2	4.0
Inter day Accuracy (%Actual)	102.0	104.5	105.5	86.9	93.7	104.1

Free Docosahexaenoic Acid

Bioequivalence Study No. 2008-1779 Free Docosahexaenoic Acid									
Parameter	**Standard Curve Samples**								
Concentration (ng/mL)	10.0	20.0	50.0	125	350	750	1500	3000	5000
Inter day Precision (%CV)	1.8	3.8	1.0	4.5	4.5	2.3	1.8	2.5	1.4
Inter day Accuracy (%Actual)	101.0	99.0	99.8	101.6	98.6	100.8	100.7	99.1	100.3
Linearity	0.9994-0.9997								
Linearity Range (ng/mL)	10.0 -5000 ng/mL								
Sensitivity/LOQ (ng/mL)	10.0 ng/mL								

Bioequivalence Study No. 2008-1779 Free Docosahexaenoic Acid						
Parameter	**Quality Control Samples**					
Concentration (ng/mL)	30.0	400	4000	669	1820	3670
Inter day Precision (%CV)	3.7	2.2	4.8	3.4	3.0	6.4
Inter day Accuracy (%Actual)	102.3	103.8	105.9	96.3	102.9	110.2

Total Eicosapentaenoic Acid

Bioequivalence Study No. 2008-1779 Eicosapentaenoic Acid								
Parameter	**Standard Curve Samples**							
Concentration (µg/mL)	1.00	2.00	5.00	10.0	25.0	50.0	100	150
Inter day Precision (%CV)*	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Inter day Accuracy (%Actual)	94.1	99.5	105.2	100.0	101.6	102.2	96.6	101.3
Linearity	0.9995 -0.9997							
Linearity Range (µg/mL)	1.00 -150 µg/mL							
Sensitivity/LOQ (µg/mL)	1.00 µg/mL							

Bioequivalence Study No. 2008-1779 Eicosapentaenoic Acid

Reference ID: 3227106

Parameter	Quality Control Samples					
Concentration (µg/mL)	3.00	20.0	120	6.12	63.1	99.3
Inter day Precision (%CV)	4.1	3.2	5.1	8.2	3.3	2.5
Inter day Accuracy (%Actual)	102.0	101.5	100.0	105.7	99.5	102.7

**Note*: Per firm's "Bioanalytical Study Report 1", Page 40, located in Module 5, Section 5.3.1.4 bioanalyt-analyt-met, "Between batch precision of the calibration standards for eicosapentaenoic acid was not calculable and accuracy ranged from 94.1 % to 105.2 % respectively".

Total Docosahexaenoic Acid

Bioequivalence Study No. 2008-1779 Docosahexaenoic Acid								
Parameter	**Standard Curve Samples**							
Concentration (µg/mL)	1.00	2.00	5.00	10.0	25.0	50.0	100	150
Inter day Precision (%CV)	6.5	5.6	3.8	2.4	2.5	1.0	0.7	0.0
Inter day Accuracy (%Actual)	99.8	98.5	100.0	102.0	97.6	105.4	95.9	101.3
Linearity	0.9991-0.9996							
Linearity Range (µg/mL)	1.00 -150 µg/mL							
Sensitivity/LOQ (µg/mL)	1.00 µg/mL							

Bioequivalence Study No. 2008-1779 Docosahexaenoic Acid						
Parameter	**Quality Control Samples**					
Concentration (µg/mL)	3.00	20.0	120	25.8	56.7	91.9
Inter day Precision (%CV)	2.5	3.9	2.0	7.7	4.8	2.8
Inter day Accuracy (%Actual)	97.0	96.5	101.7	101.2	98.4	102.4

Number of Acceptable Runs	Free EPA assay: 4 Free DHA assay: 3 Total EPA assay: 2 Total DHA assay:3
Number of Rejected Runs (Run ID, volume/page location)	Free EPA assay: None (not reported) Free DHA assay: None (not reported Total EPA assay: None (not reported) Total DHA assay:None (not reported)
If sample and QC diluted during study, specify all dilution factors	QC dilution: None Reanalysis sample dilution: Free DHA assay - dilution factor=2 Total DHA assay- dilution factor= 2
Was 100% of raw numerical data submitted?	No

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	Yes
Do you agree with the firm's accepted and rejected runs?	Agree

Comments on Study Assay Validation:

Acceptable.

Reference ID: 3227106

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes: Free EPA: 50% Free DHA: 50% Total EPA: 50% Total DHA:50%
Were chromatograms serially or randomly selected?	Serially selected: Free EPA: sub#s 1-3 Free DHA: sub#s 1-3 Total EPA: sub#s 1-3 Total DHA: sub#s 1-3

Comments on Chromatograms:

Acceptable.

Table 4. Additional Comments on Repeat Assays

Were all SOPs followed?	The analytical numerical raw data were not submitted for all the subjects in the pilot study.
Did recalculation of PK parameters change the study outcome?	Please see the above comments
Does the reviewer agree with the outcome of the repeat assays?	Please see the above comments
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays:

Incomplete. The firm did not submit the complete analytical/reanalytical raw numerical data from study runs of all the subjects related to its pilot study.

Reference ID: 3227106

4.1.1.4 Pharmacokinetic Results

Table 5. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 9 and Figure 1

Eicosapentaenoic acid (EPA; Free fatty acids)-Baseline adjusted

Pilot Study, Study No. 2008-1779, N=6									
Parameter (units)	Fasting				Fed				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	501.253	84.67	34.61	1229.17	6393.239	41.13	3808.62	10431.58	0.08
Cmax (ng/ml)	96.414	71.70	32.68	226.67	1235.239	32.08	746.82	1711.67	0.08
Tmax* (hr)	3.000	.	1.00	9.00	5.000	.	4.00	8.00	0.60

* Tmax values are presented as median, range

Eicosapentaenoic acid (EPA; Free fatty acids)-Baseline non-adjusted

Pilot Study, Study No. 2008-1779, N=6									
Parameter (units)	Fasting				Fed				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	6488.242	54.66	3312.40	13269.00	13811.72	35.77	9004.25	22548.00	0.47
Cmax (ng/ml)	222.167	53.46	149.00	463.00	1368.500	30.86	847.00	1790.00	0.16
Tmax* (hr)	1.500	.	-24.00	9.00	5.000	.	4.00	8.00	0.30

* Tmax values are presented as median, range

Eicosapentaenoic acid (EPA; Total lipids)-Baseline adjusted

Pilot Study, Study No. 2008-1779, N=6									
Parameter (units)	Fasting				Fed				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *µg/ml)	73.269	104.12	0.32	204.05	1022.862	34.34	575.46	1487.91	0.07
Cmax (µg/ml)	5.219	58.70	0.32	9.70	73.644	11.43	64.10	86.57	0.07
Tmax* (hr)	8.500	.	7.00	36.00	7.000	.	4.00	10.00	1.21

* Tmax values are presented as median, range

Reference ID: 3227106

Eicosapentaenoic acid (EPA; Total lipids)-Baseline non-adjusted

Pilot Study, Study No. 2008-1779, N=6									
Parameter (units)	Fasting				Fed				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *µg /ml)	1345.567	27.64	911.60	1888.35	2614.325	26.76	1865.50	3841.35	0.51
Cmax (µg/ml)	28.150	25.89	20.40	40.00	100.800	21.77	82.20	142.00	0.28
Tmax* (hr)	7.000	.	-21.00	36.00	7.000	.	4.00	10.00	1.00

* Tmax values are presented as median, range

Docosahexaenoic Acid (DHA; Free fatty acids)-Baseline adjusted

Pilot Study, Study No. 2008-1779, N=6									
Parameter (units)	Fasting				Fed				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	2529.972	65.94	417.50	5208.17	13926.89	40.04	7100.17	24142.17	0.18
Cmax (ng/ml)	550.306	42.06	309.00	982.33	4266.278	35.28	2185.83	5945.50	0.13
Tmax* (hr)	3.000	.	1.00	9.00	5.000	.	4.00	8.00	0.60

* Tmax values are presented as median, range

Docosahexaenoic Acid (DHA; Free fatty acids)-Baseline non-adjusted

Pilot Study, Study No. 2008-1779, N=6									
Parameter (units)	Fasting				Fed				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	27797.58	38.81	15565.50	47085.00	42895.08	30.25	29534.50	61248.50	0.65
Cmax (ng/ml)	1144.833	33.31	874.00	1870.00	4848.333	34.49	2550.00	6830.00	0.24
Tmax* (hr)	1.500	.	-24.00	9.00	5.000	.	4.00	8.00	0.30

* Tmax values are presented as median, range

Docosahexaenoic Acid (DHA; Total lipids)-Baseline adjusted

Pilot Study, Study No. 2008-1779, N=6									
Parameter (units)	Fasting				Fed				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *µg/ml)	65.669	90.89	15.63	168.26	348.987	32.80	223.93	463.01	0.19

Reference ID: 3227106

Cmax (µg/ml)	8.458	42.53	2.62	13.48	50.525	12.23	39.08	55.18	0.17
Tmax* (hr)	7.500	.	3.00	12.00	6.500	.	4.00	10.00	1.15

* Tmax values are presented as median, range

Docosahexaenoic Acid (DHA; Total lipids)-Baseline non-adjusted

Pilot Study, Study No. 2008-1779, N=6									
Parameter (units)	**Fasting**				**Fed**				**T/R**
	Mean	**%CV**	**Min**	**Max**	**Mean**	**% CV**	**Min**	**Max**	
AUC0-t (hr *µg/ml)	3755.217	33.36	2364.00	5656.20	4165.325	36.24	2593.75	6335.35	0.90
Cmax (µg/ml)	73.200	31.26	46.70	105.00	116.500	27.99	89.90	168.00	0.63
Tmax* (hr)	6.500	.	-24.00	10.00	6.500	.	4.00	10.00	1.00

* Tmax values are presented as median, range

Table 6. Geometric Means and 90% Confidence Intervals - Firm Calculated

Lovaza Dose (4 x 1000 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting and Fed Pharmacokinetic Study (Study No. 2008-1779)				
Eicosapentaenoic acid (total lipids)				
Parameter	**Fasting**	**Fed**	**Ratio**	**90% C.I.**
AUC0-t	22.30	967.54	2.30	0.45 - 11.83
Cmax	3.64	73.25	4.97	1.91 - 12.93
Docosahexaenoic acid (total lipids)				
Parameter	**Fasting**	**Fed**	**Ratio**	**90% C.I.**
AUC0-t	45.64	332.86	13.71	5.67 - 33.17
Cmax	7.59	50.18	15.13	8.93 - 25.66
Eicosapentaenoic acid (free fatty acids)				
Parameter	**Fasting**	**Fed**	**Ratio**	**90% C.I.**
AUC0-t	0.318	5.979	5.31	1.78 - 15.82
Cmax	0.080	1.177	6.79	3.54 - 13.03
Docosahexaenoic acid (free fatty acids)				
Parameter	**Fasting**	**Fed**	**Ratio**	**90% C.I.**
AUC0-t	1.965	13.073	15.03	6.81 - 33.19
Cmax	0.516	4.017	12.84	8.05 - 20.48

Table 7. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

EPA (Free fatty acids)-Baseline adjusted

Omega-3-acid ethyl esters Capsules 4 x 1 g Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Pilot Study, Study No. 2008-1779, N=6					
Parameter (units)	**Fasting**	**Fed**	**Ratio**	**90% C.I.**	
AUC0-t (hr *µg/ml)	0.318	5.979	0.053	1.78	15.82
Cmax (µg/ml)	0.080	1.177	0.068	3.54	13.03

EPA (Total lipids)-Baseline adjusted

Omega-3-acid ethyl esters Capsules 4 x 1 g Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Pilot Study, Study No. 2008-1779, N=6					
Parameter (units)	**Fasting**	**Fed**	**Ratio**	**90% C.I.**	
AUC0-t (hr *µg/ml)	22.30	967.54	0.02	0.45	11.83
Cmax (µg/ml)	3.64	73.25	0.05	1.91	12.93

DHA (Free acids)-Baseline adjusted

Omega-3-acid ethyl esters Capsules 4 x 1 g Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Pilot Study, Study No. 2008-1779, N=6					
Parameter (units)	**Fasting**	**Fed**	**Ratio**	**90% C.I.**	
AUC0-t (hr *µg/ml)	1.965	13.073	0.15	6.81	33.19
Cmax (µg/ml)	0.516	4.017	0.13	8.05	20.48

DHA (Total lipids)-Baseline adjusted

Omega-3-acid ethyl esters Capsules 4 x 1 g Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Pilot Study, Study No. 2008-1779, N=6					
Parameter (units)	**Fasting**	**Fed**	**Ratio**	**90% C.I.**	
AUC0-t (hr *µg/ml)	45.64	332.86	0.14	5.67	33.17
Cmax (µg/ml)	7.59	50.18	0.15	8.93	25.66

Reference ID: 3227106

Table 8. Additional Study Information, Fasting Study No. 2008-1779

EPA (Free fatty acids)-Baseline adjusted

Root mean square error, AUC0-t	0.8867	
Root mean square error, Cmax	0.5293	
	Fasting	**Fed**
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	Yes	Yes
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

EPA (Total lipids)-Baseline adjusted

Root mean square error, AUC0-t	1.3288	
Root mean square error, Cmax	0.7763	
	Fasting	**Fed**
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	Yes	Yes
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

DHA (Free acids)-Baseline adjusted

Root mean square error, AUC0-t	0.6437	
Root mean square error, Cmax	0.3792	
	Fasting	**Fed**
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	Yes	Yes
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

DHA (Total lipids)-Baseline adjusted

Root mean square error, AUC0-t	0.7178	
Root mean square error, Cmax	0.4289	
	Fasting	**Fed**
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	Yes	Yes
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Reference ID: 3227106

Comments on Pharmacokinetic and Statistical Analysis:

- The firm included 6 subjects using the RLD product under fasting and fed conditions for the final calculations of AUCt and Cmax of plasma free EPA and DHA fatty acids, and total EPA and DHA lipids, after baseline level adjustments.

- The 90% confidence intervals (CI's) for the least squares geometric means of Ln AUCt, and LnCmax calculated by the reviewer are in good agreement with the firm's calculations.

- The reviewer verified all statistical analyses for the pilot BE study under fasting and fed conditions (with the RLD product) using the SAS code of "CALCKE" (see V: DIVISION\BIO\SAS Programs\TWOWAYCALCKE 12FED2010 WITH TIME AND KE DATASET ENTRIES.SAS).

Summary and Conclusions, Single-Dose Pilot Bioequivalence Study under Fasting and Fed States (using RLD product):

The pilot *in vivo* bioequivalence study is inadequate due to the deficiency comments specified in Section 3.10 of this review.

Reference ID: 3227106

Table 9. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

A. EPA (Free fatty acids)-Baseline adjusted

Free eicosapentaenoic acid					
Time (hr)	Fasting (n=6)		Fed (n=6)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	34.12	105.54	25.35	82.07	1.35
1.00	57.00	148.78	15.51	147.90	3.67
2.00	37.63	105.40	110.41	135.18	0.34
3.00	43.05	83.35	212.52	97.96	0.20
4.00	76.75	74.01	520.67	93.96	0.15
5.00	11.84	117.68	598.41	95.45	0.02
6.00	2.99	162.21	551.07	60.35	0.01
7.00	0.29	244.95	526.24	54.58	0.00
8.00	1.06	244.95	678.57	99.88	0.00
9.00	15.24	244.31	455.57	101.05	0.03
10.00	6.04	244.95	396.57	128.58	0.02
12.00	2.13	244.95	143.47	108.78	0.01
16.00	0.00	.	69.80	96.91	0.00
24.00	48.60	131.03	125.30	60.61	0.39
30.00	2.74	244.95	53.97	84.04	0.05
36.00	0.36	196.91	42.47	107.43	0.01

B. EPA (Free fatty acids)-Baseline non-adjusted

Free eicosapentaenoic acid					
Time (hr)	Fasting (n=6)		Fed (n=6)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
-24.00	158.08	76.58	233.35	103.54	0.68
-21.00	107.45	75.70	120.30	78.17	0.89
-18.00	81.87	43.37	93.95	73.12	0.87
-15.00	111.87	48.61	106.97	53.49	1.05
-12.00	69.58	50.29	86.78	53.32	0.80
-1.00	142.67	69.27	158.22	69.24	0.90
1.00	167.20	87.79	131.83	87.74	1.27
2.00	149.55	43.43	232.38	106.38	0.64
3.00	154.97	60.64	338.25	83.75	0.46
4.00	188.67	63.14	653.93	87.27	0.29
5.00	115.32	50.98	731.67	84.83	0.16
6.00	90.28	41.35	684.33	59.20	0.13
7.00	79.65	32.51	659.50	41.80	0.12
8.00	79.57	31.72	811.83	78.50	0.10
9.00	108.80	43.96	588.83	71.79	0.18
10.00	84.33	40.08	525.67	90.65	0.16
12.00	76.75	35.82	266.00	49.94	0.29
16.00	76.28	48.57	182.33	36.45	0.42
24.00	158.60	76.99	258.17	34.35	0.61
30.00	90.72	37.64	170.33	33.97	0.53
36.00	82.20	52.79	151.33	37.58	0.54

Reference ID: 3227106

C. EPA (Total lipids)-Baseline adjusted

Total eicosapentaenoic acid					
Time (hr)	Fasting (n=6)		Fed (n=6)		T/R Ratio
	Mean (µg/mL)	% CV	Mean (µg/mL)	% CV	
0.00	0.02	244.95	0.01	244.95	1.20
1.00	0.27	244.95	0.82	146.11	0.33
2.00	0.27	162.20	6.88	105.28	0.04
3.00	0.50	171.75	24.45	120.36	0.02
4.00	0.64	243.67	33.39	98.43	0.02
5.00	1.03	170.36	46.19	69.38	0.02
6.00	2.75	109.56	46.24	60.32	0.06
7.00	3.79	97.80	48.56	29.70	0.08
8.00	3.90	81.33	52.68	43.65	0.07
9.00	3.75	93.04	49.93	37.29	0.08
10.00	2.82	93.22	47.66	38.05	0.06
12.00	2.57	100.50	37.29	42.57	0.07
16.00	2.27	93.88	31.46	54.32	0.07
24.00	0.80	167.00	22.63	60.98	0.04
30.00	2.75	129.40	22.03	60.54	0.12
36.00	2.97	93.72	17.53	70.64	0.17

D. EPA (Total lipids)-Baseline non-adjusted

Total eicosapentaenoic acid					
Time (hr)	Fasting (n=6)		Fed (n=6)		T/R Ratio
	Mean (µg/mL)	% CV	Mean (µg/mL)	% CV	
-24.00	22.18	43.04	29.03	69.34	0.76
-21.00	23.40	41.05	28.90	62.86	0.81
-18.00	22.12	37.16	28.62	63.32	0.77
-15.00	23.30	38.70	28.23	63.56	0.83
-12.00	21.28	34.20	25.52	56.35	0.83
-1.00	20.40	30.56	22.63	47.20	0.90
1.00	21.22	35.28	24.23	44.66	0.88
2.00	21.63	34.23	32.85	66.02	0.66
3.00	22.12	35.90	50.58	83.22	0.44
4.00	21.62	32.05	60.55	71.50	0.36
5.00	22.27	27.43	73.35	63.12	0.30
6.00	24.23	21.87	73.40	58.08	0.33
7.00	25.68	19.27	75.72	33.16	0.34
8.00	25.62	26.61	79.83	25.94	0.32
9.00	25.60	24.69	77.08	19.63	0.33
10.00	10.00	24.67	24.82	74.82	17.64
12.00	12.00	24.42	25.75	64.45	18.91
16.00	16.00	23.30	22.45	58.62	13.43
24.00	24.00	20.97	26.18	49.05	11.43
30.00	30.00	22.92	19.02	49.18	15.38
36.00	36.00	23.12	20.40	44.12	16.06

Reference ID: 3227106

E. DHA (Free fatty acids)-Baseline adjusted

Free docoshexaenoic acid					
Time (hr)	Fasting (n=6)		Fed (n=6)		T/R Ratio
	Mean (µg/mL)	% CV	Mean (ng/mL)	% CV	
0.00	199.03	97.38	197.94	97.31	1.01
1.00	302.81	116.91	35.81	169.21	8.46
2.00	247.14	79.87	252.19	164.65	0.98
3.00	250.14	54.08	530.36	90.50	0.47
4.00	466.81	54.42	1728.97	99.00	0.27
5.00	63.36	114.98	2054.44	105.95	0.03
6.00	0.00	.	1486.94	74.53	0.00
7.00	0.00	.	1375.56	72.84	0.00
8.00	0.00	.	1975.56	123.99	0.00
9.00	97.19	244.95	1178.89	124.65	0.08
10.00	39.69	244.95	1081.39	155.68	0.04
12.00	0.00	.	155.97	149.10	0.00
16.00	0.00	.	0.00	.	.
24.00	220.64	109.41	258.69	65.37	0.85
30.00	22.86	244.95	0.00	.	.
36.00	0.00	.	0.64	244.95	0.00

Reference ID: 3227106

F. DHA (Free fatty acids)-Baseline non-adjusted

Free docoshexaenoic acid					
Time (hr)	Fasting (n=6)		Fed (n=6)		T/R Ratio
	Mean (µg/mL)	% CV	Mean (ng/mL)	% CV	
-24.00	803.17	65.71	1160.17	88.67	0.69
-21.00	472.17	58.06	454.00	39.97	1.04
-18.00	332.50	55.11	352.50	54.53	0.94
-15.00	559.00	66.28	453.00	45.20	1.23
-12.00	235.67	36.86	292.67	35.88	0.81
-1.00	686.67	54.70	780.00	54.40	0.88
1.00	806.17	65.50	504.17	56.74	1.60
2.00	762.00	25.43	762.83	88.26	1.00
3.00	765.00	34.44	1083.83	60.34	0.71
4.00	981.67	45.73	2299.67	83.11	0.43
5.00	528.83	43.41	2636.50	91.32	0.20
6.00	311.00	28.77	2069.00	65.62	0.15
7.00	240.83	27.21	1950.17	52.13	0.12
8.00	249.17	25.59	2491.83	95.11	0.10
9.00	459.67	64.39	1676.33	85.55	0.27
10.00	324.17	56.08	1532.50	111.34	0.21
12.00	254.00	23.57	520.00	56.98	0.49
16.00	241.50	38.17	279.17	22.89	0.87
24.00	716.17	57.64	796.50	29.76	0.90
30.00	391.33	50.58	388.83	39.18	1.01
36.00	274.33	41.61	363.00	37.21	0.76

Reference ID: 3227106

G. DHA (Total lipids)-Baseline adjusted

Total docoshexaenoic acid					
Time (hr)	Fasting (n=6)		Fed (n=6)		T/R Ratio
	Mean (µg/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.34	187.57	0.27	244.95	1.27
1.00	1.04	118.71	1.46	157.13	0.71
2.00	1.03	142.97	8.91	97.03	0.12
3.00	2.83	115.96	18.82	96.93	0.15
4.00	2.64	150.24	26.79	79.61	0.10
5.00	2.14	134.96	28.37	68.20	0.08
6.00	4.01	90.60	24.84	50.30	0.16
7.00	4.94	93.89	29.12	46.87	0.17
8.00	4.41	89.77	28.72	70.24	0.15
9.00	4.34	91.47	22.66	81.48	0.19
10.00	3.84	110.71	23.41	79.83	0.16
12.00	3.58	102.12	10.37	101.58	0.34
16.00	0.88	128.92	6.45	80.50	0.14
24.00	0.22	179.23	2.00	156.33	0.11
30.00	1.70	178.68	5.02	106.01	0.34
36.00	1.90	104.37	4.16	88.60	0.46

Reference ID: 3227106

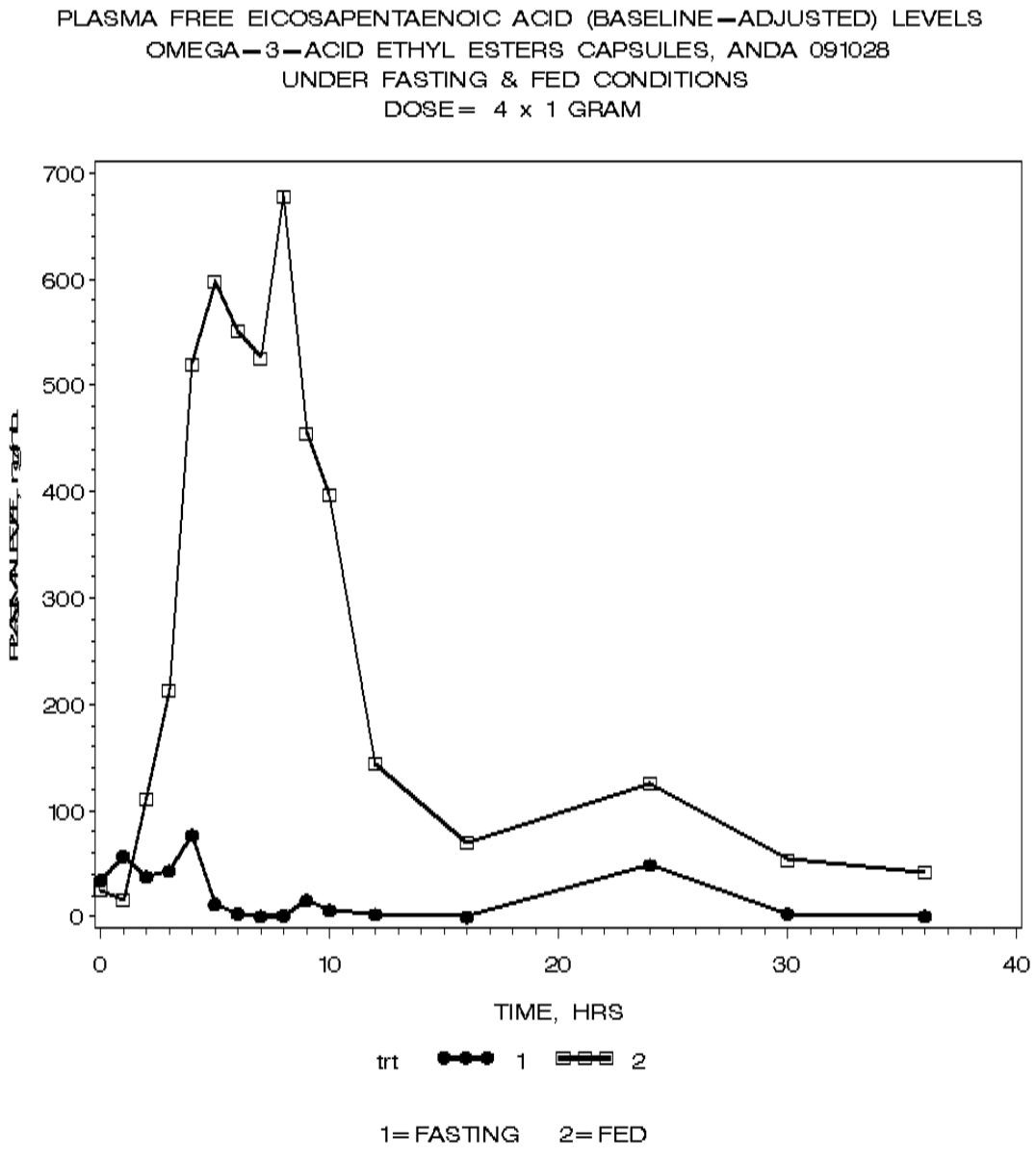
H. DHA (Total lipids)-Baseline non-adjusted

Total docoshexaenoic acid					
Time (hr)	Fasting (n=6)		Fed (n=6)		T/R Ratio
	Mean (µg/mL)	% CV	Mean (µg/mL)	% CV	
-24.00	62.62	43.37	67.60	50.69	0.93
-21.00	67.72	36.56	70.42	46.08	0.96
-18.00	64.68	37.20	67.13	49.82	0.96
-15.00	66.38	38.81	65.97	41.88	1.01
-12.00	60.90	37.31	63.98	42.53	0.95
-1.00	59.95	32.76	60.75	40.31	0.99
1.00	63.72	36.22	65.72	40.41	0.97
2.00	63.85	35.26	74.88	48.27	0.85
3.00	66.53	37.87	84.80	50.57	0.78
4.00	65.63	32.15	92.77	46.78	0.71
5.00	64.77	31.27	94.35	48.04	0.69
6.00	66.20	27.88	90.82	44.53	0.73
7.00	67.58	28.25	95.10	34.75	0.71
8.00	68.12	31.69	94.70	26.50	0.72
9.00	67.93	32.19	88.50	23.96	0.77
10.00	67.32	31.79	88.08	23.29	0.76
12.00	65.78	33.97	75.17	32.60	0.88
16.00	62.15	37.27	65.72	33.67	0.95
24.00	57.00	32.60	62.75	33.87	0.91
30.00	60.87	26.06	67.13	29.59	0.91
36.00	62.45	28.62	67.38	33.13	0.93

Reference ID: 3227106

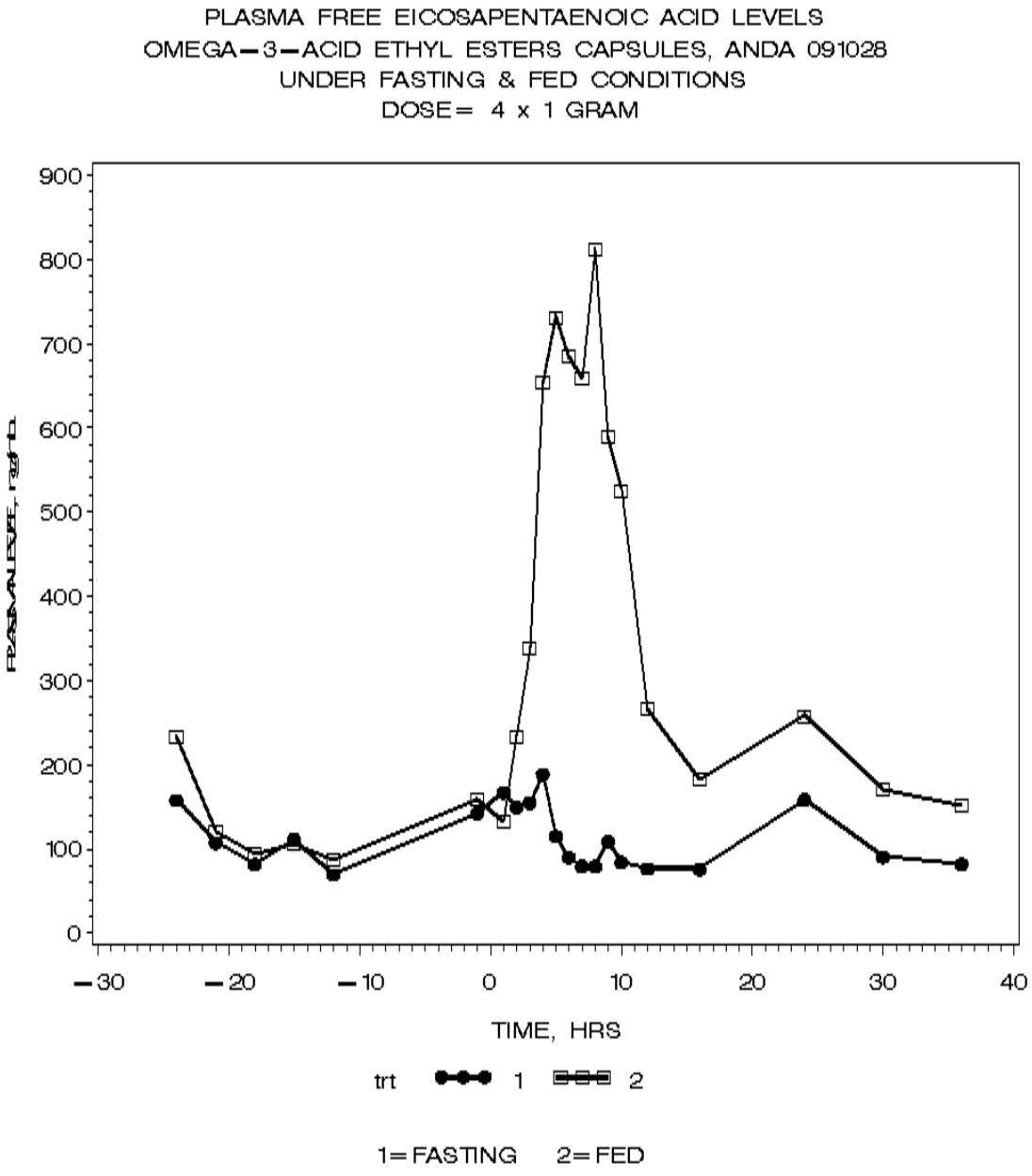
Figure 1. Mean Plasma Concentrations, Single-Dose Pilot Study

A. Baseline-adjusted: Free EPA Fatty Acids

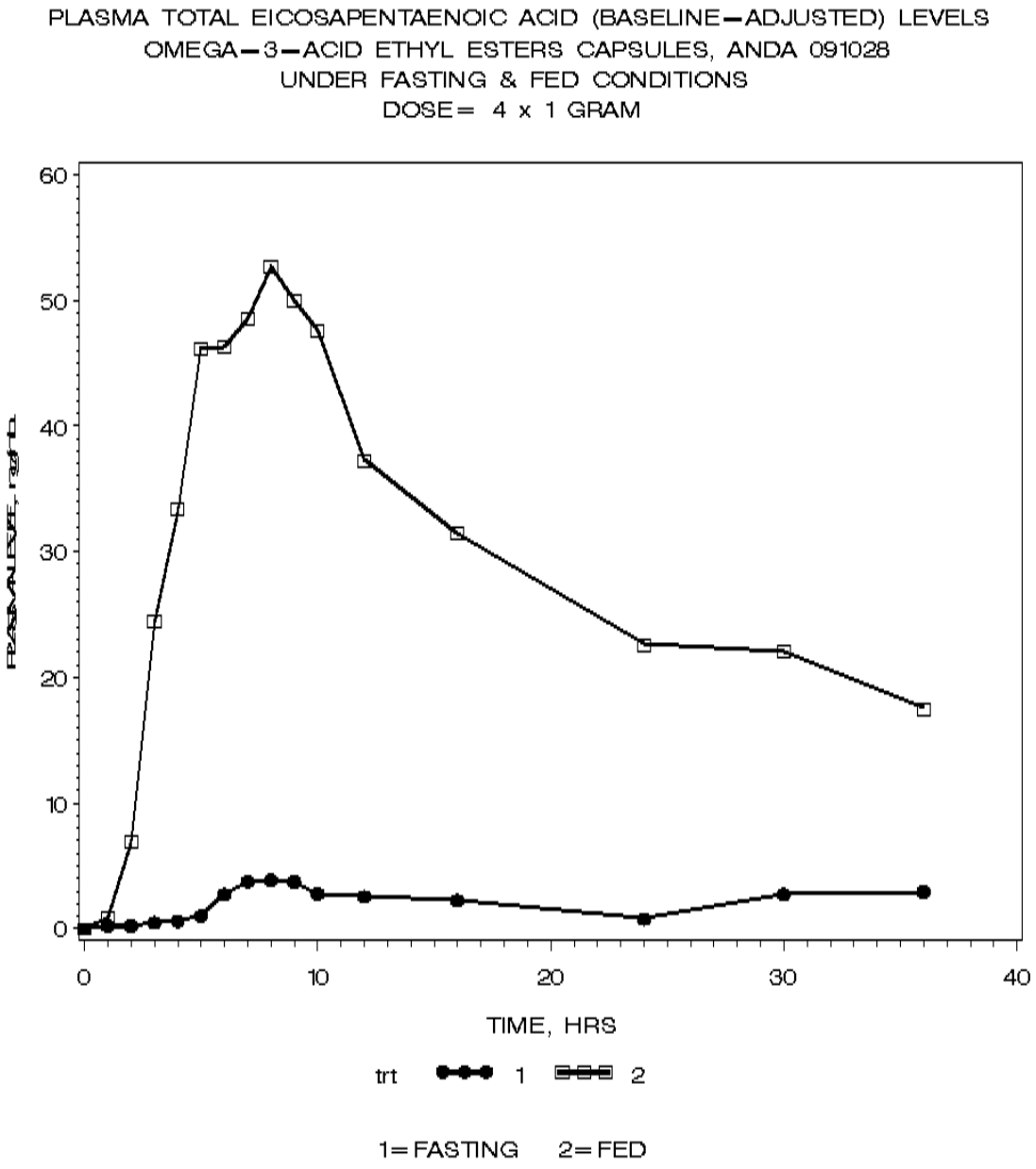


Reference ID: 3227106

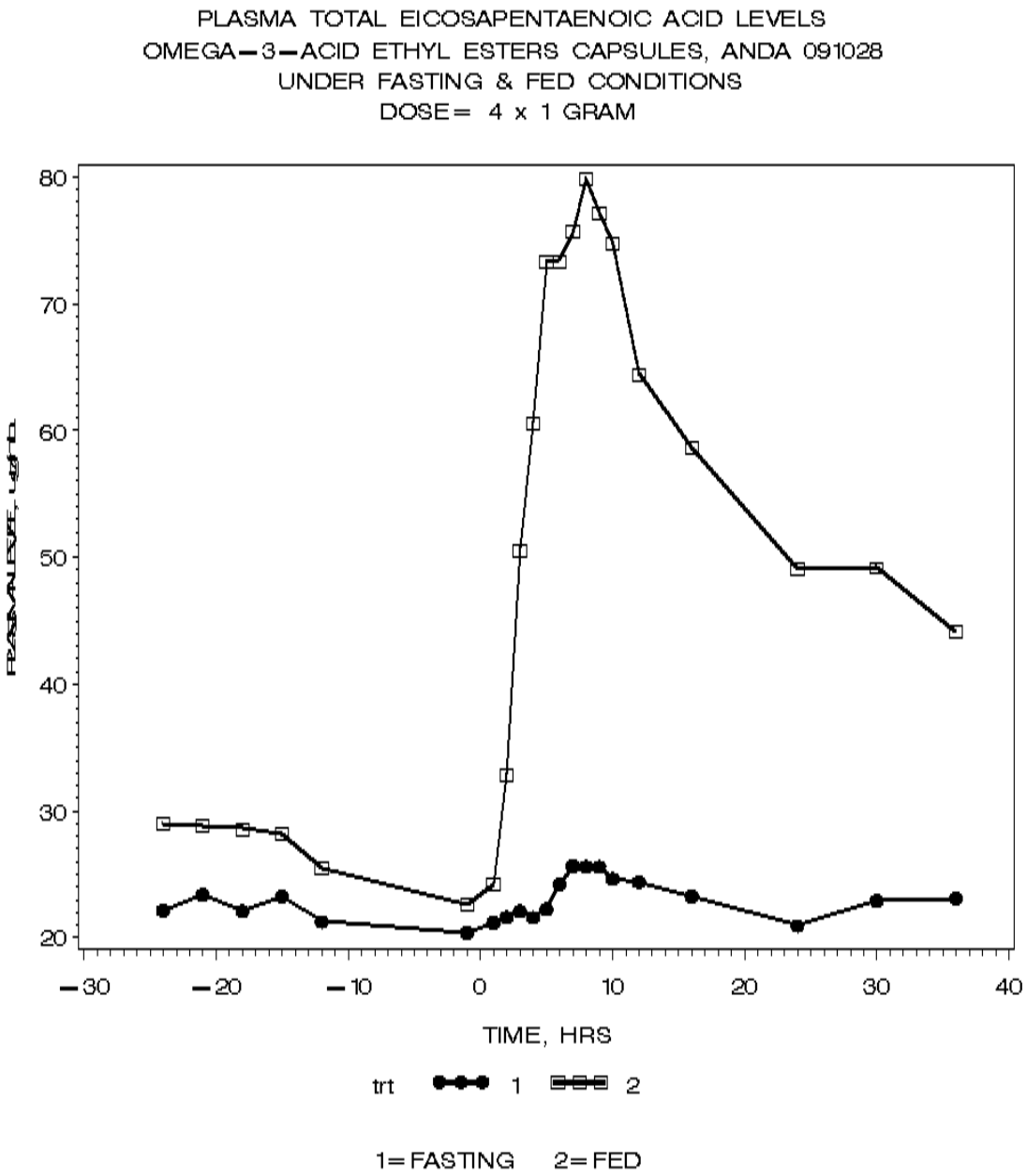
B. Baseline non-adjusted: Free EPA Fatty Acids



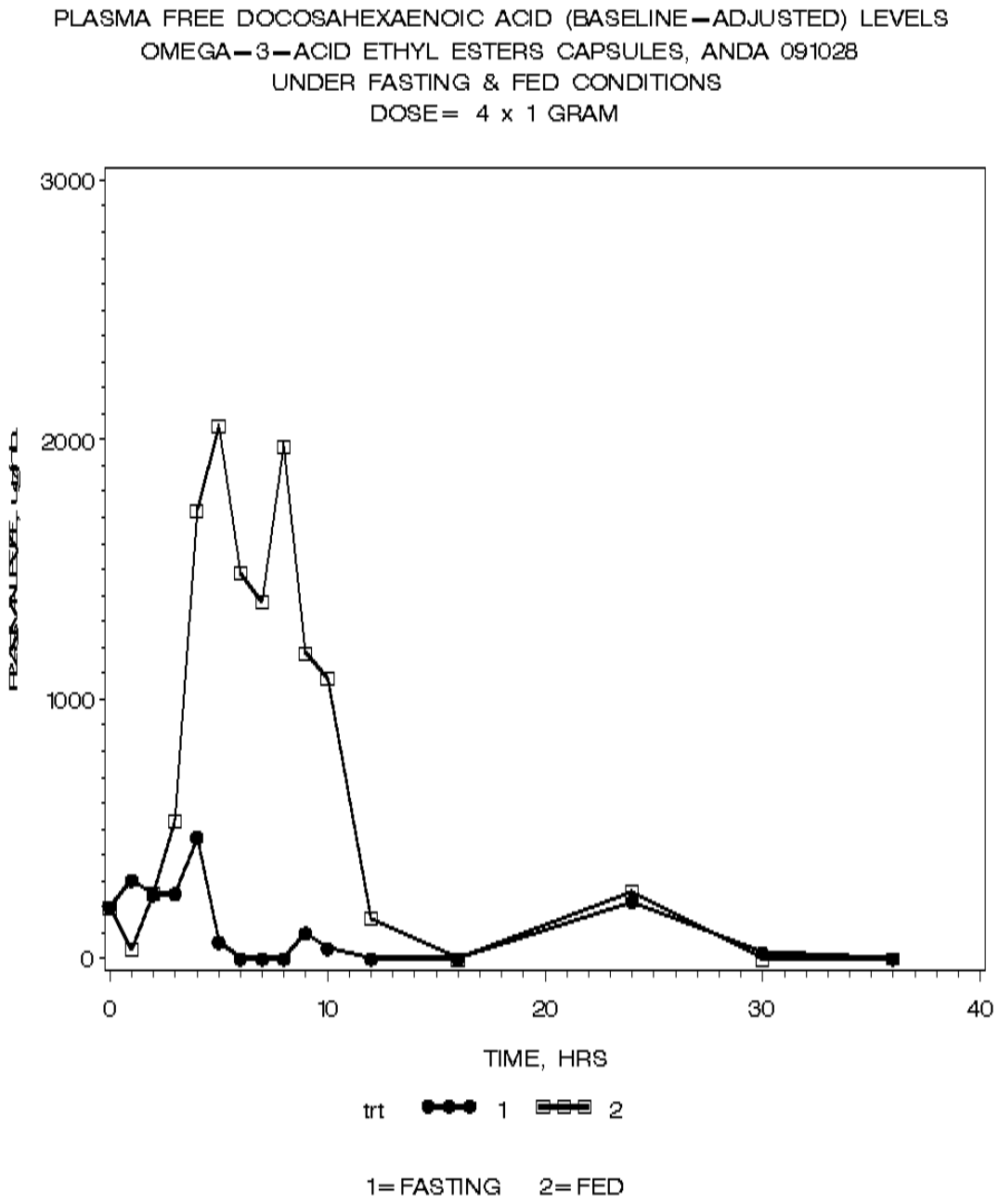
C. Baseline-adjusted: Total EPA Lipids



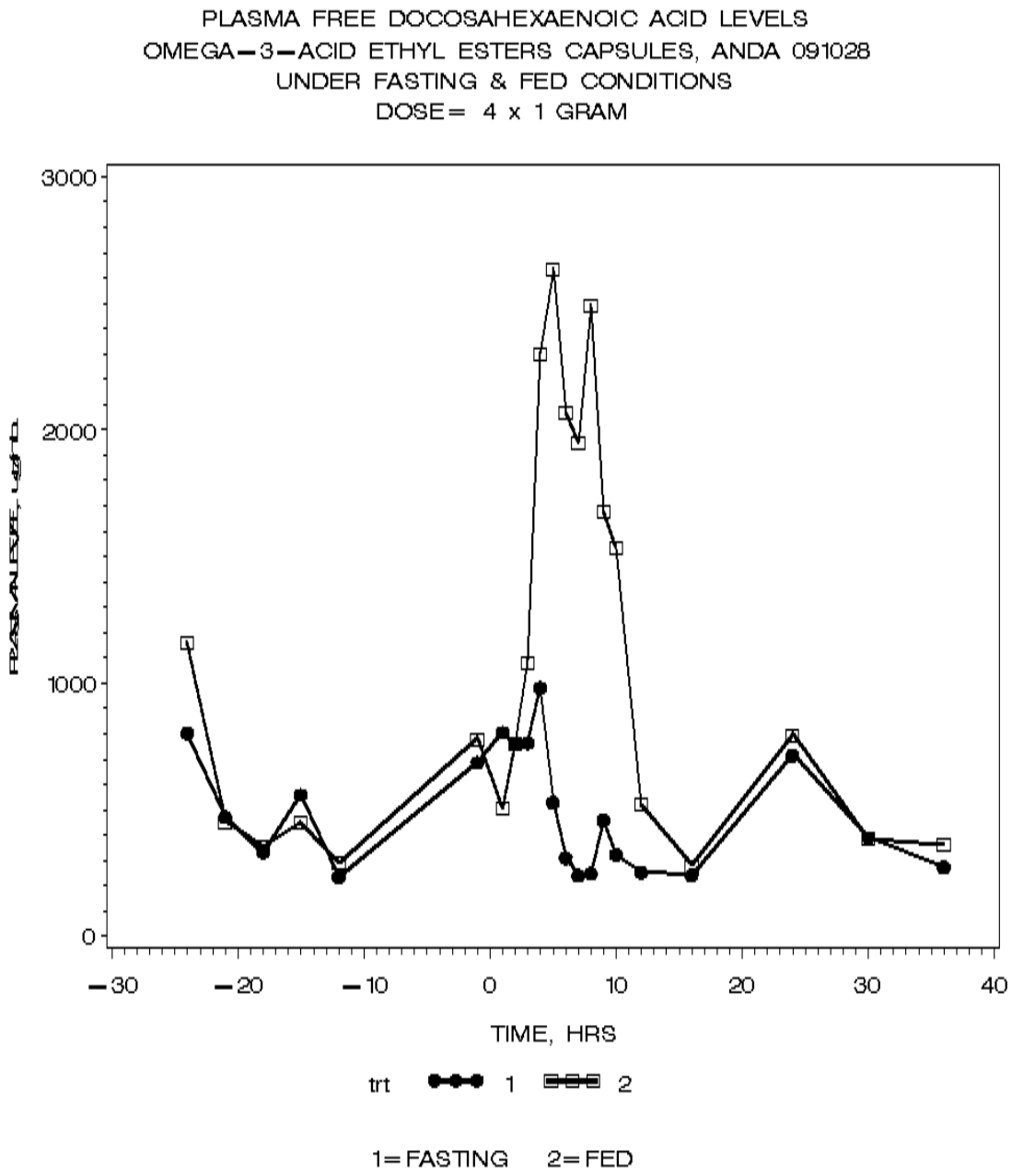
D. Baseline non-adjusted: Total EPA Lipids



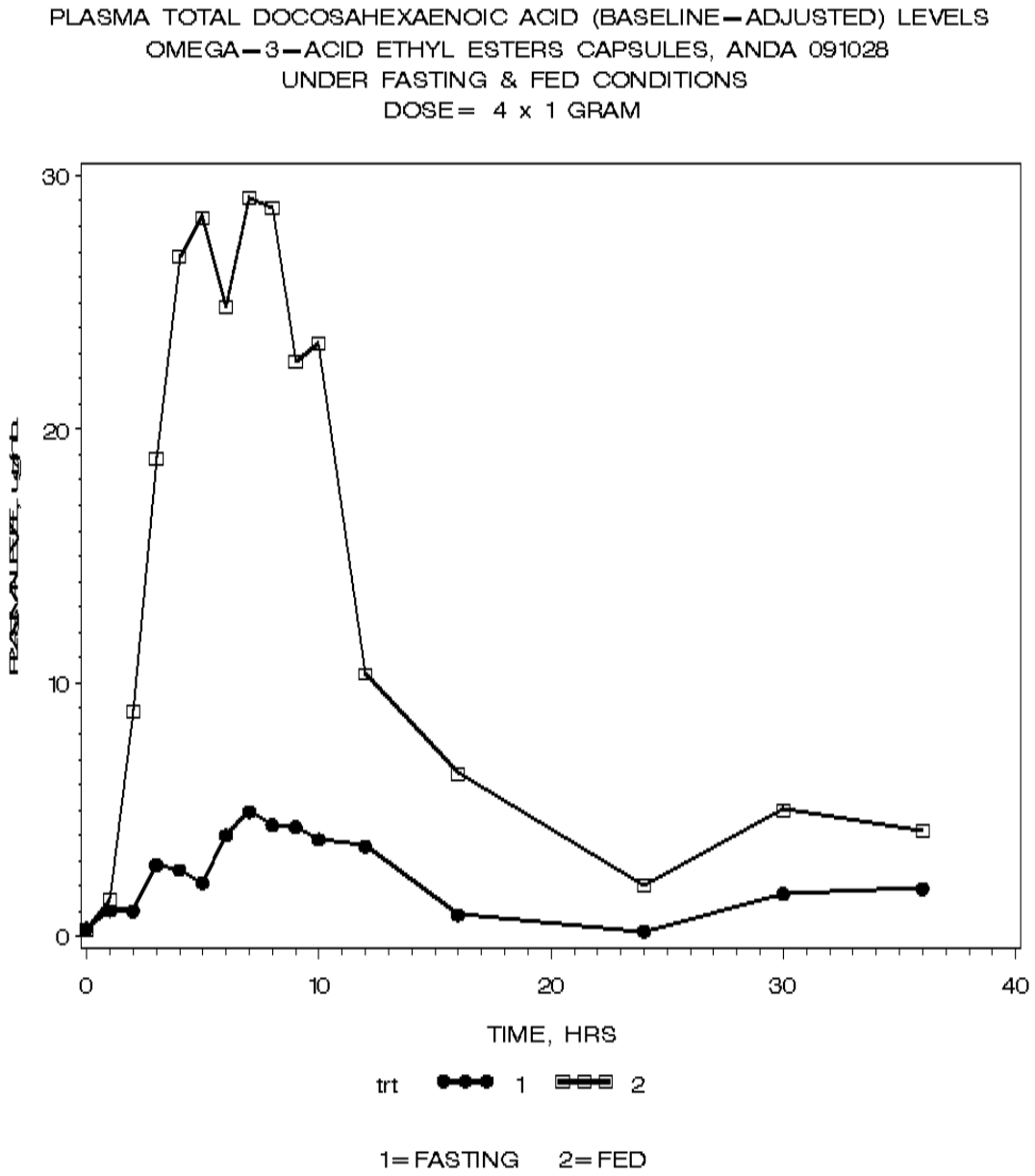
E. Baseline-adjusted: Free DHA Fatty Acids



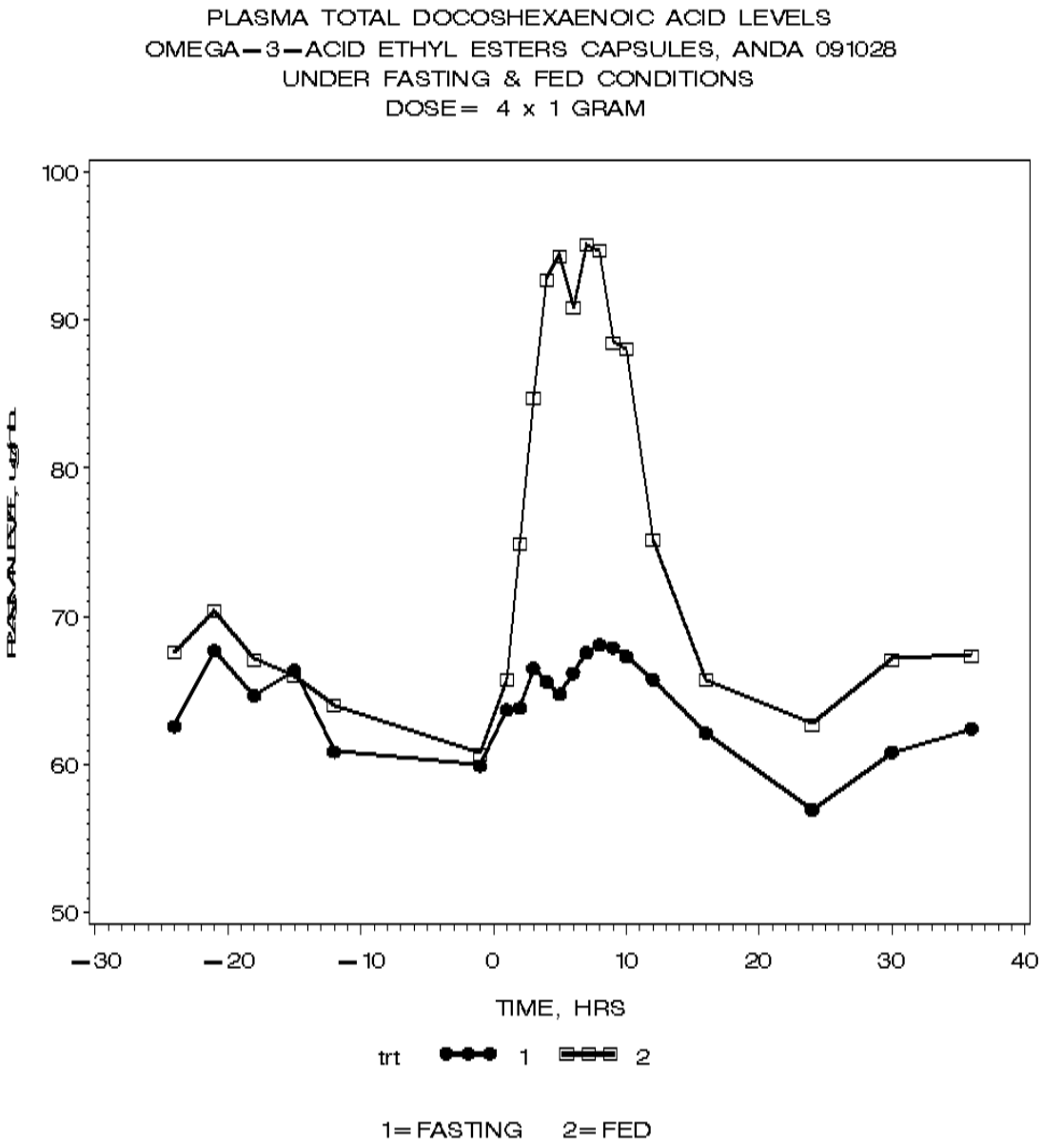
F. Baseline non-adjusted: Free DHA Fatty Acids



G. Baseline-adjusted: Total DHA Lipids



H. Baseline non-adjusted: Total DHA Lipids



4.1.2 Single-dose Pivotal Fed Bioequivalence Study

4.1.2.1 Study Design

Table 10. Study Information

Study Number	2008-1829/M1FX08001
Study Title	A Relative Bioavailability Study of 1000 mg Omega-3-Acid Ethyl Esters Capsules Versus 1000 mg Lovaza™ Capsules Under Fed Conditions
Clinical Site (Name, Address, Phone #)	Allied Research International, 1525 NW 167th Street Miami Gardens, Florida 33169. Phone: (305) 625-2183
Principal Investigator	Gilbert R. Weiner, DO, AOBFP, CPI (Principal Investigator)
Dosing Dates	Period I: August 28, 2008 Period II: September 4, 2008
Analytical Site (Name, Address, Phone #)	(b) (4)
Analysis Dates	October 08, 2008 and October 22, 2008 (Free Eicosapentaenoic acid and Free Docosahexaenoic acid) September 23, 2008 and October 8, 2008 (Eicosapentaenoic acid and Docosahexaenoic acid)
Analytical Director	(b) (6) M.Sc.
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	Fifty-six (56) days August 27, 2008 - October 22, 2008 (Free Eicosapentaenoic acid and Free Docosahexaenoic acid) Forty-two (42) days August 27, 2008 - October 8, 2008 (Eicosapentaenoic acid and Docosahexaenoic acid)

Table 11. Product Information

Product	Test	Reference
Treatment ID	A	B
Product Name	Omega-3-Acid Ethyl Esters Capsules, 1 g	Lovaza Capsules, 1 g
Manufacturer	Teva Pharmaceuticals USA	Catalent Pharma Solutions
Batch/Lot No.	P080602	7HH0014
Manufacture Date	June 24, 2008	N/A
Expiration Date	N/A	Nov 2010
Strength	1 g	1 g
Dosage Form	Capsule	Capsule
Bio-batch Size	(b) (4) Capsules	N/A
Production Batch Size	Capsules	N/A
Potency Eicosapentaenoic Acid **Docosahexaenoic Acid** **Total Omega-3 Acid Ethyl Ester**	103.4% 95.3% (b) (4) mg/capsule	103.4% 95.3% (b) (4) mg/capsule
Content Uniformity (mean, %RSD,		N/A

Reference ID: 3227106

Acceptance Value) **Eicosapentaenoic Acid** **Docosahexaenoic Acid**	 102.8%, 0.5%, 2.6 97.8%, 0.5%, 1.9	
Dose Administered	4 x 1 g capsule	4 x 1 gram capsule
Route of Administration	Oral	Oral

Table 12. Study Design, Single-Dose Fed Bioequivalence Study

No. of Subjects	Enrolled: 86 Dosed: 86 Completed: 80 Samples Analyzed: 80 Data Analyzed: 80
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	AB: 2,4,6,8,10,11,15,16,18,19,21,23,25,28,31,34,36,39,40,43, 44,45,47,49,50,54,56,57,58,61,64,65,68,71,72,73,75,77,79,81,84, and 86 BA: 1,3,5,7,9,12,13,14,17,20,22,24,26,27,29,30,32,33,35,37,38, 41,42,46,48,51,52,53,55,59,60,62,63,66,67,69,70, 74,76,78,80,82,83 and 85
Blood Sampling Times	Baseline at -24, -23, -22, -21, -20, -19, -18, -17, -16, -15, -14, -12, -10, -8, -4 and 0 hours pre-dose, and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 20, 24, 28, 32 and 36 hours post-dose.
Blood Volume Collected/Sample	10 mL
Blood Sample Processing/Storage	Blood samples were collected using a syringe through an indwelling intravenous cannula placed in the forearm vein of the subjects and then transferred into pre-labeled vacutainers containing K_2EDTA as the anticoagulant. After collection from subjects, blood samples were centrifuged at approximately 4 ^{0}C with 3500 rpm for 8 minutes to separate plasma from whole blood. Three aliquots were transferred to pre-labeled fresh polypropylene tubes and stored in a freezer at -70 ^{0}C or colder until shipment to an analytical facility.
IRB Approval	Yes, August 25, 2008
Informed Consent	Yes, August 25, 2008
Length of Fasting Before Meal	At least 10 hours overnight fast and then a high-fat, high calorie breakfast was given to the subjects 30 minutes prior to dosing.
Length of Confinement	Approximately 34.5 hours prior to drug administration per study period until 36 hours postdose.

Reference ID: 3227106

Safety Monitoring	Clinical laboratory tests were performed for each subject at the time of check-in and post-study procedures including urinalysis, serum chemistry, hematology and pregnancy (female subjects) clinical lab tests. Body temperature and physical examinations were performed at the time of each study period. Subjects were questioned regarding their health status throughout study. Medical investigator was present or on-call throughout the study.

Standard FDA Meal Used?	Yes

Comments on Study Design:

The study design is acceptable.

4.1.2.2 Clinical Results

Table 13. Demographics Profile of Subjects Completing the Bioequivalence Study

2008-1829 / M1FX08001			
		Treatment Groups	
		Test Product N = 80	Reference Product N = 80
Age (years)	Mean ± SD	46 ± 6	46 ± 6
	Range	23 - 64	23 - 64
Age Groups	< 18	0 (0%)	0 (0%)
	18 – 40	30 (37.5%)	30 (37.5%)
	41 – 64	48 (60%)	48 (60%)
	65 – 75	2 (2.5%)	2 (2.5%)
	> 75	0 (0%)	0 (0%)
Sex	Male	31 (38.75%)	31 (38.75%)
	Female	49 (61.25%)	49 (61.25%)
Race	Asian	0 (0%)	0 (0%)
	Black	5 (6.25%)	5 (6.25%)
	Caucasian	74 (92.5%)	74(92.5%)
	Other	1 (1.25%)	1 (%)
Ethnicity	Hispanic	78 (97.5%)	78 (97.5%)
	African American	2 (2.5%)	2 (2.5%)
BMI	Mean ± SD	25.8 ± 2.5	25.8 ± 2.5
	Range	20.2 - 30.0	20.2 - 30.0

Reference ID: 3227106

Table 14. Dropout Information, Fed Bioequivalence Study

Study No. 2008-1829				
Subject No	**Reason for dropout/replacement**	**Period**	**Replaced?**	**Replaced with**
14	Subject did not show for Period 2	2	N	N/A
15	Subject did not show for Period 2	2	N	N/A
35	Subject did not show for Period 2	2	N	N/A
36	Subject did not show for Period 2	2	N	N/A
85	Subject did not show for Period 2	2	N	N/A
76	Subject did not show for Period 2	2	N	N/A

Table 15. Study Adverse Events, Fed Bioequivalence Study

Body System / Adverse Event	**Reported Incidence by Treatment Groups**	
	Fed Bioequivalence Study 2008-1829 / M1FX08001	
	Test	**Reference**
Body as a whole		
Chills	1 (7.14%)	0 (0%)
Dizziness	0 (0%)	2 (13.33%)
Body ache	0 (0%)	1 (6.67%)
Pain on right bottom rib	0 (0%)	1 (6.67%)
Upper Back Pain	1 (7.14%)	0 (0%)
Neurological system		
Low SBP (Systolic Blood Pressure)	0 (0%)	1 (6.67%)
Headache	0 (0%)	2 (13.33%)
Gastrointestinal system		
Lower Abdominal Pain	0 (0%)	1 (6.67%)
Bloating	1 (7.14%)	0 (0%)
Constipation	1 (7.14%)	2 (13.33%)
Gas in Abdominal Area	1 (7.14%)	0 (0%)
Heartburn	2 (14.28%)	0 (0%)
Nausea	2 (14.28%)	2 (13.33%)
Stomach Ache	1 (7.14%)	1 (6.67%)
Vomit	1 (7.14%)	0 (0%)
Other organ systems		
Blister right bottom lip	1 (7.14%)	0 (0%)
Coughing	0 (0%)	1 (6.67%)
Discolored on face & palm of hands	0 (0%)	1 (6.67%)
Loss of voice	1 (7.14%)	0 (0%)
Rash in left forearm	1 (7.14%)	0 (0%)
Total	**14**	**15**

Subjects Experiencing Emesis (Include in eCTD)

Subject Number	**Test/Reference**	**Period**	**Time Post-Dose**	**Duration Between Dosing and Emesis (hrs)**
--	-	--	--	--

Reference ID: 3227106

Do any of the adverse events require statistical analysis consideration (e.g. vomiting)? No.

If yes, does the time exceed the Tmax limit according to the *Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products*? N/A

Was the adverse event profile observed during the pivotal bioequivalence study the same for the test and reference product? No, there was a minimal difference in overall adverse drug events (AEs) between the test and reference product (14 vs. 15) under the fed conditions. However, such a small difference in the number of AEs is not expected to impact and/or should not raise additional clinical questions on the outcome of the BE study.

Table 16. Protocol Deviations, Fed Bioequivalence Study

2008-1829/M1FX08001		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
For Period 1, the following subject were 1 minute late for their schedule breakfast, for that reason the schedule dose time was push 1 minute to follow protocol section leaving a deviation on the pharmacokinetic samples that were collected one minute prior to the schedule pre dose times.		74, 78 and 80
Period 1, Samples 01-06 Time point -14.0 were in the centrifuge by 18:08 and out of the centrifuge is missing in error. However the samples were processed by 18:19 and Flash Frozen before the 30 minutes.	02, 04 and 06	01, 03 and 05
On Period 1 the 24.0 hr Health Check were not performed until 28.0 hr for all subjects.	02,04,06,08,10,11,,15,16,18,19,21,23,25,28,31,32,34,36,39,40,43,44,45,47,49,50,54,56,57,58,61,64,65,68,71,72,73,75,77,79,81,84and 86	01,03,05,07,09,12,13,14,17,20,22,24,26,27,29,30,33,35,37,38,41,42,46,49,51,52,53,55,59,60,62,63,66,67,69,70,74,76,78,80,82,83 and 85
For Period 1, Subject 72, Day -2 during the breakfast spill some milk and Subject 72, Day 2 Dinner complete all 95% of the meal. For Period 2, Subject 75, Day -2 Lunch and Subject 38, Day -1 dinner the Check mark for meal completion in missing in error. However the staff member document the collection time, with the initial and date.	72	38
Subject 29 has check-in laboratories for period 2 that have pregnancy laboratories results for urine and serum labs although only urine is required by the protocol and documented in the source.	29	
On Period 1, Subjects 74, 78 and 80 had the vitals done for time points 6.0 and 12.0 hr one minute earlier that the time range allow by the protocol.		74,78 and 80
For Period 2 Subject 74, 78 and 80 were dosed 1 minute earlier that the 7 days washout allowed by the protocol	74,78 and 80	
During Period 1 and 2 some subject are missing the vitals signs taken time in error.	04,and 50	81

Reference ID: 3227106

2008-1829/M1FX08001		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
During Period 1 and 2 the following subject check-in late:		

Period 1:

Subject ID	Check-In Time	Dose Time
(b) (6) #32	13:04	09:28
#43	13:44	09:28
#46	10:01	08:44
#53	13:29	08:52
# 57	08:00	08:56
# 58	08:02	08:56
# 59	08:05	08:58
# 60	08:06	08:58
# 61	12:05	09:00
# 62	08:11	09:00
# 63	08:14	09:02
# 64	08:17	09:02
# 65	09:58	09:04
# 66	08:22	09:04
# 67	08:25	09:06
#68	13:01	09:06
# 69	08:33	09:08
#70	08:34	09:08
# 71	15:54	09:30
# 72	08:41	09:10
# 74	08:46	09:12
# 75	08:48	09:14
# 76	08:52	09:14
# 77	08:55	09:16
# 78	08:58	09:16
# 79	09:00	09:18
# 80	09:03	09:18
# 81	09:36	09:20
#82	12:59	09:20
#83	09:44	09:22
#84	09:53	09:22
#85	09:54	09:24
#86	10:03	09:24

32, 43, 57, 58, 61, 64,65,,68,71,72,73,75,77,79,81 and 84.

46, 53, 59, 60, 62, 63,66,67,69,70,74,76, 78,80,82 and 83.

Period 2:

Subject ID	Check-In Time	Dose Time
(b) (6) 02	09:16	08:00
04	10:09	08:02
05	10:00	08:04
#10	10:06	08:08
#13	12:20	08:12
#21	10:00	08:20

05, 13, 27, 53, 63, 66, 67, 70, 74, 80 and 82.

02, 04, 10, 21, 57, 61 and 75.

Reference ID: 3227106

2008-1829/M1FX08001					
Type				**Subject #s (Test)**	**Subject #s (Ref.)**
	(b) (6) #27	11:20	08:26		
	#53	13:50	08:52		
	#57	11:53	08:56		
	61	13:00	09:00		
	#63	12:30	09:02		
	#66	09:26	09:04		
	#67	12:18	09:06		
	#70	10:41	09:08		
	71	11:22	09:30		
	#72	11:50	09:10		
	#74	11:30	09:12		
	#75	15:28	09:14		
	80	09:30	09:18		
	#82	11:30	09:20		

2008-1829/M1FX08001

Type

Samples were less that the time required in the centrifuge:

Period 1

Time Point	Samples ID	Centrifugation	Deviation (HH:MM)
-24.0	19-24	09:27 - 09:34	00:07
-23.0	19-24	09:27 - 09:34	00:07
-22.0	79-84	11:28 - 11:33	00:05
-21.0	19-24	11:28 - 11:33	00:05
-20.0	79-84	13:27 - 13:34	00:07
-19.0	19-24	13:27 - 13:34	00:07
-18.0	49-54	14:55 - 15:02	00:07
-18.0	79-84	15:26 - 15:33	00:07
-17.0	19-24	15:26 - 15:33	00:07
-16.0	49-54	16:55 - 16:53	UNK *
-15.0	67-70, 72	18:14 - 18:52	UNK**
-14.0	49-51, 52, 53, 54	18:57 - 19:03	00:06
-12.0	49-54	20:55 - 21:02	00:07
-4.0	49-54	04:55 - 05:02	00:07
1.0	19-24	09:25 - 09:32	00:07
1.0	49-54	09:55 - 10:02	00:07
1.0	79-84	10:26 - 10:33	00:07
2.0	19-24	10:26 - 10:33	00:07
3.0	49, 50, 52-54	11:56 - 12:03	00:07
5.0	54	14:07 - 14:06	UNK***
10.0	49-54	18:55 - 19:01	00:06
28.0	19-24	12:25 - 12:32	00:07
28.0	31, 33-36	12:37 - 12:44	00:07
28.0	49-53, 54	12:55 - 13:01	00:06
28.0	67-70, 72	13:13 - 13:20	00:07
28.0	79-84	13:25 - 13:32	00:07
32.0	19-24	16:25 - 16:32	00:07
32.0	67-70, 72	17:13 – 17:20	00:07

Period 2

Time Point	Samples ID	Centrifugation	Deviation (HH:MM)
-24.0	37-42	08:43 - 08:50	00:07
- 24.0	44- 48	08:50 - 08:57	00:07
- 24.0	49 -54	08:55 - 09:02	00:07
- 24.0	73-75, 77-78	09:20 - 09:27	00:07
- 23.0	13, 16-18	09:20 - 09:27	00:07
-23.0	44 -48	09:49 - 09:56	00:07
-23.0	55 - 60	10:02 - 10:08	00:06
-21.0	49-54	11:57 -12:01	00:04
-21.0	13, 16-18	12:19 -12:26	00:07
-21.0	73-75, 77-	12:19 -12:26	00:07

Subject #s (Test)	Subject #s (Ref.)
19,21,23,,31,34,364 9,50,54,72,79,81 and 84.	20,22,24,33,35,49,51, 52,53,,67,69, ,80,82 and 83.
01,03,05, 07, 09, 12, 13,17, 20, 22, 24,	02, 04, 06, 08, 10, 11,16, 18, 19, 21, 23,

Reference ID: 3227106

2008-1829/M1FX08001					
Type				**Subject #s (Test)**	**Subject #s (Ref.)**
	78			33, 37, 38, 41, 42, 46, 48, 51, 52, 53, 55, 59, 60, 62, 63, 66, 67, 69, 70, 74, 78, 80,82,and 83.	31, 34, 39, 40, 44, 45, 47, 49, 50, 54, 56, 57, 58, 61, 64, 65, 68, 72, 73, 75, 77, 79, 81 and 84.
-20.0	07-12	12:15 - 12:22	00:07		
-20.0	67-70, 72	13:14 - 13:20	00:06		
-20.0	79 - 84	13:26 - 13:32	00:06		
-19:0	07 - 12	13:14 - 13:20	00:06		
-19.0	19-24	13:26 - 13:32	00:06		
-18.0	44 - 48	14:50 -14:56	00:06		
-17.0	37-42	15:43 -15:50	00:07		
-17.0	53	15:57 -16:04	00:07		
-17.0	67-70, 72	16:14 -16:20	00:06		
-16.0	07-12	16:14 -16:20	00:06		
-15.0	61-66	18:08 -18:15	00:07		
-14.0	01-06	18:08 - 18:15	00:07		
-10.0	13, 16-18	22:19 - 22:26	00:07		
2.0	49 - 53	10:56 - 11:03	00:07		
2.0	55 - 60	11:01 - 11:08	00:07		
3.0	12	11:18 -11:25	00:07		
3.0	44-48	11:49 -11:56	00:07		
4.0	65	13:10 -13:17	00:07		
5.0	37 - 42	13:43 -13:49	00:06		
5.0	61-66	14:09 -14:16	00:07		
6.0	01-06	14:09 -14:16	00:07		
6.0	31, 33, 34	14:35 - 14:42	00:07		
7.0	67-70, 72	16:14 - 16:21	00:07		
8.0	07-12	16:14 - 16:21	00:07		
9.0	31, 33, 34	17:35 - 17:42	00:07		
14.0	61-66	23:07 - 23:13	00:06		
20.0	07-12	04:12 - 04:11	* UNK		
24.0	13, 16-20	08:22 - 08:29	00:07		
36.0	61-64, 66	21:07- 21:13	00:06		
36.0	13, 16-18	20:19 – 20:26	00:07		
36.0	31, 33, 34	20:36 – 20:43	00:07		
36.0	44-48	20:49 – 20:56	00:07		

Comments on Adverse Events/Protocol Deviations:

Dropouts:
There were 86 subjects enrolled in the pilot study, 80 subjects completed the study and were determined for PK parameters for statistical analysis. Six subjects (Subject nos: 14, 15, 35, 36, 76 and 85) were withdrawn from the fed study all due to the reason of failure to report to the clinical study facility in Period II of the study, which were in compliance with the firm's study protocol (Protocol #CRI-00014468; Page 31) [see DARRTS for ANDA 091028: New/ANDA Original-1 View EDR; Submit/Final Date 11/10/2008, for details).

Adverse Events:
No serious adverse drug event was reported. According to the case report forms, all reported adverse events (AEs) were graded as "mild" in intensity. No vomiting event was reported in the fed BE study.

Reference ID: 3227106

Protocol Deviations:
There were some blood sampling time deviations reported during the pilot bioequivalence study which occurred in less than 5% of the nominal time points, and thus considered to be insignificant. The firm used actual sampling times for its PK calculation and the reviewer used nominal times for its PK calculation. Based on the results which are similar for both time deviations should not have an impact on the outcome of the study.

Therefore, the "Dropouts/Adverse Events/Protocol Deviations" are **acceptable.**

Reference ID: 3227106

4.1.2.3 Bioanalytical Results

Table 17. Assay Validation – During the Fed Bioequivalence Study

Free Eicosapentaenoic Acid

Bioequivalence Study No. 2008-1829 Free Eicosapentaenoic Acid									
Parameter	**Standard Curve Samples**								
Concentration (ng/mL)	10.0	20.0	50.0	125	350	750	1500	3000	5000
Inter day Precision (%CV)	1.8	3.7	3.3	2.5	2.3	2.2	2.0	1.7	1.2
Inter day Accuracy (%Actual)	101.0	98.0	99.4	99.2	100.3	100.5	100.8	102.6	98.2
Linearity	0.9976-0.9999								
Linearity Range (ng/mL)	10.0 -5000 ng/mL								
Sensitivity/LOQ (ng/mL)	10.0 ng/mL								

Bioequivalence Study No. 2008-1829 Free Eicosapentaenoic Acid						
Parameter	**Quality Control Samples**					
Concentration (ng/mL)	30.0	400	4000	182	2240	4360
Inter day Precision (%CV)	4.1	3.2	2.9	5.2	4.7	4.9
Inter day Accuracy (%Actual)	100	100.5	100.8	92.9	94.3	96.2

Free Docosahexaenoic Acid

Bioequivalence Study No. 2008-1829 Free Docosahexaenoic Acid									
Parameter	**Standard Curve Samples**								
Concentration (ng/mL)	10.0	20.0	50.0	125	350	750	1500	3000	5000
Inter day Precision (%CV)	2.0	4.6	4.1	2.9	2.4	2.6	2.4	2.0	1.4
Inter day Accuracy (%Actual)	101.0	97.5	99.6	99.2	100.0	100.5	100.7	102.5	98.2
Linearity	0.9970-0.9999								
Linearity Range (ng/mL)	10.0 -5000 ng/mL								
Sensitivity/LOQ (ng/mL)	10.0 ng/mL								

Bioequivalence Study No. 2008-1829 Free Docosahexaenoic Acid							
Parameter	**Quality Control Samples**						
Concentration (ng/mL)	30.0	400	4000	707	2070	4190	4900
Inter day Precision (%CV)	5.0	3.6	3.1	5.5	5.3	6.0	2.5
Inter day Accuracy (%Actual)	99.7	99.8	100.7	94.9	97.6	98.8	91.6

Total Eicosapentaenoic Acid

Bioequivalence Study No. 2008-1829 Eicosapentaenoic Acid								
Parameter	**Standard Curve Samples**							
Concentration (µg/mL)	1.00	2.00	5.00	10.0	25.0	50.0	100	150
Inter day Precision (%CV)	5.9	3.0	3.6	3.6	3.2	2.6	2.6	0.9
Inter day Accuracy (%Actual)	99.8	97.0	100.8	104.0	96.8	105.0	96.1	101.3
Linearity	0.9966-0.9999							
Linearity Range (µg/mL)	1.00 -150 µg/mL							
Sensitivity/LOQ (µg/mL)	1.00 µg/mL							

Bioequivalence Study No. 2008-1829 Eicosapentaenoic Acid

Reference ID: 3227106

Parameter	Quality Control Samples						
Concentration (µg/mL)	3.00	20.0	120	6.12	63.1	99.3	105
Inter day Precision (%CV)	4.8	4.4	4.0	5.1	3.9	4.1	4.5
Inter day Accuracy (%Actual)	97.7	98.5	102.5	103.6	98.7	100.6	101.0

Total Docosahexaenoic Acid

Bioequivalence Study No. 2008-1829 Docosahexaenoic Acid								
Parameter	**Standard Curve Samples**							
Concentration (µg/mL)	1.00	2.00	5.00	10.0	25.0	50.0	100	150
Inter day Precision (%CV)	5.5	3.5	4.7	4.2	2.9	2.5	3.0	1.1
Inter day Accuracy (%Actual)	99.9	96.5	101.0	104.0	96.8	104.4	96.8	100.7
Linearity	0.9963-0.9999							
Linearity Range (µg/mL)	1.00 -150 µg/mL							
Sensitivity/LOQ (µg/mL)	1.00 µg/mL							

Bioequivalence Study No. 2008-1829 Docosahexaenoic Acid							
Parameter	**Quality Control Samples**						
Concentration (µg/mL)	3.00	20.0	120	25.8	56.7	91.9	118
Inter day Precision (%CV)	4.4	4.5	4.6	5.3	4.5	3.9	3.8
Inter day Accuracy (%Actual)	97.7	98.5	102.5	100.4	100.0	103.6	101.7

Number of Acceptable Runs	Free EPA assay: 44 Free DHA assay: 44 Total EPA assay: 45 Total DHA assay:45
Number of Rejected Runs (Run ID, volume/page location)	Free EPA assay: None (not reported) Free DHA assay: None (not reported) Total EPA assay: None (not reported) Total DHA assay: None (not reported)
If sample and QC diluted during study, specify all dilution factors	QC dilution: None Reanalysis sample dilution: Free EPA assay- dilution factor=2 Free DHA assay- dilution factor=2 Total EPA assay- dilution factor= 2 & 5 Total EPA assay- dilution factor= 2 & 5
Was 100% of raw numerical data submitted?	No

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	Yes
Do you agree with the firm's accepted and rejected runs?	Agree

Comments on Study Assay Validation:

Acceptable.

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Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes Free EPA: 22.5% Free DHA: 22.5% Total EPA: 20.0% Total DHA: 20.0%
Were chromatograms serially or randomly selected?	Randomly selected: Free EPA: sub#s 39-56 Free DHA: sub#s 39-56 Total EPA: sub#s 31-34 & 37-48 Total DHA: sub#s 31-34 & 37-48

Comments on Chromatograms:

Acceptable.

Table 27. Additional Comments on Repeat Assays

Were all SOPs followed?	The analytical numerical raw data were not submitted for all the subjects in fed study.
Did recalculation of PK parameters change the study outcome?	Please see the above comments
Does the reviewer agree with the outcome of the repeat assays?	Please see the above comments
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays:

Incomplete. The firm did not submit the complete analytical/reanalytical raw numerical data from study runs of all the subjects related to its fed study.

Reference ID: 3227106

4.1.2.4 Pharmacokinetic Results

Table 28. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 32 and Figure 2

Eicosapentaenoic acid (EPA; Free fatty acids)-Baseline adjusted

Fed Bioequivalence Study, Study No. 2008-1829, N=80									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	5.437	29.74	1.21	10.00	5.590	25.15	2.73	9.99	0.97
Cmax (ng/ml)	0.896	40.74	0.12	1.69	0.940	39.24	0.31	2.43	0.95
Tmax* (hr)	6.000	.	3.00	12.00	6.000	.	3.00	12.00	1.00

* Tmax values are presented as median, range

Eicosapentaenoic acid (EPA; Free fatty acids)-Baseline non-adjusted

Fed Bioequivalence Study, Study No. 2008-1829, N=80									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	8590.511	28.85	3566.85	16350.30	8729.294	25.09	4569.65	15616.90	0.98
Cmax (ng/ml)	947.350	39.34	155.00	1750.00	994.875	37.07	361.00	2510.00	0.95
Tmax* (hr)	6.000	.	3.00	12.00	6.000	.	3.00	10.00	1.00

* Tmax values are presented as median, range

Eicosapentaenoic acid (EPA; Total lipids)-Baseline adjusted

Fed Bioequivalence Study, Study No. 2008-1829, N=80									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *µg/ml)	1001.775	38.97	250.16	3277.80	1006.446	38.07	542.25	3420.10	1.00
Cmax (µg /ml)	80.072	49.70	21.23	263.90	81.702	41.10	32.67	199.00	0.98
Tmax* (hr)	6.000	.	3.00	14.00	6.000	.	5.00	12.00	1.00

* Tmax values are presented as median, range

Reference ID: 3227106

Eicosapentaenoic acid (EPA; Total lipids)-Baseline non-adjusted

Fed Bioequivalence Study, Study No. 2008-1829, N=80									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *µg /ml)	1781.129	41.78	673.29	6624.75	1749.854	33.41	924.89	4975.20	1.02
Cmax (µg /ml)	93.546	46.62	28.30	308.00	94.274	37.44	39.80	226.00	0.99
Tmax* (hr)	6.000	.	3.00	14.00	6.000	.	5.00	12.00	1.00

* Tmax values are presented as median, range

Docosahexaenoic Acid (DHA; Free fatty acids)-Baseline adjusted

Fed Bioequivalence Study, Study No. 2008-1829, N=80									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	13.375	33.26	1.17	24.86	13.194	27.41	6.07	23.78	1.01
Cmax (ng/ml)	2.659	41.41	0.30	4.75	2.686	35.35	0.78	5.53	0.95
Tmax* (hr)	6.000	.	0.00	12.00	6.000	.	4.00	10.00	1.00

* Tmax values are presented as median, range

Docosahexaenoic Acid (DHA; Free fatty acids)-Baseline non-adjusted

Fed Bioequivalence Study, Study No. 2008-1829, N=80									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	8590.511	28.85	3566.85	16350.30	8729.294	25.09	4569.65	15616.90	0.98
Cmax (ng/ml)	947.350	39.34	155.00	1750.00	994.875	37.07	361.00	2510.00	0.95
Tmax* (hr)	6.000	.	3.00	12.00	6.000	.	3.00	10.00	1.00

* Tmax values are presented as median, range

Docosahexaenoic Acid (DHA; Total lipids)-Baseline adjusted

Fed Bioequivalence Study, Study No. 2008-1829, N=80									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *µg/ml)	389.342	81.04	7.80	2146.00	363.797	76.59	24.50	2006.15	1.07
Cmax (µg /ml)	54.096	66.03	3.80	223.00	52.276	53.51	10.20	153.30	1.03
Tmax* (hr)	5.000	.	3.00	14.00	5.500	.	5.00	12.00	0.91

* Tmax values are presented as median, range

Docosahexaenoic Acid (DHA; Total lipids)-Baseline non-adjusted

Fed Bioequivalence Study, Study No. 2008-1829, N=80									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *µg /ml)	3569.231	35.77	1652.45	10349.50	3484.638	29.97	1574.60	7518.55	1.02
Cmax (µg /ml)	109.006	42.29	44.70	359.00	105.515	32.44	41.60	245.00	1.03
Tmax* (hr)	5.000	.	4.00	36.00	5.000	.	-24.00	12.00	1.00

* Tmax values are presented as median, range

Table 29. Geometric Means and 90% Confidence Intervals - Firm Calculated

Omega-3 Acid Ethyl Esters Dose (4 x 1000 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study (Study No. 2008-1829)				
Eicosapentaenoic acid (total lipids)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	947.91	959.65	98.78	94.24 - 103.53
Cmax	72.68	75.44	96.34	90.56 - 102.49
Docosahexaenoic acid (total lipids)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	290.59	290.30	100.10	88.92 - 112.68
Cmax	44.06	44.86	98.23	89.87 - 107.36
Eicosapentaenoic acid (free fatty acids)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	5.141	5.412	94.99	90.26 - 99.96
Cmax	0.806	0.873	92.27	84.58 - 100.67
Docosahexaenoic acid (free fatty acids)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	12.369	12.688	97.49	90.76 - 104.71
Cmax	2.364	2.515	93.97	85.27 - 103.56

Table 30. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

EPA (Free fatty acids)-Baseline adjusted

Omega-3-acid ethyl esters Capsules 4 x 1 g Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. 2008-1829, N=80					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	5.14	5.41	0.95	90.25	99.94
Cmax (ng/ml)	0.81	0.87	0.92	84.58	100.67

EPA (Total lipids)-Baseline adjusted

Omega-3-acid ethyl esters Capsules 4 x 1 g Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. 2008-1829, N=80					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr * µg /ml)	947.89	959.67	0.99	94.23	103.53
Cmax (µg /ml)	72.68	75.44	0.96	90.56	102.49

DHA (Free fatty acids)-Baseline adjusted

Omega-3-acid ethyl esters Capsules 4 x 1 g Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. 2008-1829, N=80					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	12.37	12.69	0.97	90.74	104.70
Cmax (ng/ml)	2.36	2.52	0.94	85.27	103.56

DHA (Total lipids)-Baseline adjusted

Omega-3-acid ethyl esters Capsules 4 x 1 g Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. 2008-1829, N=80					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr * µg /ml)	290.58	290.33	1.00	88.91	112.67
Cmax (µg /ml)	44.06	44.86	0.98	89.87	107.36

Reference ID: 3227106

Table 31. Additional Study Information

EPA (Free fatty acids)

Root mean square error, AUC0-t	0.1937	
Root mean square error, Cmax	0.3306	
	Test	**Reference**
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	Yes	Yes
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

EPA (Total lipids)

Root mean square error, AUC0-t	0.1787	
Root mean square error, Cmax	0.2351	
	Test	**Reference**
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	Yes	Yes
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

DHA (Free fatty acids)

Root mean square error, AUC0-t	0.2716	
Root mean square error, Cmax	0.3691	
	Test	**Reference**
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	Yes	Yes
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

DHA (Total lipids)

Root mean square error, AUC0-t	0.4497	
Root mean square error, Cmax	0.3377	
	Test	**Reference**
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	Yes	Yes
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Reference ID: 3227106

Comments on Pharmacokinetic and Statistical Analysis:

- There was little available submitted data on PK parameter values for the Omega-3 Acid Ethyl Esters Capsules under the fasting and fed states for comparisons. Also, in a very limited study population (6 subjects; see Appendix 4.1 Single-dose Pilot Study of this review for details), the firm showed food may increase some PK parameters such as AUCt and Cmax. To date there is no approved ANDAs for this particular drug product. As per Lovaza® (omega-3 acid ethyl esters) label, *"In clinical studies, Lovaza was administered with meals"*. In addition, a new draft guidance for Omega-3 Acid Ethyl Esters Capsules was recently posted on September 2012 by the Division of Bioequivalence (DB), recommending fasting and fed BE studies for this drug product if firms choose to pursue *"In Vivo BE Study Option"* (see draft Guidance recommended on 9/2012 for details: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM320011.pdf).

- The pharmacokinetic measures (AUC_t and C_{max}) and confidence intervals of AUC_t and C_{max} for free EPA and DHA fatty acids, and those of total EPA and DHA lipids with baseline-adjustments, as calculated by the reviewer were in agreement with the values reported by the firm.

- The 90% confidence intervals (CIs) for free plasma EPA and DHA fatty acids of ln-transformed AUC_t and C_{max} ratios (T/R) with baseline-adjustments are within the acceptable limits of 80.00-125.00%.

- In addition, at the time the current application was submitted on November, 2008, four years before the current draft Guidance for Omega-3 Acid Ethyl Esters Capsules was posted (September 2012), there was no available BE recommendation for the drug product. Therefore, the BE study containing data for free EPA and DHA fatty acids, and total EPA and DHA lipids with baseline-adjustments was considered acceptable for filing, and no additional data on plasma EPA and DHA ethyl esters were requested at the time of filing. However, per the current draft Guidance, the firm will be asked to submit an additional fasting *in vivo* BE study if they wish to pursue *in vivo* option for their test product.

- The reviewer verified all statistical analyses for the firm's fed BE study using the SAS code of "CALCKE" (see V: DIVISION\BIO\SAS Programs\TWOWAYCALCKE 12FED2010 WITH TIME AND KE DATASET ENTRIES.SAS).

Summary/Conclusions, Single-Dose Fed Bioequivalence Study:

The fed *in vivo* bioequivalence study is inadequate due to the deficiency comments specified in the Section 3.10 (Deficiency Comments) of this review.

Reference ID: 3227106

Table 32. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

A. EPA (Free fatty acids)-Baseline adjusted

Free eicosapentaenoic acid					
Time (hr)	Test (n=80)		Reference (n=80)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.02	132.26	0.02	104.75	1.09
1.00	0.01	114.40	0.01	138.98	0.86
2.00	0.04	169.54	0.04	169.33	0.93
3.00	0.10	135.89	0.12	138.15	0.83
4.00	0.30	104.49	0.36	119.74	0.83
5.00	0.61	66.85	0.69	59.81	0.88
6.00	0.59	53.76	0.64	50.51	0.93
7.00	0.45	55.52	0.44	56.82	1.01
8.00	0.36	60.85	0.37	56.69	0.97
9.00	0.42	77.57	0.40	55.16	1.05
10.00	0.44	73.26	0.43	60.61	1.01
12.00	0.21	72.69	0.20	68.68	1.07
14.00	0.10	47.77	0.11	53.96	0.97
16.00	0.08	56.78	0.08	51.78	1.04
20.00	0.08	52.81	0.08	72.07	1.11
24.00	0.08	53.50	0.08	56.61	0.98
28.00	0.05	70.72	0.05	86.05	0.95
32.00	0.02	84.68	0.02	86.86	1.00
36.00	0.04	51.32	0.04	41.75	0.96

Reference ID: 3227106

B. EPA (Free fatty acids)-Baseline non-adjusted

Free eicosapentaenoic acid					
Time (hr)	Test (n=80)		Reference (n=80)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
-24.00	75.41	62.40	72.83	51.49	1.04
-23.00	42.16	67.57	39.52	52.84	1.07
-22.00	33.24	73.10	32.71	62.54	1.02
-21.00	36.70	60.15	37.08	56.02	0.99
-20.00	57.72	59.16	63.16	70.92	0.91
-19.00	42.75	59.20	41.52	49.47	1.03
-18.00	33.84	57.52	32.64	50.94	1.04
-17.00	33.82	59.19	33.77	47.61	1.00
-16.00	45.91	60.90	45.55	53.71	1.01
-15.00	65.15	54.88	69.36	55.20	0.94
-14.00	92.71	49.85	95.34	57.98	0.97
-12.00	32.65	62.67	30.42	47.87	1.07
-10.00	33.25	57.91	30.60	49.06	1.09
-8.00	47.43	55.40	50.00	47.19	0.95
-4.00	65.38	52.15	64.89	51.40	1.01
0.00	92.95	57.78	87.52	44.06	1.06
1.00	52.03	55.40	52.06	59.63	1.00
2.00	69.21	96.24	71.64	99.65	0.97
3.00	138.91	104.32	159.32	107.88	0.87
4.00	354.55	90.37	422.12	103.54	0.84
5.00	651.19	63.56	734.94	56.90	0.89
6.00	627.64	51.82	668.42	48.41	0.94
7.00	483.21	52.47	477.99	53.54	1.01
8.00	402.55	53.98	412.71	51.73	0.98
9.00	487.10	66.79	472.00	48.69	1.03
10.00	528.41	60.75	527.29	51.63	1.00
12.00	245.52	65.46	229.86	61.47	1.07
14.00	137.01	42.07	137.70	45.51	1.00
16.00	125.62	40.02	125.12	34.61	1.00
20.00	149.10	39.86	139.42	46.49	1.07
24.00	153.30	35.87	152.36	36.39	1.01
28.00	107.86	44.26	113.55	46.51	0.95
32.00	67.56	36.35	67.36	39.15	1.00
36.00	71.17	39.97	70.41	33.94	1.01

Reference ID: 3227106

C. EPA (Total lipids)-Baseline adjusted

Total eicosapentaenoic acid					
Time (hr)	Test (n=80)		Reference (n=80)		T/R Ratio
	Mean (µg/mL)	% CV	Mean (µg/mL)	% CV	
0.00	0.48	368.43	0.24	260.91	2.01
1.00	0.53	182.37	0.49	220.41	1.07
2.00	2.21	253.95	1.62	222.01	1.37
3.00	7.06	260.87	6.42	226.52	1.10
4.00	14.89	139.75	16.70	132.69	0.89
5.00	57.31	70.37	60.39	62.95	0.95
6.00	64.04	69.40	67.16	54.04	0.95
7.00	52.77	80.96	52.15	60.78	1.01
8.00	44.22	80.43	43.99	61.67	1.01
9.00	41.57	76.70	40.49	62.58	1.03
10.00	38.61	64.21	38.32	62.87	1.01
12.00	42.86	52.42	41.87	56.37	1.02
14.00	36.31	52.91	36.02	54.93	1.01
16.00	31.93	46.67	31.98	45.97	1.00
20.00	26.92	32.59	27.34	38.34	0.98
24.00	23.39	32.15	23.21	40.96	1.01
28.00	22.85	31.58	23.27	39.59	0.98
32.00	19.26	31.78	19.37	37.87	0.99
36.00	17.62	32.62	17.49	37.10	1.01

Reference ID: 3227106

D. EPA (Total lipids)-Baseline non-adjusted

Total eicosapentaenoic acid					
Time (hr)	Test (n=80)		Reference (n=80)		T/R Ratio
	Mean (µg/mL)	% CV	Mean (µg/mL)	% CV	
-24.00	13.15	73.45	12.76	47.03	1.03
-23.00	13.36	71.57	12.49	48.47	1.07
-22.00	13.26	71.08	12.72	49.74	1.04
-21.00	13.40	69.24	12.70	49.09	1.05
-20.00	13.46	69.90	12.74	49.13	1.06
-19.00	13.51	65.66	12.79	47.63	1.06
-18.00	13.63	65.77	12.83	46.90	1.06
-17.00	13.40	65.07	12.88	47.74	1.04
-16.00	13.68	65.56	12.97	47.69	1.06
-15.00	13.61	64.93	12.74	47.29	1.07
-14.00	13.31	64.89	12.83	47.52	1.04
-12.00	13.01	63.29	12.38	47.17	1.05
-10.00	13.00	64.61	12.28	46.44	1.06
-8.00	12.77	64.49	12.24	46.23	1.04
-4.00	12.01	62.63	11.54	46.24	1.04
0.00	12.05	64.74	11.51	46.03	1.05
1.00	12.47	62.23	12.02	46.26	1.04
2.00	14.37	66.25	13.45	49.57	1.07
3.00	19.72	103.81	18.47	84.19	1.07
4.00	28.05	84.71	29.17	78.98	0.96
5.00	70.82	60.92	73.17	53.17	0.97
6.00	77.66	61.93	79.99	47.33	0.97
7.00	66.17	70.74	65.03	52.38	1.02
8.00	57.90	67.89	56.96	51.75	1.02
9.00	55.17	64.74	53.23	52.12	1.04
10.00	51.92	55.74	51.14	51.69	1.02
12.00	55.87	48.46	54.25	47.57	1.03
14.00	49.31	49.43	48.30	46.16	1.02
16.00	44.71	45.66	44.21	38.64	1.01
20.00	38.92	34.88	38.88	34.13	1.00
24.00	36.54	30.42	35.97	32.03	1.02
28.00	36.31	29.70	36.01	31.85	1.01
32.00	32.94	29.28	32.33	30.63	1.02
36.00	30.63	30.18	29.87	28.76	1.03

Reference ID: 3227106

E. DHA (Free fatty acids)-Baseline adjusted

Free Docosahexaenoic acid					
Time (hr)	Test (n=80)		Reference (n=80)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.16	120.11	0.15	107.97	1.07
1.00	0.11	84.52	0.12	83.47	0.90
2.00	0.19	72.74	0.20	75.67	0.93
3.00	0.38	92.02	0.41	98.00	0.94
4.00	0.84	104.00	0.90	113.70	0.94
5.00	1.89	65.84	2.00	57.60	0.94
6.00	1.78	54.69	1.78	51.28	1.00
7.00	1.24	61.99	1.12	67.10	1.11
8.00	0.94	72.52	0.92	74.87	1.02
9.00	1.12	89.13	1.02	72.68	1.10
10.00	1.08	86.59	1.12	71.78	0.96
12.00	0.46	82.97	0.40	83.46	1.14
14.00	0.16	85.47	0.16	94.79	1.02
16.00	0.08	160.17	0.07	156.93	1.17
20.00	0.15	110.67	0.12	149.79	1.21
24.00	0.13	110.48	0.12	129.41	1.02
28.00	0.10	135.48	0.10	150.51	0.95
32.00	0.03	211.87	0.02	236.85	1.08
36.00	0.08	92.90	0.09	77.15	0.95

Reference ID: 3227106

F. DHA (Free fatty acids)-Baseline non-adjusted

Free Docosahexaenoic acid					
Time (hr)	Test (n=80)		Reference (n=80)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
-24.00	588.41	47.97	587.34	40.58	1.00
-23.00	298.37	59.27	287.09	47.89	1.04
-22.00	222.14	73.40	221.91	57.01	1.00
-21.00	254.72	49.81	259.80	49.30	0.98
-20.00	422.91	46.83	465.73	55.61	0.91
-19.00	347.61	51.25	345.00	46.88	1.01
-18.00	239.05	53.51	232.66	48.39	1.03
-17.00	225.51	45.92	237.32	46.31	0.95
-16.00	319.65	53.36	327.29	44.15	0.98
-15.00	480.50	47.35	525.58	45.47	0.91
-14.00	695.26	43.81	690.03	48.00	1.01
-12.00	210.08	58.22	195.68	46.17	1.07
-10.00	206.05	41.59	197.06	40.83	1.05
-8.00	350.49	45.31	377.76	46.69	0.93
-4.00	482.19	46.35	484.11	49.89	1.00
0.00	721.38	48.19	695.66	41.34	1.04
1.00	403.73	47.30	407.06	45.94	0.99
2.00	407.15	50.08	425.45	50.70	0.96
3.00	634.71	64.19	664.06	63.52	0.96
4.00	1260.91	75.39	1357.63	77.52	0.93
5.00	2239.00	58.26	2346.64	50.42	0.95
6.00	2015.53	50.49	2008.04	47.32	1.00
7.00	1465.38	54.10	1357.70	57.19	1.08
8.00	1250.66	55.18	1245.13	58.99	1.00
9.00	1583.56	62.39	1539.99	51.04	1.03
10.00	1774.75	53.29	1798.98	49.45	0.99
12.00	667.70	65.14	598.65	63.68	1.12
14.00	364.00	47.09	353.16	50.44	1.03
16.00	379.86	48.53	386.99	43.61	0.98
20.00	592.88	46.27	544.04	55.25	1.09
24.00	680.80	38.06	666.75	38.13	1.02
28.00	454.09	49.49	479.51	52.20	0.95
32.00	245.18	43.42	247.80	52.67	0.99
36.00	283.00	45.71	281.25	38.66	1.01

Reference ID: 3227106

G. DHA (Total lipids)-Baseline adjusted

Total Docosahexaenoic acid					
Time (hr)	Test (n=80)		Reference (n=80)		T/R Ratio
	Mean (µg/mL)	% CV	Mean (µg/mL)	% CV	
0.00	1.85	308.42	1.52	214.45	1.22
1.00	2.57	107.75	3.25	116.30	0.79
2.00	4.59	113.63	3.66	122.72	1.26
3.00	6.89	144.84	7.55	150.61	0.91
4.00	14.87	125.51	14.41	111.84	1.03
5.00	43.43	76.11	43.14	65.50	1.01
6.00	39.59	93.79	38.13	70.88	1.04
7.00	29.48	122.04	26.59	90.76	1.11
8.00	23.42	125.97	21.99	98.88	1.07
9.00	20.77	126.33	18.44	100.90	1.13
10.00	18.32	103.47	16.53	109.68	1.11
12.00	15.98	116.85	14.65	127.21	1.09
14.00	9.80	165.52	8.05	173.22	1.22
16.00	6.75	168.20	5.87	168.95	1.15
20.00	5.80	130.51	4.45	123.82	1.30
24.00	6.48	88.49	6.07	103.54	1.07
28.00	7.26	77.00	7.66	79.69	0.95
32.00	4.78	91.44	4.58	109.10	1.04
36.00	4.44	98.15	4.34	91.82	1.02

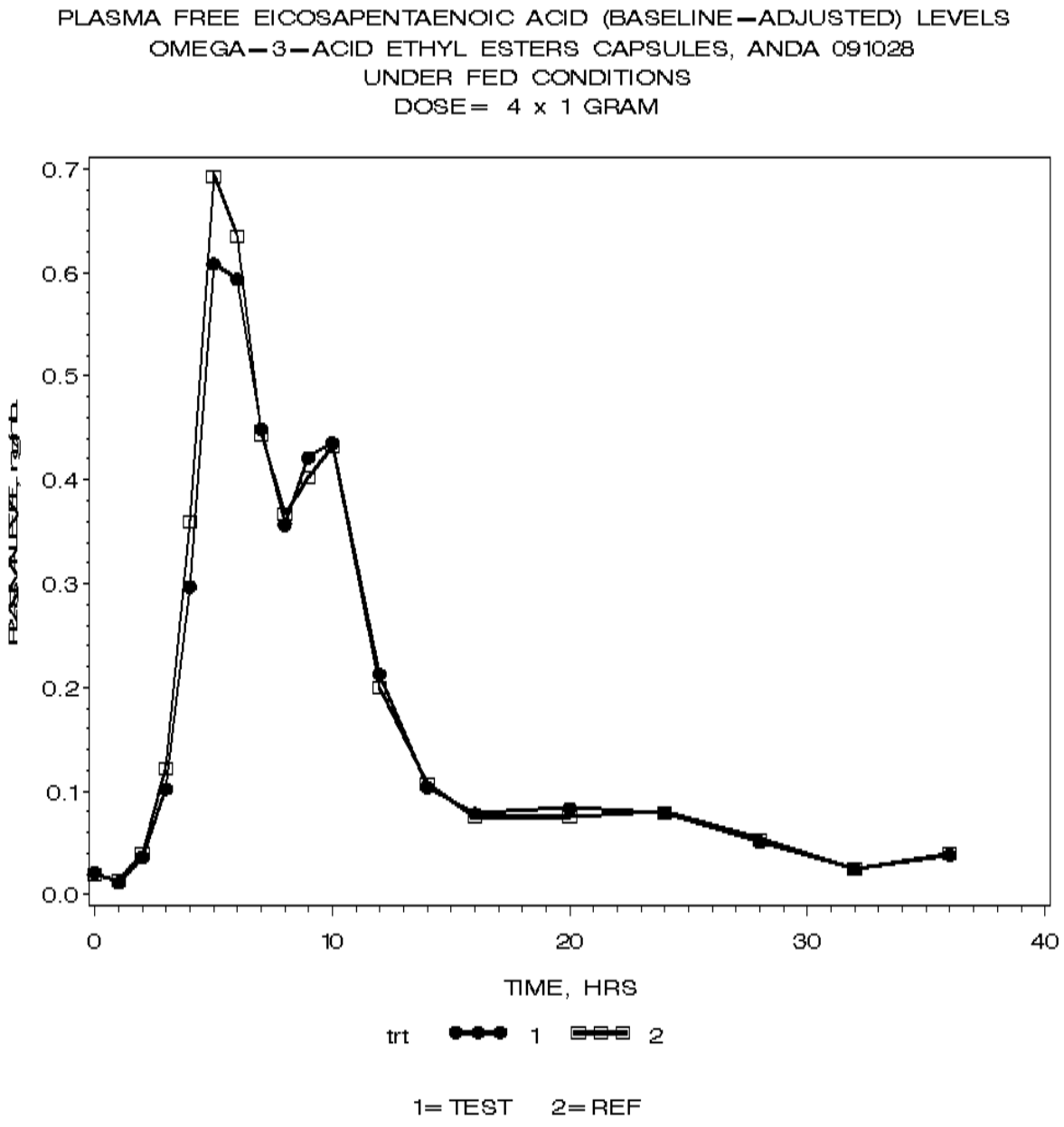
H. DHA (Total lipids)-Baseline non-adjusted

Total Docosahexaenoic acid					
Time (hr)	Test (n=80)		Reference (n=80)		T/R Ratio
	Mean (µg/mL)	% CV	Mean (µg/mL)	% CV	
-24.00	53.43	38.48	52.89	31.01	1.01
-23.00	53.29	37.94	51.96	30.90	1.03
-22.00	53.02	38.95	52.43	32.52	1.01
-21.00	53.51	37.56	52.40	32.34	1.02
-20.00	54.62	38.97	53.56	32.60	1.02
-19.00	54.92	37.25	54.24	31.28	1.01
-18.00	54.60	36.69	53.08	31.19	1.03
-17.00	54.10	37.25	53.04	31.17	1.02
-16.00	54.29	36.76	53.39	30.77	1.02
-15.00	55.72	36.60	53.64	30.64	1.04
-14.00	55.06	36.01	53.94	31.22	1.02
-12.00	53.79	36.38	52.31	30.71	1.03
-10.00	53.34	36.03	52.13	30.58	1.02
-8.00	52.20	37.45	51.62	30.63	1.01
-4.00	50.98	36.25	50.16	31.81	1.02
0.00	52.62	37.04	51.58	30.80	1.02
1.00	54.83	36.02	54.53	30.99	1.01
2.00	56.84	35.85	55.48	30.67	1.02
3.00	59.88	38.08	59.53	32.83	1.01
4.00	68.88	45.25	67.53	33.38	1.02
5.00	98.28	43.69	97.38	33.58	1.01
6.00	94.04	51.97	91.19	37.70	1.03
7.00	83.38	56.76	79.57	42.54	1.05
8.00	77.37	52.24	75.27	41.35	1.03
9.00	75.70	49.15	72.02	38.99	1.05
10.00	72.84	42.31	70.24	39.83	1.04
12.00	69.41	45.01	66.66	41.54	1.04
14.00	62.41	46.09	59.65	38.86	1.05
16.00	58.14	42.87	56.26	34.21	1.03
20.00	55.81	35.06	53.37	31.18	1.05
24.00	59.01	31.53	57.67	28.54	1.02
28.00	60.95	31.48	60.51	28.39	1.01
32.00	58.13	30.89	57.30	29.52	1.01
36.00	56.74	29.51	55.77	26.41	1.02

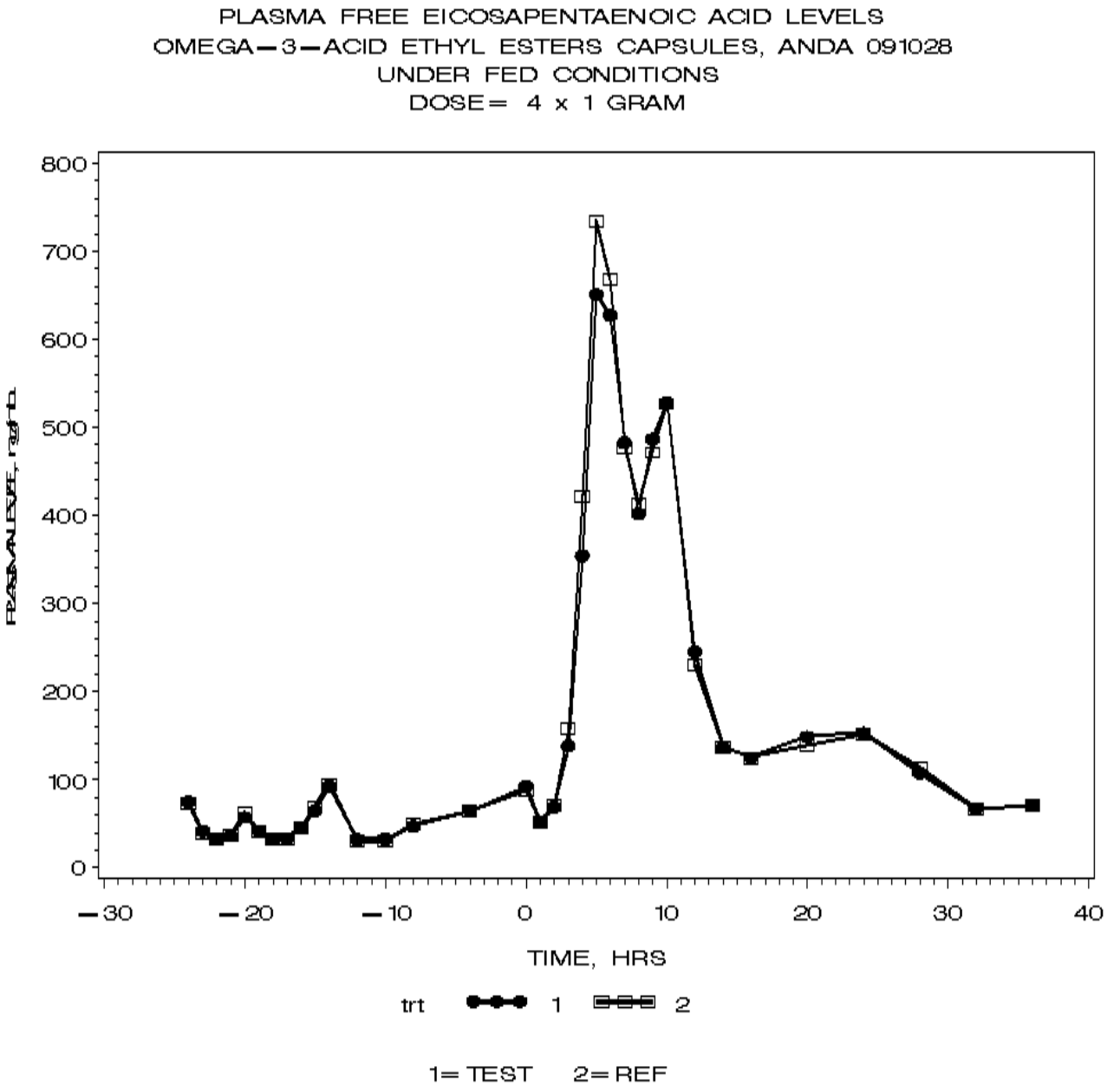
Reference ID: 3227106

Figure 2. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

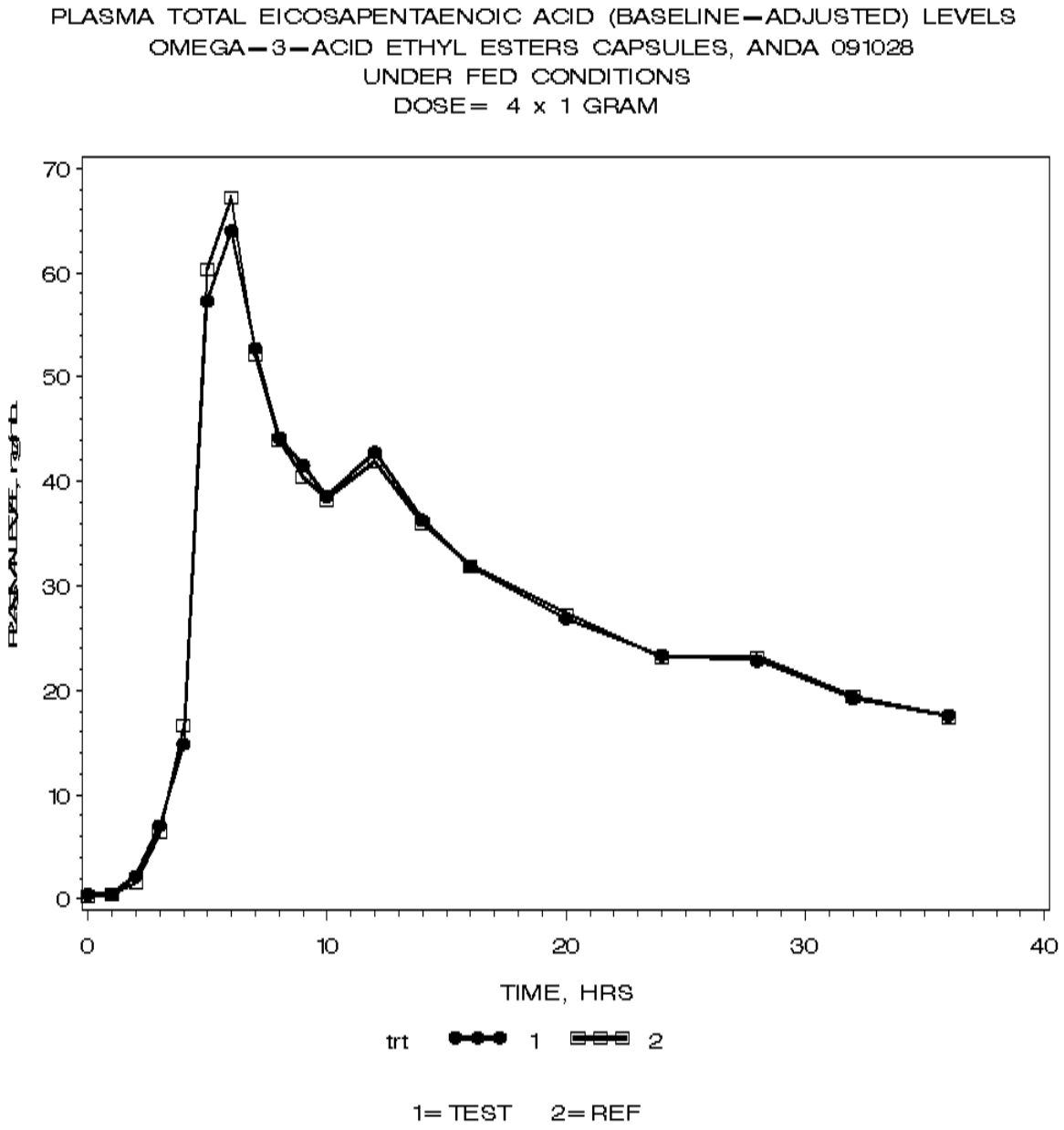
A. Baseline Adjusted: Free EPA Fatty Acids



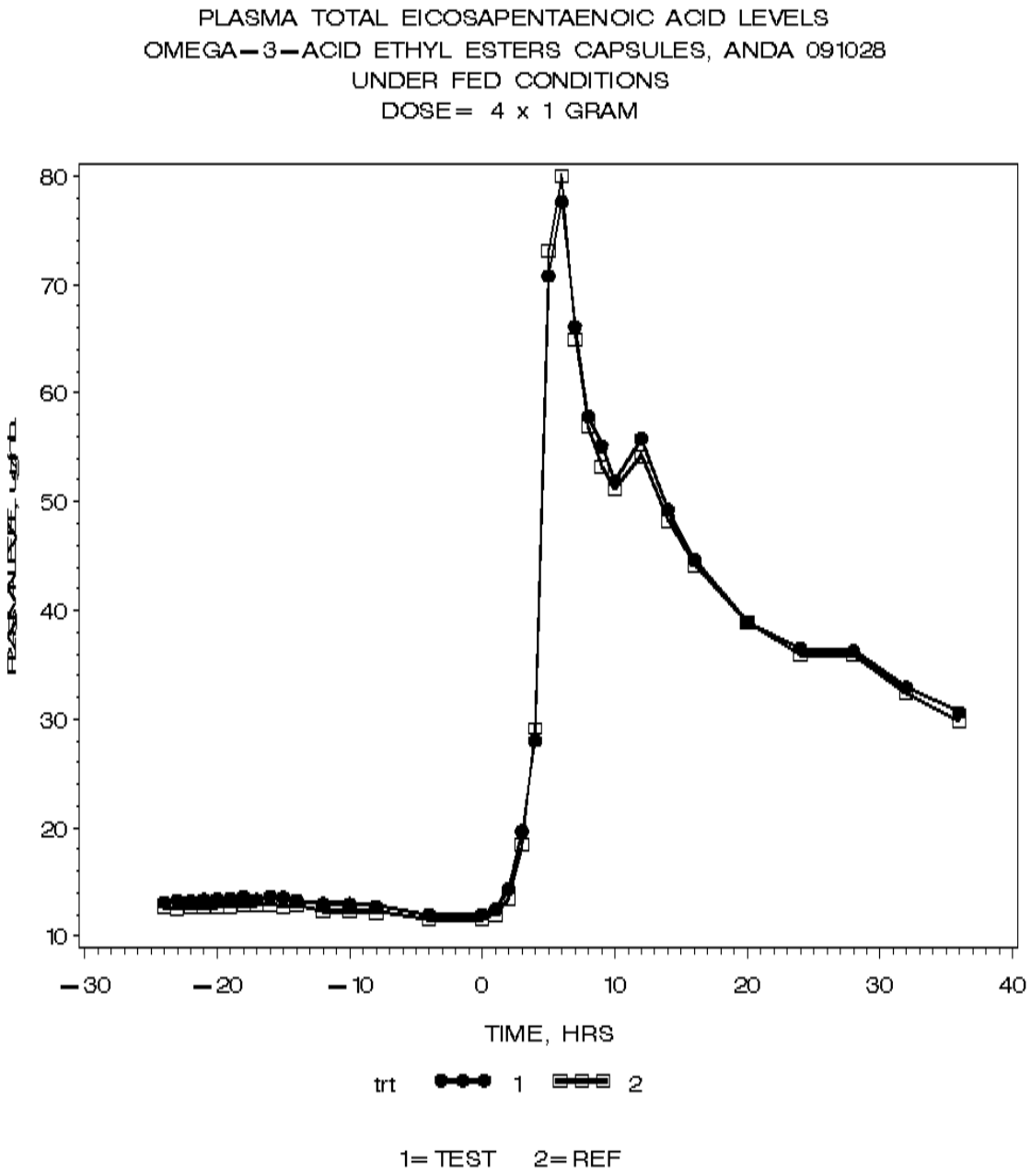
B. Baseline Non-adjusted: Free EPA Fatty Acids



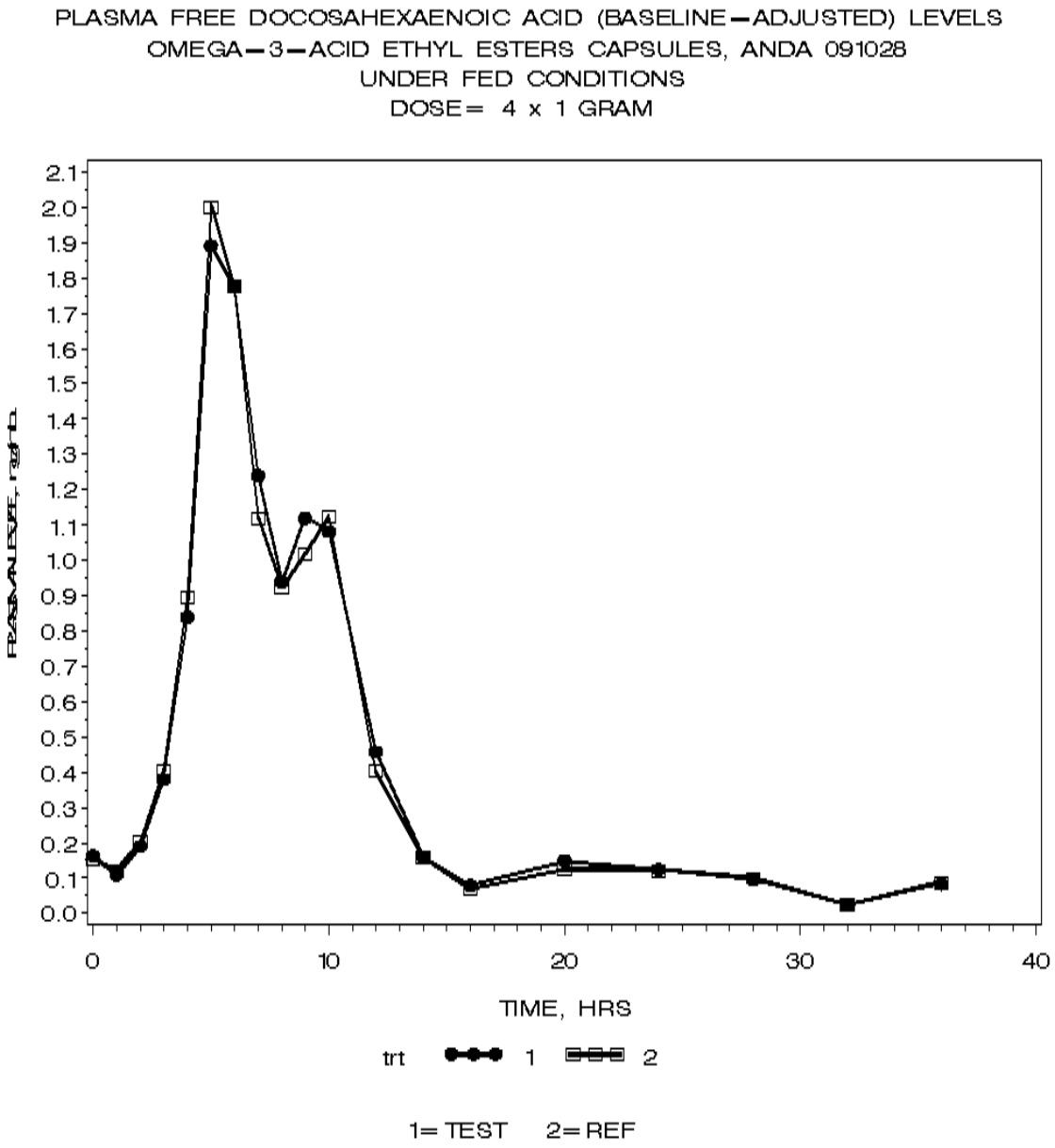
C. Baseline Adjusted: Total EPA Lipids



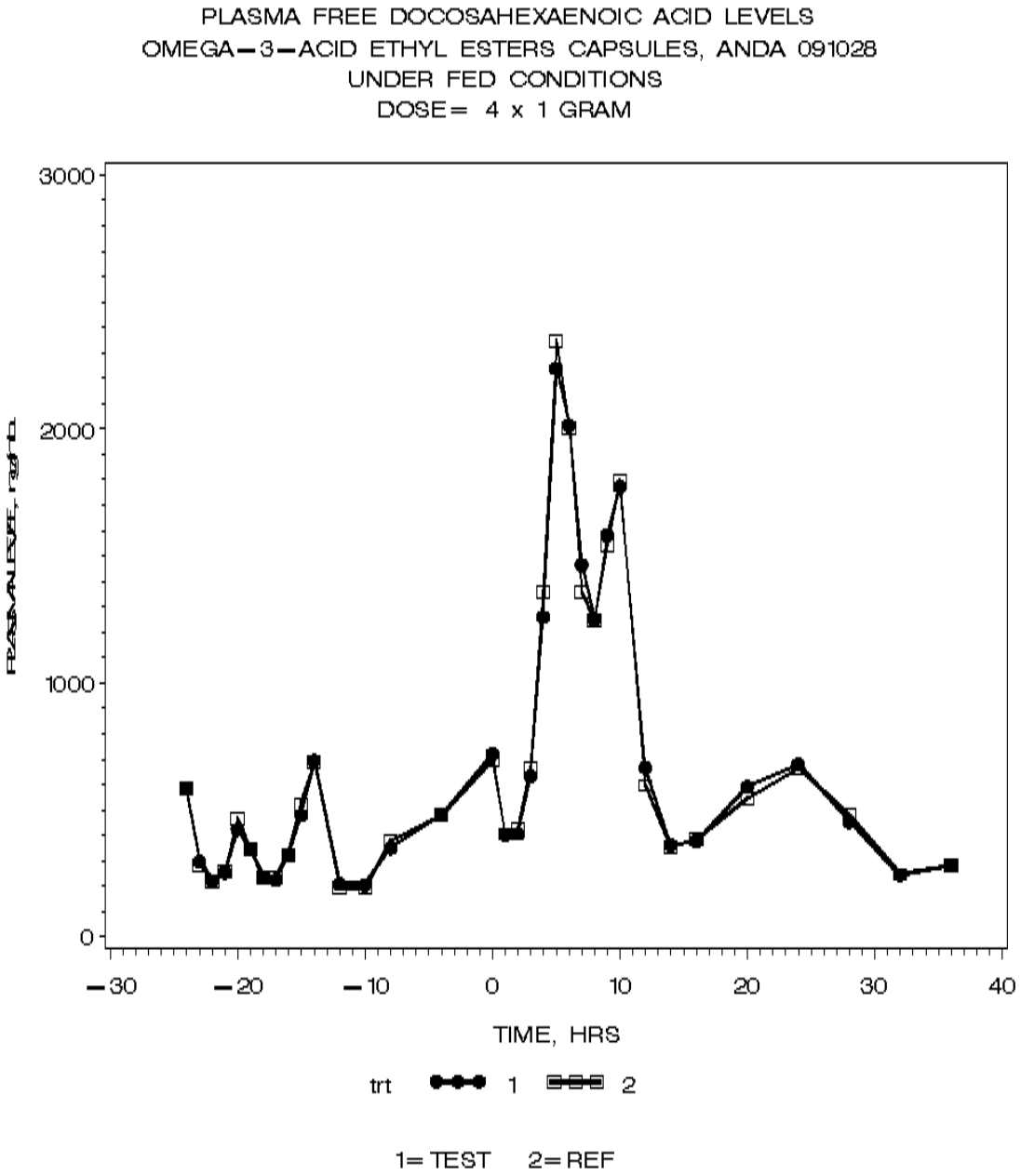
D. Baseline Non-adjusted: Total EPA Lipids



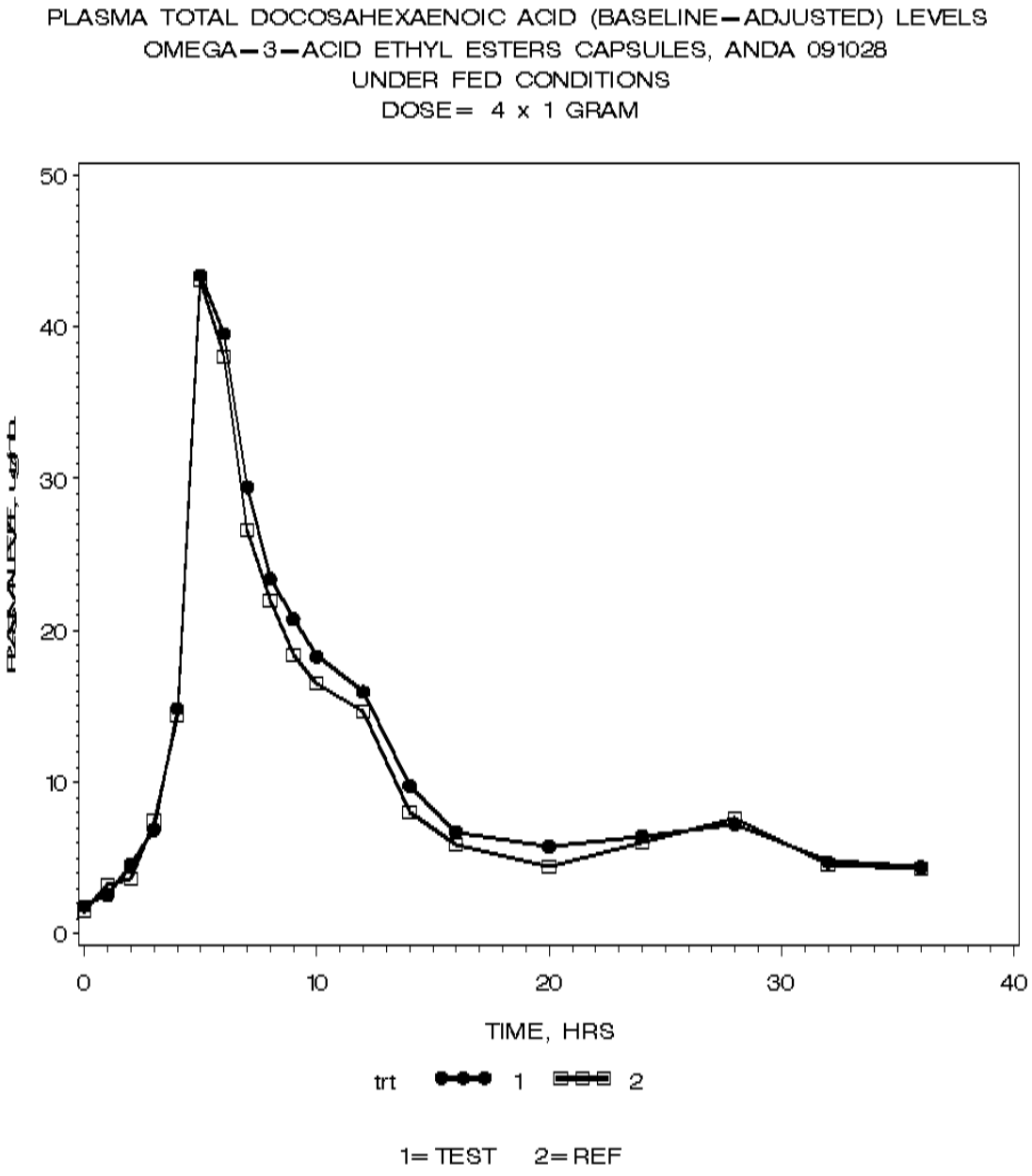
E. Baseline Adjusted: Free DHA Fatty Acids



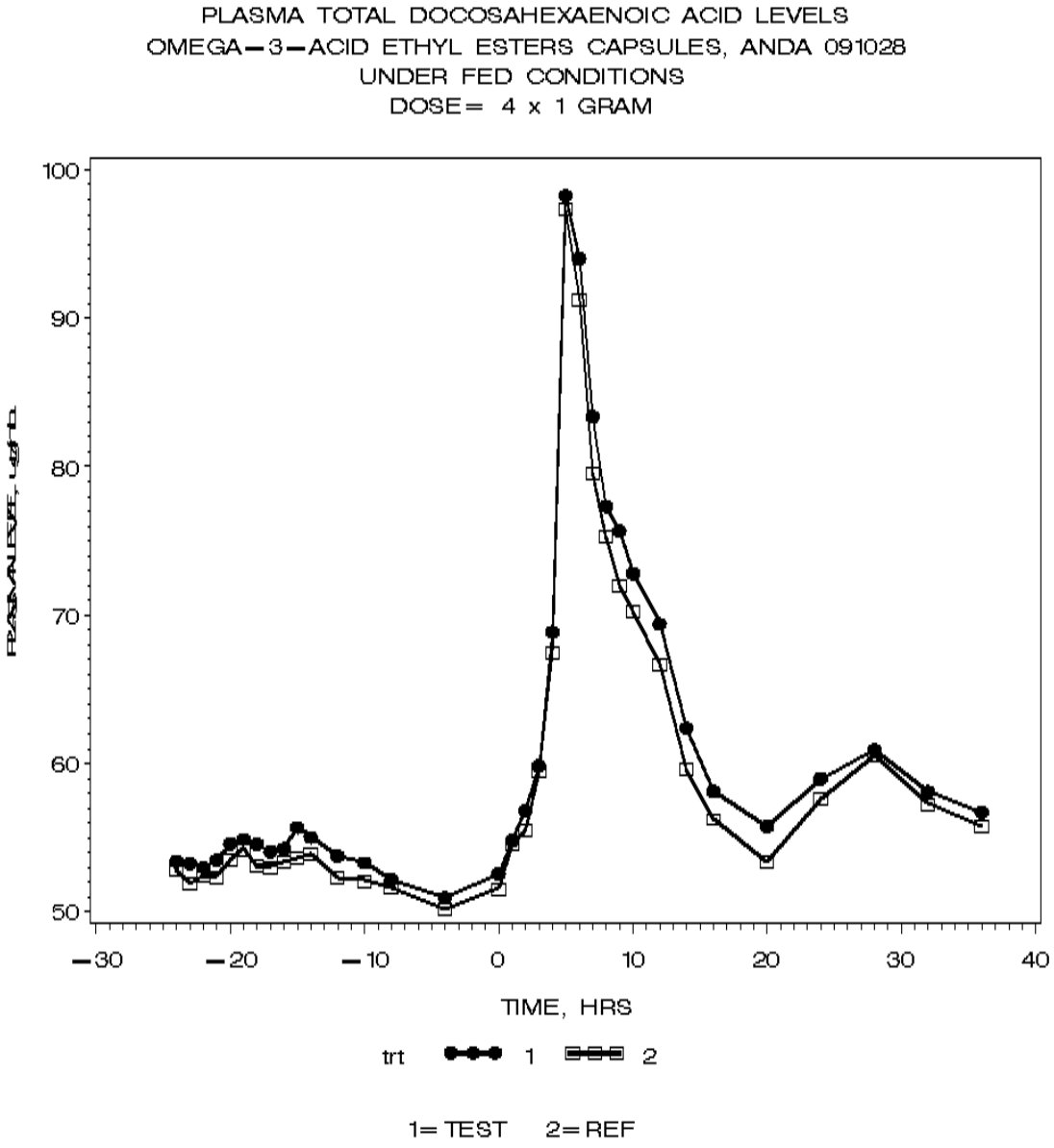
F. Baseline Non-adjusted: Free DHA Fatty Acids



G. Baseline Adjusted: Total DHA Lipids



H. Baseline Non-adjusted: Total DHA Lipids



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limits?	quantitative composition of Soft Gelatin Capsule Shell and [redacted] White-Imprinting Ink
If no, are they all above/within IIG (per day) limits?	See comment above
If no, are additional data or Pharm/Tox consult necessary?	See comment above
Are all color additives and elemental iron within limits specified by CFR (if applicable) or less than 0.1% of the total unit weight (w/w)?	See comment above
Are all strengths of the test product proportionally similar per the BA/BE guidance criteria?	See comment above
Are all strengths of the RLD product dose-proportional?	Single strength: 1 g
Are all strengths of the test formulation acceptable	Single strength pending firm's submission of quantitative composition of Soft Gelatin Capsule Shell and [redacted] White-Imprinting Ink
Additional Attachment for Formulation Calculations	N/A

Reviewer's Comments on Formulation:

- The firm referred the quantitative composition for its Soft Gelatin Capsule Shell and White Printing Ink [redacted] to the DMF #14194, and after an extensive search for the mentioned DMS, this reviewer was unable to locate the test product-specific quantitative composition related to the DMF aforementioned. Thus, the firm will be asked to provide such quantitative data in its formulation.

- Thus, the firm's formulation is **incomplete** (inadequate).

Reference ID: 3227106

4.3 Review of API Equivalence under the Current ANDA 091028

The following table is obtained from the firm's recent amendment dated 10/28/2011[8]:

Table 3: Contents of Various Omega-3 Acid Ethyl Esters in Omega-3 Acid Ethyl Esters Capsules, 1g Tested as per USP Monograph (Ref. PR10324/016)

LOT #:		P080602-B2	1ZP2071	1ZP2720	1ZP2993	0ZP4012	0ZP4015	0ZP4457	0ZP4616	0ZP5317	0ZP5319	Min for 9 Lovaza Lots	Max for 9 Lovaza Lots
Expiry:			Feb. 2014	Feb. 2014	Mar. 2014	Jul. 2013	Aug. 2013	Aug. 2013	Aug. 2013	Aug. 2013	Sep. 2013		
Component	**RRT**	**mg/g**	**mg/g**	**mg/g**	**mg/g**	**mg/g**	**mg/g**	**mg/g**	**mg/g**	**mg/g**	**mg/g**	**mg/g**	**mg/g**
C20:5 n3 EPAee	0.793	(b) (4)											
C22:6 n3 DHAee	1.000												
C18:3 n3 ALAee	0.569												
C18:4 n3 SDAee	0.594												
C20:4 n3 ETAee	0.773												
C21:5 n3 HPAee	0.889												

[8] DARRTS, ANDA 091028 Quality/Response To Information Request Original-1 View EDR; Submit/Final Date: 10/28/2011

C22:5 n3 DPAee	0.976	(b) (4)
EPAee + DHAee		
Total Omega-3 Acid ee		

Reviewer's Comments on API Equivalence:

- Per the Guidance, *"The Omega-3-Acid Ethyl Esters USP monograph defines the active pharmaceutical ingredient (API) as composed of seven individual omega-3-acid ethyl ester components. The Omega-3-Acid Ethyl Esters Capsules USP monograph establishes ranges for the two most abundant components (EPAee and DHAee) of the active pharmaceutical ingredient (API) and ranges for the sum of the two components. The reference product contains lesser quantities of the other five omega-3 acid ethyl esters, although quantitative ranges are not specified in the USP monographs. The Agency has determined the quantitative ranges of the other five omega-3-acid ethyl ester components based on assay of multiple batches of the RLD using the USP monograph analytical method"* and that *"The agency's recommendation for each component of the API varies with its content. API in each batch of a Test product must meet the quantitative ranges for all the seven components"*. The firm has submitted the data mentioned above in an amendment of October, 28, 2011[12].

- The reviewer summarize the firm's data which all met quantitative ranges recommended by the DBI in the following table:

Contents	Recommended Quantitative Ranges	Firm's Testing Results (mg/g)	Meet/Fail to meet
Eicosapentaenoic acid ethyl ester (EPAee; C20:5 n-3)	430 - 495 mg/g	(b) (4)	Meet
Docosahexaenoic acid ethyl ester (DHAee; C22:6 n-3)	347 - 403 mg/g		Meet
Sum of EPAee and DHAee	800 - 880 mg/g		Meet
Total omega-3 acid ethyl esters	NLT 90% (w/w)		Meet
Moroctic acid ethyl ester (SDAee; C18:4 n-3)	4.0-37.0 mg/g		Meet
Heneicosapentaenoic acid ethyl ester (HPAee; C21:5 n-3)	7.9-31.4 mg/g		Meet
Docosapentaenoic (Clupanodonic) acid ethyl ester (DPAee; C22:5 n-3)	16.3-50.0 mg/g		Meet
Eicosatetraenoic acid ethyl ester (ETAee; C20:4 n-3)	≥1 - <10 mg/g encapsulated oil		Meet
Alpha-linolenic acid ethyl ester (ALAee; C18:3 n-3)	below 1 mg/g		Meet
Alpha-tocopherol	4 mg/g encapsulated oil	**4 mg**	Meet

- Therefore, from the bioequivalence point of view, the firm's API is considered equivalent qualitatively and quantitatively (Q1/Q2) to the RLD and acceptable.

- However, the DBI defers to the OGD's Division of Chemistry III (DCIII) for the evaluations and recommendations of the test product to be pharmaceutically equivalent to the RLD (please see Sections 4.8 of this review for details).

4.4 Dissolution Data

Dissolution Review Path	DARRTS ANDA 091028 REN, KE 05/04/2009 REV-BIOEQ-02(Dissolution Review) Original-1 Archive and current dissolution amendment review.

Dissolution Data Table (from original submission dated 11/10/2008)

Dissolution Conditions	**Apparatus:**	USP Apparatus II (Paddles)
	Speed of Rotation:	50 RPM
	Medium:	Purified Water
	Volume:	500 mL
	Temperature:	37.0°C ± 0.5°C
Firm's Proposed Specifications	All capsules rupture in not more than (b) (4)	
Dissolution Testing Site (Name, Address)	Teva Pharmaceuticals USA 8-10 Gloria Lane Fairfield, NJ 07004	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Rupture Times (seconds)	Study Report Location
Study Report #: QDP0004605	7/29/08	Omega-3-Acid Ethyl Esters Capsules Lot P080602 June 24, 2008	1 g Capsule	12	Mean	117	Module 5.3.1.3 of the original ANDA
					Range	(b) (4)	
	7/29/08	Lovaza Capsules Lot 7HH0014 Nov 2010	1 g Capsule	12	Mean	103	
					Range	(b) (4)	

Reference ID: 3227106

Comments on Dissolution Testing

- Originally, the firm conducted its disintegration testing using the following: 500 mL of water using Apparatus II (paddle) at 50 rpm per USP <711>. The firm's proposed specification of "all capsules rupture in not more than (b) (4) for its disintegration test.

- However, the DBI recommended the firm to develop a **quantitative capsule rupture** test to evaluate the in-vitro performance of Omega-3-acid Ethyl Esters Capsules. The quantitative capsule rupture method should be discriminating to detect potential differences between the test and reference products. The firm was asked to measure drug release of two key components of the drug product, Eicosapentaenoic acid (EPA) and Docosahecaenoic acid (DHA) as percentage of the labeled amounts. The firm was advised to consider trying the following method:

Apparatus:	USP Apparatus I (Basket)
Speed:	100 rpm
Medium:	Water with a low concentration of surfactant
Volume:	900 mL
Sampling:	Once every 15 minutes until at least 80% of the labeled amount of Eicosapentaenoic acid (EPA) and Docosahecaenoic acid (DHA) is dispersed in the media

  If necessary, the firm could try varying the media volume, increasing the rotational speed, increasing the concentration of surfactant, and/or using USP Apparatus II (paddles) instead of Apparatus I. If all capsules tested rupture in less than one hour, it may be necessary to sample more frequently to adequately characterize the capsule rupture rate and profile. (Please see DARRTS for ANDA 091028 REN, KE 05/04/2009 REV-BIOEQ-02(Dissolution Review) Original-1 Archive, for details).

- On October 2, 2009, the firm submitted a dissolution amendment, along with data on a newly developed quantitative capsule rupture testing (dissolution testing).[9] (Please see Section 4.4 Review of Dissolution Amendment below, for details)

[9] DARRTS, ANDA 091028 Quality/Quality Information; Bioequivalence/Response to Information Request; Submit/Final Date: 10/02/2009.

4.5 Review of Dissolution Amendment (10/02/2009)

Dissolution Deficiency Comment #1

Currently, the DBE recommends a quantitative rupture test method be used to evaluate the in vitro performance of the drug product. Please develop your own quantitative capsule rupture method which should be discriminating to detect potential differences between the test and reference products. Please measure drug release of Eicosapentaenoic acid (EPA) and Docosahecaenoic acid (DHA). You may consider trying the following method:

Apparatus:	*USP apparatus I (basket)*
Speed:	*100 rpm*
Medium:	*Water with a low concentration of surfactant*
Volume:	*900 mL*
Sampling:	*Once every 15 minutes until at least 80% of the labeled amount of Eicosapentaenoic acid (EPA) and Docosahecaenoic acid (DHA) is dispersed in the media*
Number of Units Tested:	*12*

If necessary, we suggest you try varying the medium volume, changing the rotational speed, adjusting the concentration of surfactant used, and/or using USP Apparatus II (paddles) instead of Apparatus I. If all capsules tested rupture in less than one hour, it may be necessary to sample more frequently to adequately characterize the capsule rupture rate and profile. Please provide individual capsule data as well as the test summary data such as mean, range, % coefficient of variation (CV) at each time point. The summary of the quantitative rupture testing data should also be provided in eCTD-formatted tables.

Firm's Response to Dissolution Deficiency Comment #1

"Per your request, the following quantitative rupture test (dissolution) has been developed to evaluate the *in-vitro* performance of the drug product:

Medium:	10% Labrasol in 0.01N HCl
Volume:	900mL
Apparatus:	USP Apparatus II (Paddles)
Speed:	(b) (4) rpm
Temperature:	37 ^{0}C ± 5 ^{0}C
Sampling time:	5, 10, 15, 20, 30, 45, and 60 minutes

Provided in Module 5.3.1.3, please find the analytical report (b) (4) which summarizes the experimental work performed to develop this dissolution method for Omega-3-Acid Ethyl Esters Capsules. In addition, provided in Module 5.3.1.3 are the In-Vitro Dissolution Study Summary Tables (release of EPA and release of DHA) and a comparative report (b) (4) (b) (4)) summarizing the dissolution profile data of Teva's Omega-3-Acid Ethyl Esters Capsules, 1 g vs. the RLD (Lovaza® Capsules) generated according to the above method.

Reference ID: 3227106

However, because the drug substance is an oil which is insoluble in water, it is Teva's belief that our original rupture test is a more appropriate test for routine quality control testing of Teva's product. As such, we propose to retain the rupture test specified in the original application and summarized as follows:

Medium:	Purified Water
Volume:	500mL
Apparatus:	USP Apparatus II (Paddles)
Speed:	50 rpm
Temperature:	37 ^{0}C ± 5 ^{0}C
Specification:	All capsules rupture in NMT (b) (4)

Reviewer's Comments on Firm's Response to Dissolution Deficiency Comment #1:

- As recommended by the DBI, the firm developed a new quantitative capsule rupture test. Based on the firm's method development data (please see dissolution method development table below and also firm's data on dissolution development in the Section 4.9 Additional Attachments of this review for details) in the current dissolution amendment dated 10/2/2009, it is found that (b) (4) was not appropriate dissolution medium for the firm's oil-filled soft gelatin capsules and the USP Apparatus I (baskets) was also inappropriate, showing high variability and low capsule release. Based on all data from seven experiments in developing a dissolution method, the firm considered the above mentioned quantitative capsule rupture test more appropriate for its product.

Expt #	Apparatus	Medium	RPM	Vol (mL)	Temp (^{0}C)	Time Points (min)
1	(b) (4)					
2						
3						
4						
5						
6						
7						

- However, the firm's dissolution profiles of the test and RLD products were not discriminatory especially for the test product. For example, with the medium of 10% Labrasol in 0.1N HCl and rotation of (b) (4) rpm at the time point of (b) (4) minutes it showed drug releases of Eicosapentaenoic acid (EPA) and Docosahecaenoic acid (DHA) at (b) (4)% (range: (b) (4); %CV: 1.1) and (b) (4)% (range: (b) (4); %CV: 1.1), respectively, for the test product, as compared to those of the respective (b) (4)% (range: (b) (4); %CV: 118) and (b) (4)% (range: (b) (4); %CV: 120) for the reference product. Thus, the firm's dissolution data on

the comparative dissolution profiles particularly for the test product are found non-discriminatory throughout all sampling time points (see Tables 1.1 & 1.2 below for details). The firm has not conducted any dissolution tests under lower Labrasol concentrations and (b) (4) basket (USP Apparatus I; i.e. <100 rpm) or paddle (USP Apparatus II; i.e. <75 rpm) speeds. Hence, the firm's *in vitro* dissolution testing is considered **incomplete** at present.

- Furthermore, the reviewer searched a similar dissolution method used for the same drug product accepted by the DBI under ANDA 091018 as follows:

Medium:	Water + 5% Triton X-100 with 1% pancreatin
Apparatus;	USP Apparatus 2 (Paddle)
Speed:	75 rpm
Volume:	900 mL
Specification:	NLT (b) (4)% (Q) of EPA and DHA is dissolved in 60 minutes.

(b) (4)

compared to the new data submitted for the current proposed test method under the current ANDA (also see Tables 2.1 & 2.2 below for details).

- As per the Guidance for Omega-3-Acid Ethyl Esters Capsules posted recently (recommended on September 2012), *"Based on the information available to the Agency, as well as the recommendation given in the USP Pharm Forum,[10] USP Apparatus 4 (flow-through cell) has been shown to be the most appropriate apparatus for drugs with poor solubility, compared with the conventional USP Apparatus 1 (basket) and Apparatus 2 (paddle); and "The firm should develop the in vitro drug release method for the drug product using USP Apparatus 4 (flow-through cell). A second method using USP Apparatus 2 (paddle) may be developed in conjunction with the method using USP Apparatus 4 for comparison, if desired. The data from USP Apparatus 4, and from USP Apparatus 2 (if conducted), should be submitted to the Division of Bioequivalence for evaluation and for determination of the most suitable method"*, the DBI will ask the firm to continue to develop its dissolution testing method for the test product per the current Guidance (recommended on September 2012).

- Also, the firm will be referred to the Guidance of that *"it is critical that for USP Apparatus 4, when used for lipid-filled soft gelatin capsule (SGC) dosage forms, a modified flow-through cell designed for SGC[11] be used in the testing. In addition, for USP Apparatus 4, the firm will be asked to provide dissolution method development data showing the dissolution testing having been systemically optimized for the following parameters: (1) system mode (closed versus open) (2) type of cell (size in mm) (3) glass beads (size in mm) (4) glass bead loading (weight in gm) (5) sample load (volume in mL)*

[10] Marques MRC, Cole E et al., Stimuli to the Revision Process: Liquid-filled Gelatin Capsules. *USP Pharm Forum 2009;35(4, July-Aug)1029-41.*

[11] USP *Revision Bulletin* Official August 1, 2011 <2040> Disintegration and Dissolution of Dietary Supplements.

Reference ID: 3227106

(6) split ratio (%) (7) size of sample tube (volume in mL) and (8) flow rate. For USP Apparatus 2, when used for this dosage form, the sampling probes should remain immersed in the dissolution medium throughout the duration of testing in order to obtain reproducible results. The use of a sinker with USP Apparatus 2 may be considered in preventing the capsules from floating to the top".

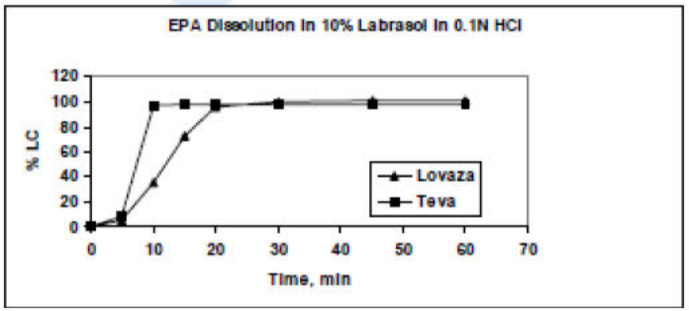
- The firm should submit a complete method development report, which should contain data for the optimization of each testing parameter as outlined in the draft guidance. The DBI will evaluate the method development and optimization data and determine the most suitable dissolution method for firm's test product and the dissolution specification will be recommended upon reviewing its complete dissolution testing data based on the most appropriate method.

- Therefore, the firm's response to the dissolution deficiency #1 is **inadequate**.

Table 1.1 Release of EPA Ethyl Esters (submitted in the amendment dated 10/02/2009)

Dissolution Conditions	**Apparatus**	USP Type II (Paddle)
	Speed of Rotation	(b) (4) rpm
	Medium	10% Labrasol in 0.1N HCl
	Volume	900 ml
	Temperature	37° C ± 0.5° C
Proposed Specification	N/A	
Dissolution Testing Site (Name & Address)	Barr Laboratories, Inc. 223 Quaker Road Pomona, NY 10970-0519	

Study Ref No.	Testing Date	Product ID/Batch No. (Test-Manufacture Date) (Reference-Expiration Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes) 5	10	15	20	30	45	60	Study Report Location
Study Report#: ARD_RPT_4248	8/10/09	Omega-3-Acid Ethyl Esters Capsules, 1 g Lot P080602-B2 Manufacture Date: 6/24/08	1 g Capsules	12								Module 5.3.1.33
				Mean	8	96	98	98	98	97	98	
				Range							(b) (4)	
				% CV	84.8	1.1	0.6	0.8	0.5	0.8	0.7	
	8/10/09	Lovaza Capsules, 1 g Exp. Date 10/2010	1 g Capsules	12								
				Mean	6	35	73	96	100	101	101	
				Range							(b) (4)	
				% CV	223	118	35.3	4.3	0.7	1.1	0.9	

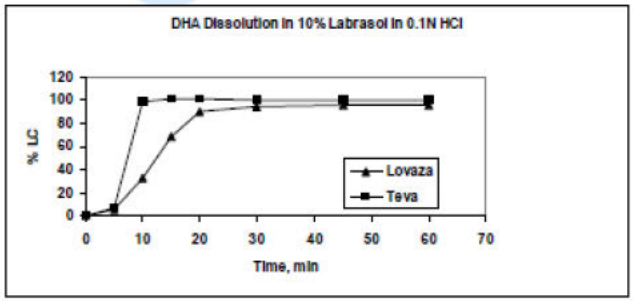


Reference ID: 3227106

Table 1.2 Release of DHA Ethyl Esters (submitted in the amendment dated 10/02/2009)

Dissolution Conditions	**Apparatus**	USP Type II (Paddle)
	Speed of Rotation	(b) (4) rpm
	Medium	10% Labrasol in 0.1N HCl
	Volume	900 ml
	Temperature	37° C ± 0.5° C
Proposed Specification	N/A	
Dissolution Testing Site (Name & Address)	Barr Laboratories, Inc. 223 Quaker Road Pomona, NY 10970-0519	

Study Ref No.	**Testing Date**	**Product ID/Batch No. (Test-Manufacture Date) (Reference-Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**	**Collection Times (minutes)**							**Study Report Location**
					5	**10**	**15**	**20**	**30**	**45**	**60**	
Study Report#: ARD_RPT_4248	8/10/09	Omega-3-Acid Ethyl Esters Capsules, 1 g Lot P080602-B2 Manufacture Date: 6/24/08	1 g Capsules	12								Module 5.3.1.33
				Mean	7	99	101	101	101	100	100	
				Range	(b) (4)							
				% CV	85	1.1	0.5	0.7	0.5	0.7	0.6	
	8/10/09	Lovaza Capsules, 1 g Exp. Date 10/2010	1 g Capsules	12								
				Mean	5	33	69	91	95	96	96	
				Range	(b) (4)							
				% CV	234	120	35.5	4.7	0.8	1.0	1.0	



Reference ID: 3227106

Table 2.1 Summary of In Vitro Dissolution (Quantitative Rupture) Studies – Drug Release of EPA Under ANDA 091018

(NOT TO BE RELEASED UNDER FOIA)

Dissolution Conditions	**Apparatus:**	II (Paddles)
	Speed of Rotation:	75 rpm
	Medium:	5% Triton X-100 solution in water with 1% pancreatin
	Volume:	900 mL
	Temperature:	37 +/- 0.5 °C
Firm's Proposed Specification	NLT (b) (4) % (Q) of EPA is dissolved in 60 minutes	
Dissolution Testing Site (Name, Address)	Par Pharmaceutical, Inc.	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 15 min	30 min	45 min	60 min	Study Report Location
Study Report# MS10-013-0	3/26/2010 - 3/29/2010	Omega-3-acid Ethyl Esters Capsules (Lot #699982/216809) Mfr. Date: 07/17/08	1 g Capsules	12	Mean	50.4 %	76.4 %	89.4 %	95.1 %	p.9 and 10
					Range	(b) (4)				
					%CV	36.7	16.8	8.9	5.3	
Study Report# MS10-013-0	3/31/2010	Lovaza ® Capsules (Lot #803040W) Exp. Date: Apr 2011	1 g Capsules	12	Mean	42.2 %	71.4 %	87.3 %	94.5 %	
					Range	(b) (4)				
					%CV	29.5	12.9	5.4	2.4	

Reference ID: 3227106

Table 2.2 Summary of In Vitro Dissolution (Quantitative Rupture) Studies – Drug Release of DHA under ANDA 091018

(NOT TO BE RELEASED UNDER FOIA)

Dissolution Conditions	**Apparatus:**	II (Paddles)
	Speed of Rotation:	75 rpm
	Medium:	5% Triton X-100 solution in water with 1% pancreatin
	Volume:	900 mL
	Temperature:	37 +/- 0.5 °C
Firm's Proposed Specification	NLT (b) (4)% (Q) of DHA is dissolved in 60 minutes	
Dissolution Testing Site (Name, Address)	Par Pharmaceutical, Inc.	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 15 min	30 min	45 min	60 min	Study Report Location
Study Report# MS10-013-0	3/26/2010 - 3/29/2010	Omega-3-acid Ethyl Esters Capsules (Lot #699982/216809) Mfr. Date: 07/17/08	1 g Capsules	12	Mean	53.6 %	81.4 %	96.0 %	102.6 %	p.9 and 10
					Range	(b) (4)				
					%CV	36.6	16.9	8.9	4.9	
Study Report# MS10-013-0	3/31/2010	Lovaza ® Capsules (Lot #803040W) Exp. Date: Apr 2011	1 g Capsules	12	Mean	45.2 %	77.0 %	94.4 %	102.8 %	
					Range	(b) (4)				
					%CV	30.6	13.2	5.9	2.8	

Reference ID: 3227106

4.6 Emails Communications between the Reviewer and DMF Reviewers in Chemistry

---

From: Gong, Li
Sent: Monday, November 05, 2012 4:57 PM
To: Rahman, Md
Cc: Braddy, April; Gong, Li
Subject: FW: DMF #14194 related to soft gelatin capsule shell and (b) (4) White composition

Hi Ashiq,

I would like to know the quantitative composition of the capsule shell and imprinting ink as follows:

Thanks,
-Li

From: Rahman, Md
Sent: Monday, November 05, 2012 4:43 PM
To: Gong, Li
Cc: Nagavelli, Laxma; Sayeed, Vilayat A; Gill, Devinder
Subject: DMF #14194 related to soft gelatin capsule shell and (b) (4) White composition

Hello Li,

Please find below the composition of the soft gelatin capsule for Omega-3. Hope this will serve your purpose and please let me know if you have question.

Thanks.

Ashiq

The quantitative composition and function of each component in the drug product is listed.

(b) (4)

Md Ashequr Rahman, Ph.D
Division of Chemistry III
Office of Generic Drugs
FDA/CDER/OPS
MPN II, Room E106
7500 Standish Place
Rockville, MD 20855
Tel: 240 276 8460, Fax: 240 276 8474
E-mail:md.rahman@fda.hhs.gov

From: Sayeed, Vilayat A
Sent: Monday, November 05, 2012 11:48 AM
To: Nagavelli, Laxma; Sears, Leigh Ann
Cc: Braddy, April; Rahman, Md; Gong, Li; Gill, Devinder
Subject: RE: DMF #14194 related to soft gelatin capsule shell and (b) (4) White composition

Li

Let Ashiq know, do you need the composition of the soft shell or the contents in the shell

Thanks

Vilayat

Vilayat A. Sayeed, Ph.D.
Director, Division of Chemistry III
FDA/CDER/OPS/OGD

7500 Standish Place
MPN II Rockville, MD 20855
Office (240) 276-8486, fax (240) 276-8474
Vilayat.Sayeed@FDA.HHS.GOV
Consider the environment before printing this e-mail

From: Nagavelli, Laxma
Sent: Monday, November 05, 2012 11:28 AM
To: Sears, Leigh Ann
Cc: Braddy, April; Sayeed, Vilayat A; Rahman, Md; Gong, Li
Subject: RE: DMF #14194 related to soft gelatin capsule shell and (b) (4) White composition

Hi Leigh Ann,

Please do not remove/move that application from Ashiq's RFS queue. Li from bio is interested in composition of omega-3-capsugel.

Ashiq,
Please provide the composition table to Li.

Thanks,
Laxma

From: Rahman, Md
Sent: Monday, October 22, 2012 11:50 AM
To: Gong, Li
Cc: Braddy, April; Sayeed, Vilayat A; Nagavelli, Laxma; Sears, Leigh Ann
Subject: DMF #14194 related to soft gelatin capsule shell and (b) (4) White composition

Hello Gong,

I am not reviewing the DMF# 14194 you referred and accordingly I don't have that information you requested. I would recommend you to order the mentioned DMF and get the information.

Leigh Ann:

All the ANDA's on Omega-3 are assigned to my RFS queue including the ANDA 91028 reviewing by Gong. Would please check and delete thos applications which are assigned to other reviewer.

Thank you.

Ashiq

Md Ashequr Rahman, Ph.D
Division of Chemistry III
Office of Generic Drugs
FDA/CDER/OPS
MPN II, Room E106
7500 Standish Place
Rockville, MD 20855
Tel: 240 276 8460, Fax: 240 276 8474
E-mail:md.rahman@fda.hhs.gov

From: Gong, Li
Sent: Monday, October 22, 2012 11:14 AM

To: Rahman, Md
Cc: Braddy, April; Gong, Li
Subject: DMF #14194 related to soft gelatin capsule shell and (b) (4) White composition

Hi MD,

I have been reviewing ANDA 091028 (Teva's Omega-3-Acid Ethyl Esters Capsules, 1 g) lately. The firm was referring the quantitative composition of the soft gelatin capsule shell and imprinting ink, (b) (4) (b) (4) of their formulation to the **DMF #14194**. This particular DMF was referred by Guoping (see email below) to you. Would you please help me to find out the quantitative amount of each following component per capsule?

(b) (4)

Sincerely,

-Li

From: Sun, Guoping
Sent: Monday, October 15, 2012 11:34 AM
To: Gong, Li
Cc: Braddy, April
Subject: RE: DMF #14194 related to soft gelatin capsule shell and (b) (4) White composition

Li:

Please contact RAHMAN, MD A. (TM34) for such info.

Thanks,

Guoping

From: Gong, Li
Sent: Friday, October 12, 2012 4:15 PM
To: Sun, Guoping
Cc: Braddy, April; Gong, Li
Subject: DMF #14194 related to soft gelatin capsule shell and (b) (4) White composition

Hi Guoping,

I have been reviewing ANDA 091028 (Teva's Omega-3-Acid Ethyl Esters Capsules, 1 g) lately. The firm was referring the quantitative composition of the soft gelatin capsule shell and imprinting ink, (b) (4) (b) (4), of their formulation to the DMF #14194. This particular DMF was reviewed by your Team and was found acceptable. Would you please help me to find out the quantitative amount of each following component per capsule?

(b) (4)

Thanks a bundle!

Li

From: Li, Haitao
Sent: Friday, October 12, 2012 3:08 PM
To: Gong, Li
Cc: Braddy, April
Subject: RE: DMF #14194 related to soft gelatin capsule shell composition

Hi Li,

According to DARRTS, that DMF has been reviewed by Guoping's team and found acceptable. If you have any questions, you may want to follow up with Guoping.

Thanks!

Haitao

From: Gong, Li
Sent: Friday, October 12, 2012 3:04 PM
To: Li, Haitao
Cc: Braddy, April; Gong, Li
Subject: DMF #14194 related to soft gelatin capsule shell composition

Hi Haitao,

I am a bioreviewer and have been reviewing ANDA 091028 (Teva's Omega-3-Acid Ethyl Esters Capsules, 1 g) lately. The firm was referring the quantitative composition of the (b) (4) , of their formulation to the DMF #14194. I wonder whether you or someone else within your Team or Chemistry Divisions, reviewed that particular DMF?

Thanks and regards,
-Li

4.7 Emails Communications between the Reviewer and the CMC Reviewer in Chemistry

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From: Nagavelli, Laxma
Sent: Tuesday, November 06, 2012 2:42 PM
To: Gong, Li
Cc: Braddy, April; Rahman, Md
Subject: RE: Pharmaceutical Equivalence for ANDA091028 (TEVA's Omega-3-Acid Ethyl Ester Capsule)

Li,
Ashiq has just started reviewing the Omega-3 applications. Once he gets to the amendment that you identified in your e-mail, he will respond to your question at that time.

Thanks,
Laxma

From: Gong, Li
Sent: Tuesday, November 06, 2012 11:46 AM
To: Nagavelli, Laxma
Cc: Braddy, April; Gong, Li
Subject: Pharmaceutical Equivalence for ANDA091028 (TEVA's Omega-3-Acid Ethyl Ester Capsule)

Hi Laxma,

I am a bioreviewer and wondering whether your team has reviewed the amendment (10/27/2011) for ANDA 091028 (Teva's Omega-3-Acid Ethyl Esters Capsules, 1 g) lately and if so, whether the Chemistry Division considers the Teva's product pharmaceutically equivalent to the RLD, Lovaza, or not?

Sincerely,
Li

Li Gong, Ph.D.
FDA/CDER/OPS/OGD/DBI
RM #1346, HFD-650
7520 Standish Place
Rockville, MD 20855
PH (240) 276-8794
Fax (240) 276-8766
li.gong@fda.hhs.gov

From: Li, Haitao
Sent: Monday, November 05, 2012 2:37 PM
To: Gong, Li; Nagavelli, Laxma
Cc: Braddy, April
Subject: RE: DMF #14194 related to soft gelatin capsule shell composition

Li,

All Omega-3 ANDAs have been transferred out of my queue, I will not do any review on this DP.

I forward your email to my TL, Laxma, Hopefully he can give you further insight.

Thanks!

Haitao

From: Gong, Li
Sent: Monday, November 05, 2012 2:35 PM
To: Li, Haitao
Cc: Braddy, April; Gong, Li
Subject: DMF #14194 related to soft gelatin capsule shell composition

Hi Haitao,

I wonder whether you have reviewed the amendment (10/27/2011) for ANDA 091028 (Teva's Omega-3-Acid Ethyl Esters Capsules, 1 g) lately and if so, whether the Chemistry Division deems the Teva's product pharmaceutically equivalent to the RLD, Lovaza, or not?

Thanks,
-Li

4.8 SAS Output

4.8.1 Pilot Study Data

PILOT FAST & FED CONCENTRATION DATASET (FREE EPA) BASELINE-NON-ADJUSTED

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16
1	1	2	1	B	1	304.0	101.0	100.0	110.0	79.2	136.0	64.9	71.2	99.2	418.0	1690.0	1080.0	680.0	357.0	341.0	284.0
2	1	2	2	A	1	80.7	75.3	91.0	180.0	58.8	80.1	84.0	94.9	112.0	127.0	69.2	57.6	59.6	57.9	87.9	67.1
3	2	1	1	A	1	86.5	77.6	50.0	62.7	44.8	126.0	86.2	183.0	122.0	145.0	103.0	81.3	72.8	66.0	63.8	54.3
4	2	1	2	B	1	117.0	72.3	53.2	59.3	57.7	83.0	62.4	73.2	158.0	181.0	145.0	238.0	680.0	1390.0	687.0	354.0
5	3	1	1	A	1	149.0	37.3	41.2	50.4	32.6	54.9	101.0	119.0	73.8	109.0	53.7	46.8	47.1	52.3	61.1	45.7
6	3	1	2	B	1	95.4	55.4	37.9	87.3	43.6	130.0	58.1	244.0	424.0	854.0	429.0	390.0	213.0	164.0	161.0	172.0
7	4	2	1	B	1	696.0	309.0	227.0	219.0	175.0	378.0	355.0	713.0	802.0	1640.0	1160.0	1190.0	690.0	514.0	422.0	309.0
8	4	2	2	A	1	393.0	264.0	141.0	170.0	118.0	332.0	463.0	263.0	340.0	426.0	218.0	146.0	118.0	117.0	162.0	128.0
9	5	2	1	B	1	67.7	84.1	63.9	81.2	74.8	98.3	91.6	81.9	72.3	81.6	119.0	370.0	1080.0	1790.0	1370.0	1460.0
10	5	2	2	A	1	75.3	68.5	79.3	89.1	55.3	111.0	124.0	93.4	142.0	138.0	108.0	91.0	81.5	86.1	171.0	116.0
11	6	1	1	A	1	164.0	122.0	88.7	119.0	108.0	152.0	145.0	144.0	140.0	187.0	140.0	119.0	98.9	98.1	107.0	94.9
12	6	1	2	B	1	120.0	100.0	81.7	85.0	90.4	124.0	159.0	211.0	474.0	749.0	847.0	838.0	614.0	656.0	552.0	575.0

Obs	c17	c18	c19	c20	c21	KE_FIRST	KE_LAST	trt
1	127.0	104.0	136.0	105.0	100.0	18	21	2
2	55.3	58.2	82.8	83.6	47.5	18	21	1
3	73.5	52.7	167.0	70.5	45.0	18	21	1
4	221.0	164.0	264.0	123.0	100.0	18	21	2
5	47.5	38.2	74.0	49.5	49.2	18	21	1
6	133.0	118.0	216.0	168.0	106.0	18	21	2

Reference ID: 3227106

Obs	c17	c18	c19	c20	c21	KE_FIRST	KE_LAST	trt
7	281.0	244.0	407.0	266.0	226.0	18	21	2
8	123.0	137.0	395.0	151.0	144.0	18	21	1
9	458.0	195.0	277.0	159.0	171.0	18	21	2
10	92.5	67.6	83.8	96.2	81.5	18	21	1
11	68.7	104.0	149.0	93.5	126.0	18	21	1
12	376.0	269.0	249.0	201.0	205.0	18	21	2

PILOT FAST & FED CONCENTRATION DATASET (FREE EPA)-BASELINE-ADJUSTED

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12
1	1	2	1	B	1	0.0000	0.000	0.000	0.000	279.63	1551.63	941.633	541.63	218.63	202.63	145.63	0.000
2	1	2	2	A	1	0.0000	0.000	0.583	17.683	32.68	0.00	0.000	0.00	0.00	0.00	0.00	0.000
3	2	1	1	A	1	51.4000	11.600	108.400	47.400	70.40	28.40	6.700	0.00	0.00	0.00	0.00	0.000
4	2	1	2	B	1	9.2500	0.000	0.000	84.250	107.25	71.25	164.250	606.25	1316.25	613.25	280.25	147.250
5	3	1	1	A	1	0.0000	40.100	58.100	12.900	48.10	0.00	0.000	0.00	0.00	0.20	0.00	0.000
6	3	1	2	B	1	55.0667	0.000	169.067	349.067	779.07	354.07	315.067	138.07	89.07	86.07	97.07	58.067
7	4	2	1	B	1	44.0000	21.000	379.000	468.000	1306.00	826.00	856.000	356.00	180.00	88.00	0.00	0.000
8	4	2	2	A	1	95.6667	226.667	26.667	103.667	189.67	0.00	0.000	0.00	0.00	0.00	0.00	0.000
9	5	2	1	B	1	19.9667	13.267	3.567	0.000	3.27	40.67	291.667	1001.67	1711.67	1291.67	1381.67	379.667
10	5	2	2	A	1	31.2500	44.250	13.650	62.250	58.25	28.25	11.250	1.75	6.35	91.25	36.25	12.750
11	6	1	1	A	1	26.3833	19.383	18.383	14.383	61.38	14.38	0.000	0.00	0.00	0.00	0.00	0.000
12	6	1	2	B	1	23.8167	58.817	110.817	373.817	648.82	746.82	737.817	513.82	555.82	451.82	474.82	275.817

Obs	c13	c14	c15	c16	KE_FIRST	KE_LAST	trt
1	0.000	0.000	0.000	0.000	8	11	2
2	0.000	0.000	0.000	0.000	8	11	1
3	0.000	92.400	0.000	0.000	8	11	1

Reference ID: 3227106

Obs	c13	c14	c15	c16	KE_FIRST	KE_LAST	trt
4	90.250	190.250	49.250	26.250	8	11	2
5	0.000	13.100	0.000	0.000	8	11	1
6	43.067	141.067	93.067	31.067	8	11	2
7	0.000	73.000	0.000	0.000	8	11	2
8	0.000	158.667	0.000	0.000	8	11	1
9	116.667	198.667	80.667	92.667	8	11	2
10	0.000	4.050	16.450	1.750	8	11	1
11	0.000	23.383	0.000	0.383	8	11	1
12	168.817	148.817	100.817	104.817	8	11	2

PILOT FAST & FED CONCENTRATION DATASET (TOTAL EPA)-BASELINE-NON-ADJUSTED

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	c20	c21	KE_FIRST	KE_LAST	trt
1	1	2	1	B	1	1960	547	678	782	446	894	381	456	713	1720	6830	3940	2620	1620	1410	1310	368	335	619	446	425	18	21	2
2	1	2	2	A	1	494	556	684	1270	328	532	575	687	864	953	477	360	336	305	642	454	284	289	528	612	242	18	21	1
3	2	1	1	A	1	400	374	201	272	172	616	435	874	628	716	427	261	217	191	203	170	249	187	719	263	142	18	21	1
4	2	1	2	B	1	503	332	189	220	190	317	318	339	670	670	593	674	1850	4600	1960	895	369	254	751	243	215	18	21	2
5	3	1	1	A	1	945	174	189	268	142	282	666	784	454	627	204	149	136	171	221	158	144	135	406	137	180	18	21	1
6	3	1	2	B	1	615	251	153	571	208	816	257	483	1280	3330	1300	1050	391	265	312	267	195	187	847	404	204	18	21	2
7	4	2	1	B	1	2900	762	438	388	282	1530	1050	2120	2300	5550	3880	3350	1740	826	666	433	499	322	1230	655	530	18	21	2
8	4	2	2	A	1	1780	945	354	579	268	1400	1870	1070	1200	1860	901	364	262	266	437	324	311	360	1510	567	363	18	21	1
9	5	2	1	B	1	464	449	372	473	395	644	499	511	530	398	666	1060	3420	6230	4350	4890	1040	233	773	262	470	18	21	2
10	5	2	2	A	1	403	262	308	511	166	629	652	520	842	787	563	363	234	333	963	618	243	162	416	517	272	18	21	1
11	6	1	1	A	1	797	522	259	454	338	661	639	637	602	947	601	369	260	229	292	221	293	316	718	252	447	18	21	1
12	6	1	2	B	1	519	383	285	284	235	479	520	668	1010	2130	2550	2340	1680	1410	1360	1400	649	344	559	323	334	18	21	2

Reference ID: 3227106

PILOT FAST & FED CONCENTRATION DATASET (TOTAL EPA)-BASELINE-ADJUSTED

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12
1	1	2	1	B	1	0.00000	0.00000	0.0000	0.0000	4.7833	68.9833	54.8833	30.0833	20.6833	22.7833	23.3833	20.5833
2	1	2	2	A	1	0.00000	0.00000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.3167
3	2	1	1	A	1	0.00000	0.00000	0.4500	0.0000	0.0000	0.9500	5.3500	5.8500	2.9500	1.8500	1.8500	0.9500
4	2	1	2	B	1	0.00000	0.85000	3.6500	5.1500	10.1500	10.9500	17.3500	42.2500	80.1500	74.2500	51.1500	34.7500
5	3	1	1	A	1	0.10000	1.60000	1.1000	2.2000	3.8000	4.5000	7.3000	9.7000	9.2000	9.6000	6.4000	6.5000
6	3	1	2	B	1	0.00000	0.00000	6.6000	41.8000	64.1000	51.8000	45.3000	38.0000	33.5000	39.6000	43.3000	35.4000
7	4	2	1	B	1	0.00000	0.00000	19.9667	74.5667	79.5667	82.5667	86.5667	68.5667	49.5667	41.8667	32.7667	21.4667
8	4	2	2	A	1	0.00000	0.00000	0.0833	0.2833	0.0000	0.0000	0.0000	0.0000	3.8833	1.5833	0.0000	0.0000
9	5	2	1	B	1	0.08333	0.98333	1.6833	1.0833	2.7833	3.2833	12.4833	60.0833	74.0833	62.5833	67.3833	60.0833
10	5	2	2	A	1	0.00000	0.00000	0.0000	0.5167	0.0167	0.7167	2.8167	4.1167	5.4167	5.8167	4.7167	4.3167
11	6	1	1	A	1	0.00000	0.00000	0.0000	0.0000	0.0000	0.0000	1.0500	3.0500	1.9500	3.6500	3.9500	3.3500
12	6	1	2	B	1	0.00000	3.08333	9.3833	24.0833	38.9833	59.5833	60.8833	52.3833	58.0833	58.4833	67.9833	51.4833

Obs	c13	c14	c15	c16	KE_FIRST	KE_LAST	trt
1	21.2833	12.1833	8.0833	4.9833	9	12	2
2	0.0000	0.0000	0.0000	0.0000	9	12	1
3	1.3500	0.0000	1.6500	1.6500	9	12	1
4	34.7500	27.8500	26.3500	18.2500	9	12	2
5	4.6000	3.2000	9.6000	6.1000	9	12	1
6	33.6000	28.8000	33.6000	24.8000	9	12	2
7	3.3667	0.0000	3.2667	0.0000	9	12	2
8	0.0000	0.0000	0.0000	0.0000	9	12	1
9	45.3833	29.5833	25.4833	27.0833	9	12	2
10	4.6167	1.6167	2.9167	4.3167	9	12	1

Reference ID: 3227106

Obs	c13	c14	c15	c16	KE_FIRST	KE_LAST	trt
11	3.0500	0.0000	2.3500	5.7500	9	12	1
12	50.3833	37.3833	35.3833	30.0833	9	12	2

PILOT FAST & FED CONCENTRATION DATASET (FREE DHA)-BASELINE-NON-ADJUSTED

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	c20	c21	KE_FIRST	KE_LAST	trt
1	1	2	1	B	1	1960	547	678	782	446	894	381	456	713	1720	6830	3940	2620	1620	1410	1310	368	335	619	446	425	18	21	2
2	1	2	2	A	1	494	556	684	1270	328	532	575	687	864	953	477	360	336	305	642	454	284	289	528	612	242	18	21	1
3	2	1	1	A	1	400	374	201	272	172	616	435	874	628	716	427	261	217	191	203	170	249	187	719	263	142	18	21	1
4	2	1	2	B	1	503	332	189	220	190	317	318	339	670	670	593	674	1850	4600	1960	895	369	254	751	243	215	18	21	2
5	3	1	1	A	1	945	174	189	268	142	282	666	784	454	627	204	149	136	171	221	158	144	135	406	137	180	18	21	1
6	3	1	2	B	1	615	251	153	571	208	816	257	483	1280	3330	1300	1050	391	265	312	267	195	187	847	404	204	18	21	2
7	4	2	1	B	1	2900	762	438	388	282	1530	1050	2120	2300	5550	3880	3350	1740	826	666	433	499	322	1230	655	530	18	21	2
8	4	2	2	A	1	1780	945	354	579	268	1400	1870	1070	1200	1860	901	364	262	266	437	324	311	360	1510	567	363	18	21	1
9	5	2	1	B	1	464	449	372	473	395	644	499	511	530	398	666	1060	3420	6230	4350	4890	1040	233	773	262	470	18	21	2
10	5	2	2	A	1	403	262	308	511	166	629	652	520	842	787	563	363	234	333	963	618	243	162	416	517	272	18	21	1
11	6	1	1	A	1	797	522	259	454	338	661	639	637	602	947	601	369	260	229	292	221	293	316	718	252	447	18	21	1
12	6	1	2	B	1	519	383	285	284	235	479	520	668	1010	2130	2550	2340	1680	1410	1360	1400	649	344	559	323	334	18	21	2

PILOT FAST & FED CONCENTRATION DATASET (FREE DHA)-BASELINE- ADJUSTED

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13
1	1	2	1	B	1	9.500	0.000	0.00	0.00	835.50	5945.50	3055.50	1735.50	735.50	525.50	425.50	0.000	0
2	1	2	2	A	1	0.000	0.000	43.00	220.00	309.00	0.00	0.00	0.00	0.00	0.00	0.00	0.000	0
3	2	1	1	A	1	276.833	95.833	534.83	288.83	376.83	87.83	0.00	0.00	0.00	0.00	0.00	0.000	0
4	2	1	2	B	1	25.167	26.167	47.17	378.17	378.17	301.17	382.17	1558.17	4308.17	1668.17	603.17	77.167	0

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13
5	3	1	1	A	1	0.000	332.667	450.67	120.67	293.67	0.00	0.00	0.00	0.00	0.00	0.00	0.000	0
6	3	1	2	B	1	380.333	0.000	47.33	844.33	2894.33	864.33	614.33	0.00	0.00	0.00	0.00	0.000	0
7	4	2	1	B	1	480.000	0.000	1070.00	1250.00	4500.00	2830.00	2300.00	690.00	0.00	0.00	0.00	0.000	0
8	4	2	2	A	1	512.333	982.333	182.33	312.33	972.33	13.33	0.00	0.00	0.00	0.00	0.00	0.000	0
9	5	2	1	B	1	177.833	32.833	44.83	63.83	0.00	199.83	593.83	2953.83	5763.83	3883.83	4423.83	573.833	0
10	5	2	2	A	1	249.167	272.167	140.17	462.17	407.17	183.17	0.00	0.00	0.00	583.17	238.17	0.000	0
11	6	1	1	A	1	155.833	133.833	131.83	96.83	441.83	95.83	0.00	0.00	0.00	0.00	0.00	0.000	0
12	6	1	2	B	1	114.833	155.833	303.83	645.83	1765.83	2185.83	1975.83	1315.83	1045.83	995.83	1035.83	284.833	0

Obs	c14	c15	c16	KE_FIRST	KE_LAST	trt
1	0.000	0.000	0.00000	3	6	2
2	0.000	0.000	0.00000	3	6	1
3	379.833	0.000	0.00000	3	6	1
4	459.167	0.000	0.00000	3	6	2
5	72.667	0.000	0.00000	3	6	1
6	411.333	0.000	0.00000	3	6	2
7	180.000	0.000	0.00000	3	6	2
8	622.333	0.000	0.00000	3	6	1
9	306.833	0.000	3.83333	3	6	2
10	36.167	137.167	0.00000	3	6	1
11	212.833	0.000	0.00000	3	6	1

PILOT FAST & FED CONCENTRATION DATASET (TOTAL DHA)-BASELINE-NON-ADJUSTED

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16
1	1	2	1	B	1	92.8	99.4	93.6	89.2	92.5	83.7	90.7	95.2	97.7	104.0	147.0	129.0	112.0	104.0	108.0	104.0

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16
2	1	2	2	A	1	105.0	99.9	99.4	104.0	99.8	88.2	96.4	97.4	102.0	95.1	93.7	90.3	93.0	99.7	101.0	98.2
3	2	1	1	A	1	37.2	45.2	40.3	37.4	36.4	41.2	39.3	43.2	40.2	41.0	41.0	46.7	45.1	42.7	40.5	40.1
4	2	1	2	B	1	35.1	37.3	37.4	35.0	34.1	34.8	39.4	43.5	42.0	46.2	46.1	50.1	63.8	89.9	77.4	64.8
5	3	1	1	A	1	43.5	46.0	45.2	49.3	43.5	45.0	47.3	47.4	50.8	55.9	53.0	55.0	58.9	53.5	54.3	51.9
6	3	1	2	B	1	49.5	51.6	45.4	50.4	45.8	44.9	45.6	51.5	79.1	98.6	79.0	63.5	56.5	52.4	55.3	59.2
7	4	2	1	B	1	125.0	121.0	122.0	109.0	102.0	97.9	106.0	139.0	163.0	168.0	150.0	149.0	147.0	130.0	112.0	105.0
8	4	2	2	A	1	85.4	95.7	86.4	88.6	69.6	80.6	87.3	84.0	92.5	85.5	83.6	86.1	88.0	84.4	83.7	84.2
9	5	2	1	B	1	46.8	52.6	45.9	52.3	49.8	51.4	54.8	55.7	55.1	56.1	51.5	60.4	97.9	95.5	95.8	98.6
10	5	2	2	A	1	43.7	51.4	49.3	49.9	52.0	49.8	50.8	46.4	49.3	49.5	52.3	51.4	54.3	54.8	57.7	59.3
11	6	1	1	A	1	60.9	68.1	67.5	69.1	64.1	54.9	61.2	64.7	64.4	66.8	65.0	67.7	66.2	73.6	70.4	70.2
12	6	1	2	B	1	56.4	60.6	58.5	59.9	59.7	51.8	57.8	64.4	71.9	83.7	92.5	92.9	93.4	96.4	82.5	96.9

Obs	c17	c18	c19	c20	c21	KE_FIRST	KE_LAST	trt
1	99.4	101.0	93.8	84.5	87.2	18	21	2
2	102.0	101.0	84.7	82.8	83.7	18	21	1
3	37.4	36.3	37.3	41.1	39.9	18	21	1
4	49.0	44.3	43.7	47.8	42.1	18	21	2
5	52.3	46.3	46.4	53.2	49.3	18	21	1
6	47.7	42.8	47.9	55.1	51.8	18	21	2
7	106.0	77.7	85.4	97.0	101.0	18	21	2
8	77.6	74.5	75.3	75.5	81.1	18	21	1
9	77.9	58.3	51.8	51.0	59.1	18	21	2
10	58.3	52.1	49.7	50.3	53.0	18	21	1
11	67.1	62.7	48.6	62.3	67.7	18	21	1
12	71.0	70.2	53.9	67.4	63.1	18	21	2

PILOT FAST & FED CONCENTRATION DATASET (TOTAL DHA)-BASELINE- ADJUSTED

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12
1	1	2	1	B	1	0.00000	0.00000	3.3333	5.8333	12.1333	55.1333	37.1333	20.1333	12.1333	16.1333	12.1333	7.5333
2	1	2	2	A	1	0.00000	0.00000	0.0000	2.6167	0.0000	0.0000	0.0000	0.0000	0.3167	1.6167	0.0000	2.6167
3	2	1	1	A	1	1.58333	0.00000	3.5833	0.5833	1.3833	1.3833	7.0833	5.4833	3.0833	0.8833	0.4833	0.0000
4	2	1	2	B	1	0.00000	3.78333	7.8833	6.3833	10.5833	10.4833	14.4833	28.1833	54.2833	41.7833	29.1833	13.3833
5	3	1	1	A	1	0.00000	1.88333	1.9833	5.3833	10.4833	7.5833	9.5833	13.4833	8.0833	8.8833	6.4833	6.8833
6	3	1	2	B	1	0.00000	0.00000	3.5667	31.1667	50.6667	31.0667	15.5667	8.5667	4.4667	7.3667	11.2667	0.0000
7	4	2	1	B	1	0.00000	0.00000	26.1833	50.1833	55.1833	37.1833	36.1833	34.1833	17.1833	0.0000	0.0000	0.0000
8	4	2	2	A	1	0.00000	2.91667	0.0000	8.1167	1.1167	0.0000	1.7167	3.6167	0.0167	0.0000	0.0000	0.0000
9	5	2	1	B	1	1.60000	5.00000	5.9000	5.3000	6.3000	1.7000	10.6000	48.1000	45.7000	46.0000	48.8000	28.1000
10	5	2	2	A	1	0.45000	1.45000	0.0000	0.0000	0.1500	2.9500	2.0500	4.9500	5.4500	8.3500	9.9500	8.9500
11	6	1	1	A	1	0.00000	0.00000	0.6000	0.3000	2.7000	0.9000	3.6000	2.1000	9.5000	6.3000	6.1000	3.0000
12	6	1	2	B	1	0.00000	0.00000	6.5833	14.0833	25.8833	34.6833	35.0833	35.5833	38.5833	24.6833	39.0833	13.1833

Obs	c13	c14	c15	c16	KE_FIRST	KE_LAST	trt
1	9.1333	1.93333	0.0000	0.00000	6	9	2
2	1.6167	0.00000	0.0000	0.00000	6	9	1
3	0.0000	0.00000	1.4833	0.28333	6	9	1
4	8.6833	8.08333	12.1833	6.48333	6	9	2
5	0.8833	0.98333	7.7833	3.88333	6	9	1
6	0.0000	0.00000	7.1667	3.86667	6	9	2
7	0.0000	0.00000	0.0000	0.00000	6	9	2
8	0.0000	0.00000	0.0000	0.00000	6	9	1
9	8.5000	2.00000	1.2000	9.30000	6	9	2
10	2.7500	0.35000	0.9500	3.65000	6	9	1
11	0.0000	0.00000	0.0000	3.60000	6	9	1

Reference ID: 3227106

4.8.2 Pilot Study Output

PILOT FAST & FED STATISTICAL OUTPUT (FREE EPA) – BASELINE-NON-ADJUSTED

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	6	1 2 3 4 5 6
trt	2	1 2
per	2	1 2
seq	2	1 2

Number of Observations Read	12
Number of Observations Used	12

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	3.52853125	0.50407589	20.71	0.0054
Error	4	0.09736486	0.02434122		
Corrected Total	11	3.62589611			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.973147	1.718123	0.156017	9.080647

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.33297536	0.33297536	13.68	0.0209
sub(seq)	4	1.23535069	0.30883767	12.69	0.0152
per	1	0.00000185	0.00000185	0.00	0.9935
trt	1	1.96020335	1.96020335	80.53	0.0009

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.33297536	0.33297536	13.68	0.0209
sub(seq)	4	1.23535069	0.30883767	12.69	0.0152
per	1	0.00000185	0.00000185	0.00	0.9935

Reference ID: 3227106

Source	DF	Type III SS	Mean Square	F Value	Pr > F
trt	1	1.96020335	1.96020335	80.53	0.0009

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.33297536	0.33297536	1.08	0.3578

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.80833230	0.09007629	-8.97	0.0009

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	3.83351025	0.54764432	2.55	0.1917
Error	4	0.85987979	0.21496995		
Corrected Total	11	4.69339003			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.816789	4.648102	0.463649	9.975006

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.18938350	0.18938350	0.88	0.4011
sub(seq)	4	2.57990509	0.64497627	3.00	0.1562
per	1	0.20822723	0.20822723	0.97	0.3807
trt	1	0.85599443	0.85599443	3.98	0.1167

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.18938350	0.18938350	0.88	0.4011
sub(seq)	4	2.57990509	0.64497627	3.00	0.1562
per	1	0.20822723	0.20822723	0.97	0.3807
trt	1	0.85599443	0.85599443	3.98	0.1167

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.18938350	0.18938350	0.29	0.6167

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.53416428	0.26768760	-2.00	0.1167

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	11.33863502	1.61980500	15.32	0.0096
Error	4	0.42303260	0.10575815		
Corrected Total	11	11.76166763			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.964033	5.205325	0.325205	6.247540

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.57379082	0.57379082	5.43	0.0803
sub(seq)	4	0.40239693	0.10059923	0.95	0.5187
per	1	0.02692406	0.02692406	0.25	0.6404
trt	1	10.33552321	10.33552321	97.73	0.0006

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.57379082	0.57379082	5.43	0.0803
sub(seq)	4	0.40239693	0.10059923	0.95	0.5187
per	1	0.02692406	0.02692406	0.25	0.6404
trt	1	10.33552321	10.33552321	97.73	0.0006

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.57379082	0.57379082	5.70	0.0753

Reference ID: 3227106

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-1.85611810	0.18775707	-9.89	0.0006

PILOT FAST & FED STATISTICAL OUTPUT (FREE EPA) – BASELINE- ADJUSTED

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	6	1 2 3 4 5 6
trt	2	1 2
per	2	1 2
seq	2	1 2

Data for Analysis of AUCT CMAX LAUCT LCMAX	
Number of Observations Read	12
Number of Observations Used	12

Data for Analysis of AUCI LAUCI	
Number of Observations Read	12
Number of Observations Used	7

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	31.26191486	4.46598784	5.68	0.0563
Error	4	3.14530025	0.78632506		
Corrected Total	11	34.40721511			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.908586	12.26743	0.886750	7.228488

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.05768759	0.05768759	0.07	0.7999

Reference ID: 3227106

Source	DF	Type I SS	Mean Square	F Value	Pr > F
sub(seq)	4	5.34939357	1.33734839	1.70	0.3098
per	1	0.01146138	0.01146138	0.01	0.9097
trt	1	25.84337233	25.84337233	32.87	0.0046

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.05768759	0.05768759	0.07	0.7999
sub(seq)	4	5.34939357	1.33734839	1.70	0.3098
per	1	0.01146138	0.01146138	0.01	0.9097
trt	1	25.84337233	25.84337233	32.87	0.0046

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.05768759	0.05768759	0.04	0.8456

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-2.93503960	0.51196519	-5.73	0.0046

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	6	6.20004855	1.03334143	.	.
Error	0	0.00000000	.		
Corrected Total	6	6.20004855			

R-Square	Coeff Var	Root MSE	LAUCI Mean
1.000000	.	.	8.435984

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.85380884	0.85380884	.	.
sub(seq)	4	0.70064987	0.17516247	.	.
per	1	4.64558984	4.64558984	.	.
trt	0	0.00000000	.	.	.

Reference ID: 3227106

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	0	0.00000000	.	.	.
sub(seq)	4	0.99323613	0.24830903	.	.
per	0	0.00000000	.	.	.
trt	0	0.00000000	.	.	.

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	0	0	.	.	.

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	23.35793773	3.33684825	11.91	0.0153
Error	4	1.12042319	0.28010580		
Corrected Total	11	24.47836092			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.954228	9.242857	0.529250	5.726046

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.35685727	0.35685727	1.27	0.3221
sub(seq)	4	1.23239047	0.30809762	1.10	0.4643
per	1	0.07548337	0.07548337	0.27	0.6311
trt	1	21.69320662	21.69320662	77.45	0.0009

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.35685727	0.35685727	1.27	0.3221
sub(seq)	4	1.23239047	0.30809762	1.10	0.4643
per	1	0.07548337	0.07548337	0.27	0.6311
trt	1	21.69320662	21.69320662	77.45	0.0009

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F

Reference ID: 3227106

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.35685727	0.35685727	1.16	0.3424

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-2.68906468	0.30556276	-8.80	0.0009

PILOT FAST & FED STATISTICAL OUTPUT (TOTAL EPA) – BASELINE-NON-ADJUSTED

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	6	1 2 3 4 5 6
trt	2	1 2
per	2	1 2
seq	2	1 2

Number of Observations Read	12
Number of Observations Used	12

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	2.03098295	0.29014042	132.12	0.0001
Error	4	0.00878399	0.00219600		
Corrected Total	11	2.03976694			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.995694	0.624237	0.046861	7.507003

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.23108088	0.23108088	105.23	0.0005
sub(seq)	4	0.45726329	0.11431582	52.06	0.0011

Source	DF	Type I SS	Mean Square	F Value	Pr > F
per	1	0.00326912	0.00326912	1.49	0.2894
trt	1	1.33936966	1.33936966	609.91	<.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.23108088	0.23108088	105.23	0.0005
sub(seq)	4	0.45726329	0.11431582	52.06	0.0011
per	1	0.00326912	0.00326912	1.49	0.2894
trt	1	1.33936966	1.33936966	609.91	<.0001

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.23108088	0.23108088	2.02	0.2282

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.66817404	0.02705549	-24.70	<.0001

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	6.50387129	0.92912447	0.92	0.5686
Error	4	4.04123210	1.01030803		
Corrected Total	11	10.54510339			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.616767	11.11163	1.005141	9.045847

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	2.07188661	2.07188661	2.05	0.2254
sub(seq)	4	2.84764794	0.71191198	0.70	0.6286
per	1	0.78079481	0.78079481	0.77	0.4290
trt	1	0.80354193	0.80354193	0.80	0.4229

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	2.07188661	2.07188661	2.05	0.2254
sub(seq)	4	2.84764794	0.71191198	0.70	0.6286
per	1	0.78079481	0.78079481	0.77	0.4290
trt	1	0.80354193	0.80354193	0.80	0.4229

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	2.07188661	2.07188661	2.91	0.1632

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	0.51753967	0.58031831	0.89	0.4229

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	5.40889057	0.77269865	61.46	0.0007
Error	4	0.05028876	0.01257219		
Corrected Total	11	5.45917934			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.990788	2.836216	0.112126	3.953358

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.18019991	0.18019991	14.33	0.0193
sub(seq)	4	0.27677596	0.06919399	5.50	0.0637
per	1	0.00033770	0.00033770	0.03	0.8778
trt	1	4.95157701	4.95157701	393.85	<.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.18019991	0.18019991	14.33	0.0193
sub(seq)	4	0.27677596	0.06919399	5.50	0.0637
per	1	0.00033770	0.00033770	0.03	0.8778
trt	1	4.95157701	4.95157701	393.85	<.0001

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.18019991	0.18019991	2.60	0.1819

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-1.28472786	0.06473585	-19.85	<.0001

PILOT FAST & FED STATISTICAL OUTPUT (TOTAL EPA) – BASELINE- ADJUSTED

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	6	1 2 3 4 5 6
trt	2	1 2
per	2	1 2
seq	2	1 2

Data for Analysis of AUCT CMAX LAUCT LCMAX	
Number of Observations Read	12
Number of Observations Used	12

Data for Analysis of AUCI LAUCI	
Number of Observations Read	12
Number of Observations Used	11

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	66.02631218	9.43233031	5.34	0.0623
Error	4	7.06286910	1.76571728		
Corrected Total	11	73.08918128			

Reference ID: 3227106

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.903366	26.63148	1.328803	4.989594

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	7.84217223	7.84217223	4.44	0.1028
sub(seq)	4	11.54882711	2.88720678	1.64	0.3227
per	1	3.98943350	3.98943350	2.26	0.2072
trt	1	42.64587934	42.64587934	24.15	0.0080

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	7.84217223	7.84217223	4.44	0.1028
sub(seq)	4	11.54882711	2.88720678	1.64	0.3227
per	1	3.98943350	3.98943350	2.26	0.2072
trt	1	42.64587934	42.64587934	24.15	0.0080

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	7.84217223	7.84217223	2.72	0.1747

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-3.77031738	0.76718474	-4.91	0.0080

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	36.41984012	5.20283430	12.81	0.0301
Error	3	1.21865736	0.40621912		
Corrected Total	10	37.63849748			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.967622	10.61393	0.637353	6.004877

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	1.04868910	1.04868910	2.58	0.2065

Reference ID: 3227106

Source	DF	Type I SS	Mean Square	F Value	Pr > F
sub(seq)	4	9.97058538	2.49264634	6.14	0.0840
per	1	0.39059806	0.39059806	0.96	0.3991
trt	1	25.00996758	25.00996758	61.57	0.0043

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	2.10567833	2.10567833	5.18	0.1073
sub(seq)	4	6.89072265	1.72268066	4.24	0.1325
per	1	0.15042608	0.15042608	0.37	0.5858
trt	1	25.00996758	25.00996758	61.57	0.0043

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	2.10567833	2.10567833	1.22	0.3309

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-3.22812946	0.41140973	-7.85	0.0043

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	32.25903695	4.60843385	7.65	0.0338
Error	4	2.41052290	0.60263072		
Corrected Total	11	34.66955984			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.930471	27.79186	0.776293	2.793238

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	1.07035456	1.07035456	1.78	0.2535
sub(seq)	4	2.79245043	0.69811261	1.16	0.4450
per	1	1.37134395	1.37134395	2.28	0.2059
trt	1	27.02488802	27.02488802	44.84	0.0026

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	1.07035456	1.07035456	1.78	0.2535
sub(seq)	4	2.79245043	0.69811261	1.16	0.4450
per	1	1.37134395	1.37134395	2.28	0.2059
trt	1	27.02488802	27.02488802	44.84	0.0026

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	1.07035456	1.07035456	1.53	0.2833

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-3.00138235	0.44819294	-6.70	0.0026

PILOT FAST & FED STATISTICAL OUTPUT (FREE DHA) - BASELINE-NON-ADJUTED

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	6	1 2 3 4 5 6
trt	2	1 2
per	2	1 2
seq	2	1 2

Number of Observations Read	12
Number of Observations Used	12

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	1.66387075	0.23769582	9.08	0.0250
Error	4	0.10467745	0.02616936		
Corrected Total	11	1.76854820			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.940812	1.555308	0.161769	10.40112

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.71118344	0.71118344	27.18	0.0065
sub(seq)	4	0.32974278	0.08243570	3.15	0.1462
per	1	0.00551182	0.00551182	0.21	0.6701
trt	1	0.61743270	0.61743270	23.59	0.0083

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.71118344	0.71118344	27.18	0.0065
sub(seq)	4	0.32974278	0.08243570	3.15	0.1462
per	1	0.00551182	0.00551182	0.21	0.6701
trt	1	0.61743270	0.61743270	23.59	0.0083

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.71118344	0.71118344	8.63	0.0425

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.45366386	0.09339765	-4.86	0.0083

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	10.10337818	1.44333974	3.86	0.1048
Error	4	1.49540397	0.37385099		
Corrected Total	11	11.59878215			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.871072	5.296182	0.611434	11.54480

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.78061353	0.78061353	2.09	0.2220
sub(seq)	4	8.12313740	2.03078435	5.43	0.0650

Source	DF	Type I SS	Mean Square	F Value	Pr > F
per	1	0.89255417	0.89255417	2.39	0.1972
trt	1	0.30707308	0.30707308	0.82	0.4160

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.78061353	0.78061353	2.09	0.2220
sub(seq)	4	8.12313740	2.03078435	5.43	0.0650
per	1	0.89255417	0.89255417	2.39	0.1972
trt	1	0.30707308	0.30707308	0.82	0.4160

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.78061353	0.78061353	0.38	0.5688

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	0.31993389	0.35301133	0.91	0.4160

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	6.96369245	0.99481321	14.24	0.0110
Error	4	0.27952394	0.06988099		
Corrected Total	11	7.24321640			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.961409	3.425547	0.264350	7.717020

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.68752420	0.68752420	9.84	0.0350
sub(seq)	4	0.14307071	0.03576768	0.51	0.7338
per	1	0.04397408	0.04397408	0.63	0.4720
trt	1	6.08912346	6.08912346	87.14	0.0007

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.68752420	0.68752420	9.84	0.0350
sub(seq)	4	0.14307071	0.03576768	0.51	0.7338
per	1	0.04397408	0.04397408	0.63	0.4720
trt	1	6.08912346	6.08912346	87.14	0.0007

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.68752420	0.68752420	19.22	0.0118

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-1.42467815	0.15262261	-9.33	0.0007

PILOT FAST & FED STATISTICAL OUTPUT (FREE DHA) - BASELINE-ADJUTED

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	6	1 2 3 4 5 6
trt	2	1 2
per	2	1 2
seq	2	1 2

Number of Observations Read	12
Number of Observations Used	12

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	13.73563922	1.96223417	4.74	0.0759
Error	4	1.65719346	0.41429836		

Reference ID: 3227106

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Corrected Total	11	15.39283268			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.892340	7.545199	0.643660	8.530725

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.10574160	0.10574160	0.26	0.6400
sub(seq)	4	2.67284642	0.66821161	1.61	0.3273
per	1	0.18212964	0.18212964	0.44	0.5436
trt	1	10.77492155	10.77492155	26.01	0.0070

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.10574160	0.10574160	0.26	0.6400
sub(seq)	4	2.67284642	0.66821161	1.61	0.3273
per	1	0.18212964	0.18212964	0.44	0.5436
trt	1	10.77492155	10.77492155	26.01	0.0070

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.10574160	0.10574160	0.16	0.7111

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-1.89516240	0.37161735	-5.10	0.0070

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	9.46556779	1.35222397	4.60	0.0795
Error	4	1.17554016	0.29388504		
Corrected Total	11	10.64110795			

R-Square	Coeff Var	Root MSE	LAUCI Mean

Reference ID: 3227106

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.889528	6.176705	0.542112	8.776712

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.04099581	0.04099581	0.14	0.7277
sub(seq)	4	2.72462098	0.68115524	2.32	0.2178
per	1	0.24432937	0.24432937	0.83	0.4135
trt	1	6.45562163	6.45562163	21.97	0.0094

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.04099581	0.04099581	0.14	0.7277
sub(seq)	4	2.72462098	0.68115524	2.32	0.2178
per	1	0.24432937	0.24432937	0.83	0.4135
trt	1	6.45562163	6.45562163	21.97	0.0094

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.04099581	0.04099581	0.06	0.8183

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-1.46692668	0.31298831	-4.69	0.0094

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	13.57821337	1.93974477	13.49	0.0121
Error	4	0.57530358	0.14382590		
Corrected Total	11	14.15351696			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.959353	5.215036	0.379244	7.272123

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.41857380	0.41857380	2.91	0.1632

Reference ID: 3227106

Source	DF	Type I SS	Mean Square	F Value	Pr > F
sub(seq)	4	0.39684796	0.09921199	0.69	0.6361
per	1	0.12503601	0.12503601	0.87	0.4039
trt	1	12.63775560	12.63775560	87.87	0.0007

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.41857380	0.41857380	2.91	0.1632
sub(seq)	4	0.39684796	0.09921199	0.69	0.6361
per	1	0.12503601	0.12503601	0.87	0.4039
trt	1	12.63775560	12.63775560	87.87	0.0007

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.41857380	0.41857380	4.22	0.1092

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-2.05245833	0.21895654	-9.37	0.0007

PILOT FAST & FED STATISTICAL OUTPUT (TOTAL DHA) – BASELINE-NON-ADJUSTED

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	6	1 2 3 4 5 6
trt	2	1 2
per	2	1 2
seq	2	1 2

Number of Observations Read	12
Number of Observations Used	12

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	1.16807796	0.16686828	34.25	0.0021
Error	4	0.01949030	0.00487258		
Corrected Total	11	1.18756827			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.983588	0.847783	0.069804	8.233691

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.55513473	0.55513473	113.93	0.0004
sub(seq)	4	0.58162423	0.14540606	29.84	0.0031
per	1	0.00360591	0.00360591	0.74	0.4382
trt	1	0.02771309	0.02771309	5.69	0.0756

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.55513473	0.55513473	113.93	0.0004
sub(seq)	4	0.58162423	0.14540606	29.84	0.0031
per	1	0.00360591	0.00360591	0.74	0.4382
trt	1	0.02771309	0.02771309	5.69	0.0756

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.55513473	0.55513473	3.82	0.1224

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.09611294	0.04030127	-2.38	0.0756

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	9.68653285	1.38379041	2.38	0.2103
Error	4	2.32786705	0.58196676		
Corrected Total	11	12.01439990			

Reference ID: 3227106

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.806244	7.550506	0.762867	10.10353

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	1.64856686	1.64856686	2.83	0.1676
sub(seq)	4	7.26533528	1.81633382	3.12	0.1481
per	1	0.11668407	0.11668407	0.20	0.6775
trt	1	0.65594664	0.65594664	1.13	0.3482

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	1.64856686	1.64856686	2.83	0.1676
sub(seq)	4	7.26533528	1.81633382	3.12	0.1481
per	1	0.11668407	0.11668407	0.20	0.6775
trt	1	0.65594664	0.65594664	1.13	0.3482

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	1.64856686	1.64856686	0.91	0.3947

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.46759906	0.44044173	-1.06	0.3482

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	1.45268258	0.20752608	16.31	0.0085
Error	4	0.05088036	0.01272009		
Corrected Total	11	1.50356294			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.966160	2.511649	0.112783	4.490411

Source	DF	Type I SS	Mean Square	F Value	Pr > F

Reference ID: 3227106

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.37509067	0.37509067	29.49	0.0056
sub(seq)	4	0.39922208	0.09980552	7.85	0.0354
per	1	0.00011743	0.00011743	0.01	0.9281
trt	1	0.67825240	0.67825240	53.32	0.0019

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.37509067	0.37509067	29.49	0.0056
sub(seq)	4	0.39922208	0.09980552	7.85	0.0354
per	1	0.00011743	0.00011743	0.01	0.9281
trt	1	0.67825240	0.67825240	53.32	0.0019

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.37509067	0.37509067	3.76	0.1246

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.47548305	0.06511551	-7.30	0.0019

PILOT FAST & FED STATISTICAL OUTPUT (TOTAL DHA) – BASELINE- ADJUSTED

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	6	1 2 3 4 5 6
trt	2	1 2
per	2	1 2
seq	2	1 2

Data for Analysis of AUCT CMAX LAUCT LCMAX	
Number of Observations Read	12
Number of Observations Used	12

Data for Analysis of AUCI LAUCI	
Number of Observations Read	12

Reference ID: 3227106

Data for Analysis of AUCI LAUCI	
Number of Observations Used	11

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	14.90281277	2.12897325	4.13	0.0943
Error	4	2.06097451	0.51524363		
Corrected Total	11	16.96378728			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.878507	14.90994	0.717805	4.814271

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.72665472	0.72665472	1.41	0.3007
sub(seq)	4	2.02734090	0.50683523	0.98	0.5062
per	1	0.30578113	0.30578113	0.59	0.4841
trt	1	11.84303602	11.84303602	22.99	0.0087

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.72665472	0.72665472	1.41	0.3007
sub(seq)	4	2.02734090	0.50683523	0.98	0.5062
per	1	0.30578113	0.30578113	0.59	0.4841
trt	1	11.84303602	11.84303602	22.99	0.0087

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.72665472	0.72665472	1.43	0.2973

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-1.98687661	0.41442475	-4.79	0.0087

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	10.52469218	1.50352745	1.66	0.3662
Error	3	2.71721707	0.90573902		
Corrected Total	10	13.24190924			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.794802	18.60350	0.951703	5.115720

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.09418352	0.09418352	0.10	0.7683
sub(seq)	4	2.00644634	0.50161159	0.55	0.7143
per	1	0.03810194	0.03810194	0.04	0.8506
trt	1	8.38596038	8.38596038	9.26	0.0557

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.46962245	0.46962245	0.52	0.5235
sub(seq)	4	1.65959173	0.41489793	0.46	0.7674
per	1	0.15047965	0.15047965	0.17	0.7109
trt	1	8.38596038	8.38596038	9.26	0.0557

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.46962245	0.46962245	1.13	0.3473

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-1.86926460	0.61432179	-3.04	0.0557

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	11.64531742	1.66361677	9.05	0.0251
Error	4	0.73566752	0.18391688		
Corrected Total	11	12.38098494			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.940581	14.43260	0.428855	2.971434

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.10718818	0.10718818	0.58	0.4878
sub(seq)	4	0.57772058	0.14443015	0.79	0.5898
per	1	0.26405161	0.26405161	1.44	0.2970
trt	1	10.69635705	10.69635705	58.16	0.0016

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.10718818	0.10718818	0.58	0.4878
sub(seq)	4	0.57772058	0.14443015	0.79	0.5898
per	1	0.26405161	0.26405161	1.44	0.2970
trt	1	10.69635705	10.69635705	58.16	0.0016

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.10718818	0.10718818	0.74	0.4376

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-1.88824054	0.24759973	-7.63	0.0016

4.8.3 Fed Study Data

FED CONCENTRATION DATASET (FREE EPA): BASELINE NON-ADJUSTED

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	c20
1	1	2	1	B	1	61.4	47.5	40.6	67.7	109.0	49.3	39.7	48.2	75.6	148.0	169.0	35.9	55.6	71.5	68.2	89.7	58.3	44.8	72.4	325.0
2	1	2	2	A	1	116.0	92.9	96.2	110.0	163.0	87.6	82.0	84.9	89.7	109.0	138.0	87.8	76.7	107.0	127.0	181.0	126.0	103.0	109.0	193.0
3	2	1	1	A	1	57.7	36.0	35.0	32.5	33.2	39.0	28.6	29.4	46.8	40.7	74.4	36.1	30.6	51.5	48.8	42.0	35.6	40.9	54.3	135.0
4	2	1	2	B	1	30.8	25.2	26.9	25.6	36.7	35.7	29.0	44.6	39.0	44.6	50.4	34.8	35.7	72.9	45.9	43.0	47.0	270.0	620.0	1140.0
5	3	2	1	B	1	44.8	24.6	24.3	28.1	41.5	30.2	28.1	27.5	48.9	87.9	60.9	26.1	37.2	58.1	52.8	57.0	29.6	38.4	83.6	264.0
6	3	2	2	A	1	48.8	29.8	31.7	39.9	60.5	42.0	35.1	37.4	42.7	74.0	91.5	32.1	28.8	37.3	50.8	66.2	40.8	58.6	167.0	205.0
7	4	1	1	A	1	73.9	55.2	43.5	41.7	52.2	52.0	42.0	47.5	55.0	65.9	91.0	52.2	47.8	44.7	50.5	94.6	50.4	46.2	56.4	173.0
8	4	1	2	B	1	65.1	54.7	54.1	45.0	55.0	76.8	66.0	72.4	63.1	75.3	106.0	59.4	42.4	45.3	67.6	100.0	86.2	78.5	61.5	73.2
9	5	2	1	B	1	71.8	54.1	53.5	46.2	47.1	52.8	52.2	45.5	58.9	71.5	75.0	48.4	41.6	57.4	51.5	87.9	67.9	55.7	69.5	168.0
10	5	2	2	A	1	56.1	56.4	47.5	46.5	56.5	58.2	47.7	41.8	48.2	46.8	52.1	56.5	51.4	47.6	65.4	69.9	78.5	82.1	79.1	159.0
11	6	1	1	A	1	23.8	19.0	13.2	23.6	38.2	20.8	16.8	19.1	28.4	37.8	52.4	17.3	21.7	31.3	27.6	31.0	58.6	139.0	368.0	945.0
12	6	1	2	B	1	31.7	21.8	18.3	25.2	42.0	31.5	22.9	28.1	38.7	49.7	59.3	27.5	29.9	31.0	34.4	59.6	30.7	89.5	306.0	1620.0
13	7	2	1	B	1	78.7	44.5	38.6	48.3	71.6	57.5	38.8	44.4	46.9	69.8	80.3	29.0	39.6	44.6	38.3	103.0	91.5	184.0	400.0	1000.0
14	7	2	2	A	1	111.0	81.8	68.9	57.2	115.0	68.5	71.3	49.6	63.1	88.6	97.2	50.1	45.8	80.0	53.7	130.0	120.0	299.0	776.0	1480.0
15	8	1	1	A	1	137.0	69.9	50.4	49.0	63.8	59.1	50.3	52.9	70.2	127.0	175.0	47.0	52.9	68.0	78.7	167.0	87.1	58.2	95.6	315.0
16	8	1	2	B	1	118.0	73.4	57.8	51.2	85.9	66.2	51.7	43.2	49.5	109.0	100.0	50.5	56.0	70.2	74.3	170.0	202.0	207.0	308.0	603.0
17	9	2	1	B	1	92.5	55.0	36.9	55.7	50.2	43.6	34.3	39.4	42.5	68.3	58.9	37.8	37.2	70.5	67.1	54.5	62.1	61.8	94.1	363.0
18	9	2	2	A	1	91.6	55.6	45.1	35.1	49.5	42.8	46.7	52.2	65.0	63.5	66.1	46.3	57.1	90.9	79.6	81.8	66.5	58.7	57.4	93.7
19	10	1	1	A	1	56.2	22.0	22.4	18.2	36.7	17.7	16.1	22.4	20.1	21.5	22.1	20.7	19.2	17.4	26.0	35.5	24.6	31.9	109.0	388.0
20	10	1	2	B	1	75.2	45.2	36.7	31.4	49.5	47.0	45.3	33.9	43.7	32.3	34.1	30.7	33.1	59.0	56.8	83.6	48.1	85.2	226.0	608.0
21	11	1	1	A	1	67.6	49.7	35.6	57.4	89.3	52.8	37.2	32.1	36.0	56.5	106.0	33.2	39.9	53.3	102.0	89.0	37.8	41.2	286.0	1090.0
22	11	1	2	B	1	66.9	39.6	42.6	42.9	77.6	58.3	40.6	39.9	39.1	40.5	42.5	41.1	43.2	58.6	80.5	122.0	53.4	61.1	189.0	725.0
23	12	2	1	B	1	68.4	31.7	23.4	34.5	54.6	27.6	23.3	27.5	31.8	34.0	69.8	31.0	41.3	32.1	54.0	90.3	30.8	27.0	30.5	60.9
24	12	2	2	A	1	59.2	42.2	45.2	41.6	58.2	39.9	52.4	50.1	53.6	76.2	131.0	36.5	48.5	46.1	91.1	128.0	54.7	40.6	62.2	65.2

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	c20
25	13	2	1	B	1	95.4	37.5	42.0	48.8	38.5	39.1	38.7	59.4	49.8	95.7	36.0	43.9	50.9	60.9	128.0	39.7	38.3	47.6	116.0	741.0
26	13	2	2	A	1	43.3	28.4	31.4	45.4	37.4	43.3	41.3	53.2	87.9	107.0	45.5	46.5	65.7	31.9	111.0	133.0	47.9	214.0	142.0	274.0
27	16	1	1	A	1	89.1	53.4	41.6	42.7	60.5	52.5	47.5	44.0	77.0	71.9	61.1	40.1	38.1	55.3	70.1	99.0	64.5	61.0	165.0	463.0
28	16	1	2	B	1	144.0	99.0	122.0	90.7	168.0	95.8	94.8	68.6	148.0	162.0	140.0	86.5	85.4	126.0	109.0	146.0	99.8	257.0	243.0	361.0
29	17	2	1	B	1	97.7	75.5	86.1	113.0	266.0	96.5	62.0	77.8	102.0	155.0	225.0	64.5	58.5	68.1	63.9	126.0	66.8	96.4	127.0	499.0
30	17	2	2	A	1	86.2	69.9	58.7	90.9	162.0	89.8	70.6	75.0	97.2	124.0	119.0	69.6	115.0	140.0	137.0	264.0	95.3	113.0	264.0	800.0
31	18	1	1	A	1	80.6	39.9	37.5	37.6	94.4	48.6	48.6	42.4	41.3	83.8	125.0	36.5	40.3	62.0	56.5	135.0	68.9	48.2	69.9	223.0
32	18	1	2	B	1	74.6	38.8	25.1	24.3	36.4	31.3	25.8	24.7	35.2	96.2	133.0	28.0	31.3	60.2	79.7	114.0	65.2	50.0	42.9	116.0
33	19	1	1	A	1	25.5	22.2	16.0	18.3	35.1	28.5	19.1	23.5	38.8	42.6	54.1	20.9	18.1	35.2	17.4	27.5	19.1	26.0	77.3	262.0
34	19	1	2	B	1	58.1	41.6	30.6	31.5	29.4	38.9	44.3	42.7	56.2	78.1	68.2	28.7	27.1	63.6	34.2	69.2	34.5	32.1	63.4	166.0
35	20	2	1	B	1	53.2	25.1	18.3	30.6	49.0	29.5	21.8	27.5	40.1	66.8	76.9	21.0	15.8	25.4	90.3	86.7	32.3	45.1	258.0	596.0
36	20	2	2	A	1	66.6	35.7	36.4	51.7	63.5	39.8	33.6	35.1	88.6	105.0	138.0	30.6	30.1	47.2	109.0	137.0	36.8	319.0	719.0	968.0
37	21	1	1	A	1	121.0	56.9	45.0	68.5	123.0	64.7	44.1	44.9	85.7	112.0	179.0	41.3	41.7	74.8	72.8	172.0	74.2	53.7	83.9	97.7
38	21	1	2	B	1	153.0	69.3	79.7	62.4	243.0	71.4	57.5	57.2	117.0	110.0	257.0	52.8	59.5	89.7	97.4	130.0	103.0	98.1	217.0	417.0
39	22	2	1	B	1	98.7	48.0	33.6	30.4	31.8	28.7	29.4	31.9	69.0	72.9	93.5	25.2	29.8	43.0	72.5	120.0	47.8	35.0	183.0	601.0
40	22	2	2	A	1	145.0	70.5	68.6	69.8	93.5	76.6	69.4	73.1	105.0	108.0	157.0	62.9	50.7	74.0	125.0	235.0	80.3	68.2	68.6	331.0
41	23	1	1	A	1	213.0	125.0	131.0	76.7	105.0	95.9	85.3	81.7	122.0	129.0	177.0	86.9	92.7	90.9	111.0	233.0	110.0	98.1	110.0	245.0
42	23	1	2	B	1	147.0	83.0	59.5	54.2	72.2	67.6	63.4	49.4	65.7	90.0	144.0	57.8	53.9	82.3	96.6	104.0	159.0	169.0	322.0	588.0
43	24	2	1	B	1	59.3	44.2	30.1	24.8	40.3	33.7	25.9	24.6	31.4	43.0	76.2	27.9	23.1	43.3	88.3	93.4	52.3	40.2	45.5	102.0
44	24	2	2	A	1	96.8	63.7	46.7	69.6	89.1	70.8	47.1	31.4	28.1	30.0	73.9	55.8	33.6	46.7	52.3	72.7	83.7	66.9	80.8	123.0
45	25	1	1	A	1	40.8	24.1	17.4	16.3	58.6	24.7	25.2	28.0	54.4	93.5	129.0	19.8	19.3	26.7	73.7	77.9	35.1	24.9	76.2	222.0
46	25	1	2	B	1	69.6	34.3	31.1	20.8	78.3	56.0	58.7	60.6	93.2	148.0	163.0	38.2	24.8	52.0	54.7	99.2	60.8	74.4	152.0	909.0
47	26	2	1	B	1	63.3	31.3	20.7	28.8	91.1	40.6	26.8	21.0	27.8	51.2	114.0	26.3	20.7	50.1	77.7	82.5	24.7	17.8	29.6	194.0
48	26	2	2	A	1	72.2	36.9	24.5	29.5	56.4	41.6	28.9	27.1	43.2	83.4	145.0	31.3	27.5	38.1	69.9	105.0	49.6	40.4	34.4	229.0
49	27	2	1	B	1	37.3	27.2	24.3	30.1	67.4	46.7	28.1	40.4	44.5	77.9	137.0	24.5	27.7	40.2	56.0	62.0	34.2	37.7	89.6	225.0
50	27	2	2	A	1	58.3	27.4	20.8	43.0	38.5	28.1	31.6	28.9	58.0	80.8	99.9	42.3	31.2	42.8	53.5	82.7	41.4	33.6	51.0	223.0

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	c20
51	28	1	1	A	1	51.4	27.9	23.1	21.3	64.4	25.6	19.2	24.4	22.3	45.8	73.9	14.9	18.0	33.7	70.3	75.0	29.5	24.8	33.0	86.6
52	28	1	2	B	1	53.5	34.3	24.2	19.3	39.2	19.7	19.1	20.3	30.9	41.8	70.6	21.0	20.5	30.7	49.5	85.6	53.3	44.9	39.3	56.4
53	29	2	1	B	1	49.2	37.0	21.1	25.9	41.9	28.5	35.6	27.8	30.4	43.0	41.5	23.8	24.6	24.9	55.7	76.4	30.5	31.8	44.3	144.0
54	29	2	2	A	1	52.6	27.9	23.4	24.2	39.2	28.9	22.3	33.9	44.2	83.4	142.0	19.7	30.2	23.0	51.7	101.0	28.2	24.6	62.8	132.0
55	30	2	1	B	1	91.5	33.4	30.9	61.9	113.0	45.2	30.2	31.5	29.6	41.6	90.2	33.1	39.6	37.3	107.0	129.0	53.3	40.5	299.0	1080.0
56	30	2	2	A	1	125.0	62.0	39.2	49.0	55.7	39.4	34.2	35.4	53.8	120.0	170.0	35.4	37.1	32.1	68.6	115.0	68.2	47.4	239.0	637.0
57	31	1	1	A	1	55.8	21.7	10.8	16.7	37.7	17.1	12.9	13.6	18.5	23.5	59.4	17.7	18.8	27.6	95.6	55.0	27.9	35.2	154.0	314.0
58	31	1	2	B	1	57.2	32.1	30.6	117.0	93.9	25.7	18.9	17.7	30.8	142.0	208.0	23.0	33.2	108.0	71.0	93.0	39.9	68.6	75.4	194.0
59	32	1	1	A	1	52.3	27.0	20.9	22.3	52.4	18.9	17.4	14.2	17.6	46.6	49.9	16.7	19.8	20.2	27.4	56.4	32.1	40.1	56.7	96.1
60	32	1	2	B	1	63.8	51.4	29.7	24.2	40.7	25.8	22.1	26.7	24.6	52.1	101.0	28.4	28.4	62.6	64.1	65.8	37.0	27.0	92.0	300.0
61	33	2	1	B	1	61.0	27.8	25.6	35.0	65.4	49.5	26.1	29.7	42.9	69.8	98.2	22.5	25.6	32.3	67.6	98.6	52.3	47.0	40.3	278.0
62	33	2	2	A	1	98.3	58.5	36.0	41.2	71.4	55.7	41.9	40.3	47.0	57.8	77.6	33.1	33.1	41.2	47.5	105.0	69.5	49.0	103.0	324.0
63	34	1	1	A	1	46.1	17.7	14.2	25.1	41.3	19.1	17.4	15.0	19.2	45.4	94.8	12.0	14.8	79.3	24.9	40.1	16.5	19.3	25.7	84.6
64	34	1	2	B	1	42.9	23.5	22.4	26.9	45.7	24.2	22.4	23.4	42.3	67.0	89.5	23.0	16.8	37.9	38.7	50.4	24.2	24.1	25.4	141.0
65	37	2	1	B	1	170.0	103.0	64.8	53.9	126.0	101.0	70.9	60.2	79.3	136.0	210.0	60.7	47.7	43.7	94.4	175.0	107.0	85.9	167.0	377.0
66	37	2	2	A	1	236.0	173.0	136.0	121.0	184.0	162.0	110.0	96.1	116.0	137.0	259.0	134.0	93.1	146.0	176.0	195.0	142.0	165.0	363.0	661.0
67	38	2	1	B	1	29.1	12.9	16.0	40.6	79.4	28.9	21.7	33.9	42.1	53.9	68.4	15.6	16.2	35.0	26.6	41.8	16.5	396.0	677.0	1050.0
68	38	2	2	A	1	71.6	40.3	34.2	39.3	59.3	32.5	24.9	30.9	45.2	81.0	118.0	25.0	43.0	69.5	60.8	52.5	29.3	319.0	440.0	1330.0
69	39	1	1	A	1	108.0	36.5	32.0	45.3	83.6	47.9	31.1	38.6	78.3	72.3	140.0	29.3	44.5	61.4	73.0	133.0	38.3	34.4	184.0	498.0
70	39	1	2	B	1	198.0	105.0	88.9	91.4	182.0	98.8	71.0	85.6	101.0	140.0	183.0	75.2	87.7	94.0	127.0	158.0	106.0	80.0	97.6	207.0
71	40	1	1	A	1	74.4	29.4	29.1	20.1	36.5	21.6	28.3	32.2	26.4	26.4	44.9	25.2	28.4	30.2	140.0	107.0	58.8	48.4	48.7	111.0
72	40	1	2	B	1	112.0	54.3	56.1	45.0	61.5	33.8	38.2	39.2	90.9	167.0	181.0	38.0	52.2	66.0	215.0	177.0	83.7	78.2	199.0	1840.0
73	41	2	1	B	1	43.2	15.8	15.1	24.3	45.3	40.4	26.8	14.9	28.9	57.8	89.5	22.6	15.2	86.4	31.0	89.1	26.8	59.1	172.0	338.0
74	41	2	2	A	1	40.7	32.2	28.1	38.3	74.2	44.8	20.3	19.0	27.7	55.9	80.7	26.1	23.5	48.9	67.1	104.0	40.0	82.4	136.0	441.0
75	42	2	1	B	1	29.9	12.9	10.1	21.6	50.1	21.3	16.2	16.5	26.9	38.4	72.2	14.0	17.2	16.8	42.7	31.0	40.1	29.6	157.0	391.0
76	42	2	2	A	1	52.9	25.0	22.5	17.7	34.8	22.4	27.7	33.2	44.2	84.8	98.0	26.5	20.8	33.9	28.8	85.4	42.2	121.0	165.0	605.0

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	c20
77	43	1	1	A	1	50.6	23.5	23.3	39.4	48.2	33.7	24.4	26.1	32.4	53.6	70.9	18.4	21.0	26.2	109.0	56.3	30.2	22.4	58.1	173.0
78	43	1	2	B	1	66.1	22.3	24.7	28.8	42.3	30.0	22.3	27.0	35.2	54.6	65.2	19.3	25.3	31.1	56.6	57.6	29.3	44.2	216.0	349.0
79	44	1	1	A	1	29.0	10.7	0.0	10.1	18.8	13.9	11.8	11.5	10.3	16.3	18.3	0.0	12.8	13.5	20.8	41.3	17.6	14.2	97.6	517.0
80	44	1	2	B	1	73.8	44.7	19.6	17.6	21.9	23.4	25.8	25.1	26.0	41.0	68.3	31.0	24.8	42.0	39.8	77.1	40.2	44.2	226.0	816.0
81	45	1	1	A	1	37.9	18.7	16.5	18.5	44.9	18.8	13.0	23.9	25.7	63.4	71.7	12.9	25.0	35.1	40.0	73.1	35.2	28.4	34.6	78.7
82	45	1	2	B	1	71.2	45.9	32.4	29.7	45.9	30.5	21.2	25.7	25.1	45.3	99.0	23.1	32.4	29.7	53.9	91.5	54.8	78.7	130.0	537.0
83	46	2	1	B	1	33.6	23.7	19.6	15.8	32.5	35.3	25.6	16.7	19.4	44.6	49.9	16.7	17.4	27.7	29.3	74.5	37.4	30.3	37.5	118.0
84	46	2	2	A	1	45.1	31.6	23.0	29.2	40.5	49.3	33.5	21.9	27.4	39.9	55.3	18.9	21.0	31.2	33.0	76.9	34.5	33.8	79.2	314.0
85	47	1	1	A	1	95.7	36.3	26.7	38.6	80.6	47.7	24.1	28.8	44.1	76.6	112.0	21.8	45.3	87.8	55.1	88.5	49.3	91.4	284.0	1030.0
86	47	1	2	B	1	76.8	48.6	30.3	50.0	106.0	48.5	32.7	33.8	66.5	137.0	272.0	31.6	29.9	87.9	54.2	127.0	56.7	335.0	736.0	1090.0
87	48	2	1	B	1	47.5	24.3	19.0	30.6	78.5	26.8	26.6	21.5	51.3	63.0	98.9	18.2	21.3	59.0	55.5	72.9	69.4	50.6	215.0	742.0
88	48	2	2	A	1	45.0	33.4	23.2	26.7	64.7	29.8	27.2	29.5	30.2	60.8	127.0	20.8	24.6	39.5	39.2	72.6	35.3	27.8	151.0	845.0
89	49	1	1	A	1	56.6	23.4	14.7	20.1	27.9	17.7	20.6	19.5	31.3	36.3	59.3	20.5	19.4	28.1	26.9	77.1	33.7	29.9	26.3	259.0
90	49	1	2	B	1	39.3	27.7	18.7	28.8	83.0	32.9	17.6	19.2	52.0	73.3	59.8	18.0	23.5	32.4	49.8	52.8	31.4	108.0	879.0	2510.0
91	50	1	1	A	1	76.6	35.7	18.7	20.9	53.1	18.9	22.3	23.9	52.6	81.1	155.0	14.8	17.4	29.0	49.0	98.7	45.3	32.9	30.9	54.6
92	50	1	2	B	1	98.4	60.3	39.4	32.6	90.1	54.1	26.5	37.9	57.5	94.7	94.2	24.5	25.4	56.7	34.4	92.2	82.7	52.6	43.4	46.6
93	51	2	1	B	1	53.4	22.2	13.4	16.6	17.8	13.5	15.4	19.4	24.2	22.6	40.2	14.6	13.5	13.3	41.9	48.2	21.1	21.5	32.4	104.0
94	51	2	2	A	1	67.3	31.9	20.8	19.1	21.9	21.8	21.0	21.7	20.1	24.6	73.1	23.6	31.8	26.0	33.5	41.6	39.4	39.0	302.0	780.0
95	52	2	1	B	1	41.1	25.9	16.3	16.1	19.9	16.1	18.0	22.7	31.6	38.8	54.3	19.6	20.3	36.9	70.5	48.0	27.1	18.2	21.8	98.5
96	52	2	2	A	1	54.1	23.5	17.4	21.9	31.8	34.0	21.9	21.0	28.6	42.3	46.8	31.5	27.6	29.4	40.2	59.9	35.9	34.3	103.0	234.0
97	53	2	1	B	1	39.9	21.3	15.1	19.1	25.9	18.4	13.8	16.4	18.8	27.9	47.5	13.5	16.1	40.0	25.4	92.9	31.1	19.1	23.9	95.5
98	53	2	2	A	1	44.3	50.6	37.9	28.1	30.0	45.2	30.6	32.7	31.6	43.2	73.4	42.0	28.5	45.1	73.1	78.9	59.4	57.2	91.2	452.0
99	54	1	1	A	1	42.0	14.1	0.0	0.0	0.0	13.3	0.0	10.5	12.3	24.7	37.6	19.2	12.8	20.2	26.4	35.0	26.8	24.6	23.4	67.9
100	54	1	2	B	1	89.1	14.5	13.8	13.9	18.5	22.4	16.9	15.9	18.3	22.3	41.7	16.6	15.6	27.2	26.1	63.9	28.8	24.3	21.5	39.0
101	55	2	1	B	1	69.3	24.3	27.9	13.3	22.0	24.8	16.5	19.2	30.6	32.4	41.0	11.4	14.2	19.1	19.4	81.6	63.5	72.4	110.0	177.0
102	55	2	2	A	1	70.4	29.3	28.9	29.5	41.0	43.4	37.4	33.6	41.6	65.1	60.7	35.6	27.9	41.2	39.8	72.5	114.0	168.0	220.0	309.0

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	c20
103	56	1	1	A	1	42.8	24.4	16.9	18.6	35.4	31.3	24.2	24.3	27.4	61.2	96.6	20.9	18.3	27.8	57.6	43.1	28.5	21.4	26.8	61.4
104	56	1	2	B	1	44.1	19.3	16.0	24.6	34.3	44.3	25.9	19.9	29.1	53.1	110.0	28.7	16.9	28.9	39.1	35.3	23.3	37.9	39.9	45.4
105	57	1	1	A	1	72.7	32.8	40.7	57.8	89.8	24.1	26.7	31.6	42.7	66.0	125.0	29.5	31.4	51.3	61.1	103.0	52.5	51.5	117.0	256.0
106	57	1	2	B	1	73.8	47.4	77.5	53.4	138.0	48.9	38.4	44.5	73.2	136.0	209.0	28.0	50.5	131.0	97.7	188.0	41.4	58.2	113.0	414.0
107	58	1	1	A	1	330.0	157.0	108.0	89.6	157.0	102.0	78.0	130.0	161.0	237.0	197.0	57.5	73.8	91.2	118.0	273.0	129.0	113.0	130.0	621.0
108	58	1	2	B	1	237.0	102.0	77.7	77.8	87.9	75.0	74.6	77.5	93.9	151.0	183.0	59.9	48.9	80.3	158.0	238.0	112.0	141.0	214.0	848.0
109	59	2	1	B	1	41.6	20.6	26.7	53.8	84.4	20.6	16.1	22.7	49.2	40.2	54.5	15.0	21.3	40.6	22.5	75.5	23.0	29.8	86.2	309.0
110	59	2	2	A	1	64.7	43.6	25.7	34.4	62.6	26.8	22.4	22.3	27.0	22.9	48.1	20.8	33.6	54.6	81.1	75.9	92.6	239.0	471.0	804.0
111	60	2	1	B	1	116.0	48.9	40.3	40.2	52.4	59.5	43.6	47.1	63.2	83.9	187.0	35.9	27.8	51.7	73.3	142.0	62.6	67.3	53.7	97.4
112	60	2	2	A	1	100.0	87.3	52.2	49.1	67.2	90.2	69.6	47.7	55.4	88.3	112.0	57.3	49.5	55.2	159.0	146.0	97.0	96.4	72.0	142.0
113	61	1	1	A	1	70.3	29.2	19.4	22.7	39.0	44.6	20.8	21.1	26.1	33.0	57.4	22.4	20.6	29.6	65.4	86.1	33.9	28.4	36.0	55.0
114	61	1	2	B	1	105.0	37.8	18.9	17.3	27.4	34.8	29.5	23.8	34.7	25.5	64.5	18.4	21.0	48.0	124.0	81.5	49.3	51.0	33.2	66.6
115	62	2	1	B	1	36.2	21.2	16.9	16.9	48.8	25.5	18.6	23.9	22.6	36.4	64.8	20.8	19.6	24.9	43.1	42.0	23.5	61.0	128.0	367.0
116	62	2	2	A	1	40.6	26.0	17.5	19.0	38.1	44.9	27.0	23.5	26.1	54.5	61.0	23.0	20.9	33.9	53.7	35.7	22.1	67.4	230.0	335.0
117	63	2	1	B	1	62.6	22.2	14.3	20.5	44.7	17.4	18.5	16.2	21.3	21.7	55.3	15.6	16.4	39.1	92.8	109.0	22.8	24.6	28.8	54.1
118	63	2	2	A	1	75.6	20.5	12.2	11.4	23.9	13.5	12.0	17.2	25.6	53.9	110.0	12.4	14.0	13.0	62.0	76.9	25.1	26.6	46.7	37.1
119	64	1	1	A	1	127.0	78.0	57.0	51.9	69.8	71.9	58.9	47.5	82.4	68.1	139.0	41.2	43.1	72.1	82.6	176.0	99.4	98.7	328.0	965.0
120	64	1	2	B	1	129.0	75.3	58.9	53.9	48.7	92.4	74.2	56.7	53.6	62.8	103.0	44.4	45.0	59.6	71.9	81.8	92.4	98.8	297.0	496.0
121	65	1	1	A	1	57.2	27.4	21.3	22.2	35.9	36.6	23.9	18.7	22.1	20.6	41.8	22.9	19.0	34.4	43.8	52.2	35.4	22.1	23.5	28.2
122	65	1	2	B	1	77.9	34.4	27.6	30.9	41.5	58.1	29.8	27.2	57.0	117.0	192.0	39.4	28.0	44.4	62.2	84.3	46.8	34.3	53.2	79.9
123	66	2	1	B	1	58.5	32.1	23.5	30.5	79.3	41.4	28.3	30.2	31.9	48.8	99.6	24.8	20.1	31.8	69.5	99.6	53.0	39.9	72.3	160.0
124	66	2	2	A	1	107.0	52.5	39.8	50.8	60.6	44.9	34.2	29.7	42.3	112.0	115.0	67.9	30.3	71.8	81.0	157.0	77.0	73.1	126.0	556.0
125	67	2	1	B	1	61.2	21.3	16.1	19.1	25.6	21.7	15.9	17.7	18.5	31.5	53.9	18.5	16.2	18.3	52.6	60.7	37.1	28.1	38.0	99.9
126	67	2	2	A	1	72.9	24.1	19.1	23.9	27.2	27.0	18.3	19.7	24.2	30.6	78.0	19.9	17.6	28.0	28.7	64.1	38.7	37.1	43.8	34.0
127	68	1	1	A	1	97.3	44.7	24.2	23.9	44.2	34.2	26.8	24.2	44.2	64.0	103.0	37.1	20.3	58.1	48.1	65.5	35.5	28.0	40.1	151.0
128	68	1	2	B	1	72.0	29.8	26.0	27.2	28.0	29.0	26.1	27.6	33.9	65.0	84.8	38.7	22.0	63.6	41.6	55.7	44.4	35.5	55.4	116.0

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	c20
129	69	2	1	B	1	67.6	40.5	27.9	35.4	62.8	38.2	28.4	29.5	42.4	59.0	74.5	28.4	29.0	45.3	116.0	109.0	50.4	35.3	61.3	192.0
130	69	2	2	A	1	56.8	29.7	18.5	24.8	69.8	39.4	25.9	24.4	59.3	78.7	114.0	25.4	23.4	30.8	49.8	63.9	35.8	40.6	38.3	70.4
131	70	2	1	B	1	40.3	21.6	15.7	27.3	43.9	33.9	23.4	23.8	21.1	22.5	37.8	18.6	20.7	28.4	30.6	60.1	33.8	31.7	40.4	206.0
132	70	2	2	A	1	46.2	29.9	22.6	26.9	29.7	29.6	20.2	31.7	32.7	35.0	41.0	25.5	24.6	27.6	36.6	63.3	58.0	204.0	304.0	235.0
133	71	1	1	A	1	127.0	58.0	32.3	35.8	47.5	46.3	40.2	27.4	38.3	49.8	73.0	24.9	23.7	37.9	61.7	128.0	52.7	34.9	79.6	286.0
134	71	1	2	B	1	47.1	34.0	19.1	25.3	42.7	26.2	20.6	19.8	21.1	39.0	42.8	24.6	21.5	35.8	52.2	87.9	43.9	27.5	70.0	217.0
135	72	1	1	A	1	72.2	25.5	20.6	27.3	53.0	61.0	35.0	30.8	40.5	59.7	78.2	20.9	28.8	94.5	115.0	63.8	29.7	37.5	167.0	769.0
136	72	1	2	B	1	60.8	31.1	25.0	30.4	112.0	70.4	30.9	28.0	52.3	94.3	96.1	27.4	30.6	71.0	92.9	85.4	49.0	31.7	181.0	617.0
137	73	1	1	A	1	60.5	28.1	18.9	15.8	43.2	22.7	19.7	19.8	25.1	79.2	138.0	22.9	12.6	20.1	36.6	65.1	24.9	23.1	22.4	55.2
138	73	1	2	B	1	70.7	35.1	21.7	21.9	42.8	29.4	26.8	20.6	23.3	27.7	55.2	40.3	17.0	30.1	39.1	93.1	67.0	81.0	397.0	351.0
139	74	2	1	B	1	67.6	30.9	25.5	57.9	51.9	36.1	25.0	55.1	36.7	49.0	62.6	21.2	23.8	41.1	40.8	74.1	31.1	41.6	152.0	324.0
140	74	2	2	A	1	119.0	69.0	53.8	74.9	95.7	105.0	62.6	54.2	90.9	103.0	166.0	60.5	54.3	75.3	116.0	154.0	63.5	117.0	413.0	575.0
141	75	1	1	A	1	50.6	29.6	18.3	22.3	38.5	25.0	21.7	19.7	26.9	35.1	53.5	21.0	23.4	32.2	31.9	58.3	41.9	39.0	107.0	494.0
142	75	1	2	B	1	76.6	50.5	39.5	35.2	52.3	45.0	40.4	32.2	40.7	65.4	61.8	24.7	25.3	43.5	65.4	78.2	41.6	104.0	569.0	1060.0
143	77	1	1	A	1	44.7	22.7	21.6	24.4	28.1	28.3	26.3	23.8	31.3	28.0	33.0	21.8	27.0	29.8	36.3	51.9	41.2	30.6	41.6	151.0
144	77	1	2	B	1	66.1	25.6	22.8	28.0	37.5	27.8	27.0	35.2	27.3	25.6	33.3	26.7	36.4	45.0	53.6	59.1	26.6	33.0	31.2	226.0
145	78	2	1	B	1	57.1	30.8	21.0	29.6	61.3	34.0	26.7	30.1	40.6	51.4	64.0	19.9	22.4	35.8	26.4	100.0	26.4	29.1	39.7	132.0
146	78	2	2	A	1	66.6	27.3	21.6	29.7	51.3	28.1	29.9	28.0	33.8	71.7	62.7	24.8	33.9	38.0	49.1	90.3	32.0	33.7	42.2	94.2
147	79	1	1	A	1	49.6	22.7	22.5	33.0	33.4	24.9	20.7	24.3	33.9	63.7	84.5	17.2	22.6	48.7	28.4	51.1	19.5	24.0	54.5	111.0
148	79	1	2	B	1	51.7	27.1	25.9	23.8	30.2	25.0	27.9	30.0	41.1	58.4	96.4	28.7	21.4	31.3	49.3	58.3	29.8	30.2	43.5	81.7
149	80	2	1	B	1	26.8	13.8	10.5	14.9	21.4	14.9	11.2	18.7	21.0	47.5	64.0	10.4	12.8	15.1	24.8	36.4	16.9	13.4	27.6	115.0
150	80	2	2	A	1	40.4	19.4	14.2	18.5	35.0	23.3	15.1	12.2	12.2	22.1	45.3	10.8	16.1	25.0	65.7	36.9	15.7	20.7	57.9	243.0
151	81	1	1	A	1	40.1	18.0	11.8	15.7	23.8	21.5	22.5	18.1	19.8	25.9	30.2	14.5	17.2	14.8	20.6	45.5	31.7	28.0	30.6	108.0
152	81	1	2	B	1	58.0	27.8	25.6	26.8	27.6	23.6	21.8	24.9	33.8	39.9	42.9	19.6	21.4	33.1	54.6	43.5	39.7	36.1	37.3	95.9
153	82	2	1	B	1	71.1	42.7	37.1	53.3	84.4	49.5	31.8	31.1	38.0	83.4	111.0	33.0	29.2	69.2	125.0	73.2	73.4	257.0	278.0	729.0
154	82	2	2	A	1	57.5	39.3	50.8	39.8	58.3	58.8	32.0	25.7	31.3	39.2	54.0	29.2	21.0	40.2	66.0	58.3	51.3	50.5	50.1	151.0

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	c20
155	83	2	1	B	1	61.9	35.7	22.6	35.8	51.9	39.8	28.9	34.2	47.7	80.1	79.4	28.1	24.9	53.0	81.3	54.0	31.6	28.5	40.5	87.6
156	83	2	2	A	1	27.7	40.5	27.4	26.1	33.0	35.6	23.5	26.7	38.5	56.0	89.6	24.4	26.7	49.5	78.8	49.2	45.8	76.5	224.0	490.0
157	84	1	1	A	1	33.1	19.3	16.4	26.5	30.8	28.4	19.2	15.0	28.5	32.8	44.3	16.9	20.1	31.0	36.6	30.6	27.6	22.5	21.4	128.0
158	84	1	2	B	1	47.6	35.5	20.1	31.6	34.0	36.6	19.2	17.1	20.6	50.8	51.3	26.2	20.3	39.1	65.7	49.2	43.8	77.9	329.0	406.0
159	86	1	1	A	1	65.3	40.0	23.2	23.2	24.5	41.2	35.8	26.9	28.5	33.6	55.6	22.7	27.3	38.1	81.1	84.4	57.7	70.2	93.9	220.0
160	86	1	2	B	1	83.0	45.5	33.7	31.3	34.9	50.5	34.4	28.3	39.1	56.7	87.4	31.3	32.0	66.1	38.1	62.3	57.4	50.2	108.0	192.0

Obs	c21	c22	c23	c24	c25	c26	c27	c28	c29	c30	c31	c32	c33	c34	KE_FIRST	KE_LAST	trt
1	1410.0	810.0	702.0	590.0	490.0	520	143.0	143.0	130.0	142.0	178.0	170.0	89.9	68.6	30	33	2
2	519.0	713.0	763.0	414.0	266.0	396	180.0	154.0	125.0	167.0	180.0	235.0	87.3	109.0	30	33	1
3	460.0	655.0	547.0	400.0	395.0	440	200.0	158.0	186.0	86.4	124.0	124.0	59.7	54.5	30	33	1
4	914.0	557.0	421.0	223.0	213.0	276	160.0	149.0	131.0	110.0	154.0	138.0	100.0	65.8	30	33	2
5	418.0	604.0	505.0	560.0	787.0	733	234.0	115.0	99.1	113.0	116.0	86.0	81.9	55.2	30	33	2
6	307.0	446.0	434.0	515.0	502.0	350	218.0	136.0	120.0	140.0	181.0	116.0	70.3	98.8	30	33	1
7	639.0	1040.0	981.0	669.0	642.0	732	315.0	188.0	162.0	218.0	204.0	156.0	119.0	101.0	30	33	1
8	83.7	225.0	452.0	525.0	607.0	682	670.0	408.0	268.0	292.0	322.0	265.0	129.0	161.0	30	33	2
9	615.0	1160.0	1110.0	816.0	574.0	480	271.0	161.0	134.0	137.0	164.0	125.0	103.0	93.4	30	33	2
10	373.0	876.0	876.0	760.0	720.0	689	379.0	222.0	170.0	171.0	225.0	197.0	134.0	131.0	30	33	1
11	842.0	612.0	353.0	254.0	261.0	267	148.0	97.6	111.0	108.0	90.2	88.5	45.3	53.3	30	33	1
12	1180.0	957.0	351.0	209.0	200.0	247	200.0	149.0	121.0	107.0	101.0	77.3	72.1	86.5	30	33	2
13	1500.0	1430.0	1000.0	506.0	407.0	620	183.0	161.0	156.0	208.0	191.0	256.0	103.0	95.8	30	33	2
14	1380.0	860.0	914.0	467.0	463.0	467	285.0	187.0	169.0	227.0	248.0	272.0	125.0	153.0	30	33	1
15	1420.0	1110.0	529.0	331.0	310.0	492	210.0	169.0	183.0	158.0	207.0	129.0	90.2	111.0	30	33	1
16	864.0	813.0	370.0	277.0	275.0	564	263.0	150.0	149.0	148.0	165.0	132.0	92.2	125.0	30	33	2
17	867.0	659.0	551.0	376.0	350.0	438	139.0	118.0	196.0	124.0	201.0	123.0	60.8	92.2	30	33	2
18	497.0	556.0	576.0	326.0	320.0	283	194.0	143.0	110.0	131.0	184.0	123.0	73.3	109.0	30	33	1

Obs	c21	c22	c23	c24	c25	c26	c27	c28	c29	c30	c31	c32	c33	c34	KE_FIRST	KE_LAST	trt
19	538.0	655.0	593.0	593.0	555.0	401	222.0	177.0	167.0	125.0	163.0	122.0	66.5	72.5	30	33	1
20	608.0	943.0	799.0	529.0	383.0	347	256.0	194.0	158.0	156.0	229.0	123.0	89.7	105.0	30	33	2
21	1440.0	753.0	452.0	345.0	500.0	468	163.0	149.0	156.0	188.0	153.0	90.6	89.4	86.2	30	33	1
22	1650.0	778.0	509.0	438.0	198.0	226	155.0	141.0	201.0	175.0	176.0	125.0	88.0	113.0	30	33	2
23	229.0	277.0	457.0	292.0	469.0	689	543.0	188.0	220.0	201.0	196.0	160.0	93.8	96.5	30	33	2
24	54.9	267.0	569.0	633.0	940.0	863	462.0	222.0	191.0	228.0	198.0	204.0	107.0	105.0	30	33	1
25	995.0	698.0	321.0	305.0	283.0	163	130.0	118.0	136.0	103.0	79.8	55.3	48.1	51.9	30	33	2
26	235.0	137.0	148.0	99.0	229.0	686	1130.0	305.0	183.0	133.0	150.0	106.0	95.4	75.8	30	33	1
27	1560.0	1020.0	647.0	479.0	532.0	668	292.0	166.0	188.0	141.0	194.0	128.0	65.2	94.8	30	33	1
28	1170.0	1110.0	1020.0	439.0	748.0	669	416.0	210.0	230.0	250.0	322.0	168.0	129.0	112.0	30	33	2
29	593.0	542.0	714.0	821.0	774.0	874	244.0	165.0	156.0	211.0	187.0	283.0	94.3	102.0	30	33	2
30	1110.0	1030.0	650.0	410.0	335.0	374	211.0	172.0	185.0	254.0	213.0	304.0	111.0	119.0	30	33	1
31	714.0	757.0	315.0	437.0	629.0	1690	186.0	132.0	117.0	155.0	164.0	144.0	61.8	69.0	30	33	1
32	654.0	773.0	498.0	359.0	357.0	698	161.0	88.7	96.4	100.0	143.0	141.0	60.8	59.2	30	33	2
33	810.0	1050.0	989.0	687.0	403.0	203	123.0	97.4	84.2	64.9	69.2	55.2	48.8	51.0	30	33	1
34	845.0	1170.0	1140.0	663.0	656.0	762	209.0	114.0	126.0	93.1	105.0	76.2	64.5	60.7	30	33	2
35	661.0	731.0	551.0	463.0	356.0	476	140.0	93.2	103.0	202.0	111.0	142.0	60.2	55.9	30	33	2
36	969.0	800.0	553.0	409.0	362.0	577	205.0	127.0	104.0	190.0	159.0	125.0	67.9	85.1	30	33	1
37	173.0	277.0	185.0	238.0	367.0	902	666.0	235.0	151.0	158.0	222.0	109.0	84.3	104.0	30	33	1
38	1150.0	825.0	893.0	393.0	283.0	312	167.0	150.0	133.0	120.0	161.0	150.0	63.0	88.5	30	33	2
39	1200.0	995.0	438.0	371.0	320.0	311	174.0	123.0	101.0	110.0	120.0	71.5	59.4	59.3	30	33	2
40	1100.0	1220.0	797.0	439.0	267.0	402	230.0	167.0	145.0	157.0	186.0	133.0	67.2	65.3	30	33	1
41	431.0	515.0	563.0	802.0	1410.0	889	458.0	265.0	220.0	164.0	242.0	130.0	100.0	112.0	30	33	1
42	533.0	510.0	377.0	371.0	310.0	388	344.0	229.0	181.0	163.0	252.0	110.0	111.0	107.0	30	33	2
43	373.0	1060.0	1010.0	457.0	414.0	484	213.0	89.0	75.5	147.0	204.0	61.7	55.0	70.5	30	33	2
44	251.0	545.0	418.0	201.0	217.0	399	361.0	100.0	104.0	169.0	235.0	108.0	97.4	51.2	30	33	1

Obs	c21	c22	c23	c24	c25	c26	c27	c28	c29	c30	c31	c32	c33	c34	KE_FIRST	KE_LAST	trt
45	586.0	452.0	162.0	250.0	517.0	920	183.0	69.2	89.2	113.0	90.4	104.0	44.5	38.1	30	33	1
46	725.0	496.0	192.0	107.0	149.0	150	128.0	74.2	87.4	213.0	82.5	69.8	60.6	49.2	30	33	2
47	473.0	527.0	385.0	397.0	458.0	475	145.0	87.2	98.7	89.6	73.5	76.4	46.2	51.9	30	33	2
48	447.0	342.0	444.0	387.0	297.0	341	186.0	120.0	102.0	185.0	109.0	75.2	53.7	64.8	30	33	1
49	375.0	288.0	236.0	357.0	903.0	1040	253.0	124.0	133.0	105.0	132.0	143.0	57.4	57.8	30	33	2
50	456.0	567.0	513.0	285.0	337.0	599	298.0	150.0	137.0	162.0	87.7	94.3	64.8	69.7	30	33	1
51	67.0	55.7	70.4	56.0	91.8	155	137.0	93.9	72.6	108.0	70.2	41.1	36.0	36.3	30	33	1
52	39.1	86.9	212.0	375.0	447.0	380	190.0	117.0	110.0	285.0	122.0	85.9	65.3	63.3	30	33	2
53	400.0	477.0	652.0	427.0	431.0	443	149.0	101.0	82.3	90.3	101.0	126.0	57.3	47.4	30	33	2
54	540.0	658.0	660.0	423.0	281.0	251	102.0	73.6	65.7	80.9	91.2	75.0	50.3	49.0	30	33	1
55	1240.0	1010.0	556.0	347.0	320.0	339	210.0	121.0	114.0	134.0	164.0	120.0	68.6	69.2	30	33	2
56	1180.0	1270.0	680.0	397.0	263.0	291	184.0	127.0	117.0	172.0	216.0	140.0	90.5	83.8	30	33	1
57	422.0	195.0	152.0	257.0	609.0	1570	263.0	121.0	262.0	126.0	92.7	67.2	38.2	42.9	30	33	1
58	1110.0	998.0	295.0	318.0	624.0	988	256.0	83.3	164.0	125.0	187.0	333.0	52.2	52.2	30	33	2
59	93.7	67.1	36.6	80.0	359.0	1080	426.0	169.0	191.0	128.0	237.0	82.6	65.2	67.0	30	33	1
60	537.0	428.0	142.0	122.0	220.0	946	725.0	253.0	171.0	188.0	263.0	171.0	97.5	79.2	30	33	2
61	779.0	1250.0	746.0	447.0	418.0	294	107.0	103.0	95.3	78.8	126.0	106.0	42.9	56.2	30	33	2
62	891.0	798.0	680.0	465.0	449.0	493	172.0	128.0	101.0	128.0	143.0	157.0	82.1	57.9	30	33	1
63	223.0	259.0	323.0	416.0	538.0	348	84.8	77.3	96.3	90.3	76.6	56.2	35.4	36.4	30	33	1
64	300.0	405.0	213.0	175.0	209.0	476	121.0	71.2	72.5	117.0	69.9	51.1	54.7	38.0	30	33	2
65	560.0	479.0	404.0	274.0	511.0	771	364.0	321.0	212.0	295.0	260.0	161.0	154.0	97.2	30	33	2
66	759.0	877.0	650.0	372.0	424.0	652	498.0	332.0	374.0	401.0	283.0	189.0	141.0	148.0	30	33	1
67	669.0	499.0	476.0	571.0	499.0	453	131.0	101.0	127.0	85.9	84.2	155.0	47.3	39.2	30	33	2
68	604.0	592.0	543.0	351.0	398.0	356	112.0	90.2	99.5	144.0	129.0	87.9	65.4	54.5	30	33	1
69	949.0	729.0	561.0	396.0	728.0	583	313.0	113.0	163.0	217.0	140.0	131.0	81.0	76.1	30	33	1
70	465.0	638.0	604.0	831.0	1010.0	719	433.0	224.0	131.0	371.0	211.0	139.0	145.0	104.0	30	33	2

Obs	c21	c22	c23	c24	c25	c26	c27	c28	c29	c30	c31	c32	c33	c34	KE_FIRST	KE_LAST	trt
71	742.0	402.0	215.0	373.0	953.0	1090	451.0	173.0	124.0	197.0	167.0	125.0	82.9	86.1	30	33	1
72	1130.0	662.0	253.0	388.0	762.0	1570	528.0	261.0	148.0	329.0	219.0	132.0	73.4	118.0	30	33	2
73	1380.0	851.0	225.0	245.0	219.0	286	136.0	71.4	74.0	91.5	59.8	72.7	33.0	49.9	30	33	2
74	1100.0	832.0	283.0	180.0	460.0	249	134.0	65.3	69.4	164.0	88.9	82.7	48.2	59.6	30	33	1
75	1120.0	1060.0	576.0	291.0	518.0	363	119.0	63.9	64.5	77.2	160.0	92.4	40.0	50.9	30	33	2
76	609.0	713.0	400.0	507.0	416.0	279	121.0	101.0	84.6	201.0	93.9	88.4	62.0	70.3	30	33	1
77	436.0	588.0	469.0	624.0	688.0	688	257.0	121.0	108.0	114.0	104.0	102.0	49.6	57.3	30	33	1
78	770.0	1010.0	601.0	316.0	231.0	271	195.0	142.0	104.0	235.0	111.0	66.0	54.5	42.7	30	33	2
79	641.0	435.0	245.0	307.0	248.0	287	147.0	78.8	64.0	115.0	91.5	69.0	38.7	57.3	30	33	1
80	727.0	454.0	215.0	146.0	246.0	277	180.0	102.0	96.6	115.0	113.0	86.5	53.8	51.8	30	33	2
81	206.0	276.0	394.0	1170.0	1750.0	1660	245.0	107.0	65.2	121.0	138.0	44.4	42.9	57.8	30	33	1
82	1360.0	666.0	357.0	408.0	568.0	638	222.0	123.0	78.2	169.0	165.0	69.9	47.1	67.8	30	33	2
83	1310.0	798.0	392.0	209.0	346.0	299	79.4	51.0	66.9	53.5	88.5	82.4	43.6	56.8	30	33	2
84	1280.0	517.0	326.0	191.0	261.0	434	106.0	76.5	101.0	68.3	144.0	110.0	63.3	41.0	30	33	1
85	1690.0	1080.0	607.0	364.0	389.0	442	123.0	82.9	81.0	52.6	103.0	131.0	33.8	45.9	30	33	1
86	1270.0	688.0	516.0	234.0	294.0	393	111.0	132.0	135.0	163.0	184.0	98.2	47.9	78.9	30	33	2
87	939.0	789.0	395.0	285.0	465.0	439	100.0	96.9	99.9	74.1	100.0	76.7	54.1	58.6	30	33	2
88	1220.0	619.0	292.0	182.0	259.0	399	123.0	97.2	88.7	102.0	96.8	85.4	40.7	63.8	30	33	1
89	692.0	874.0	398.0	307.0	458.0	546	122.0	68.8	59.5	94.5	110.0	77.8	37.4	39.0	30	33	1
90	1530.0	595.0	316.0	269.0	225.0	234	88.3	72.6	93.5	86.0	97.0	63.1	34.9	47.4	30	33	2
91	39.3	33.7	36.0	37.9	92.0	278	188.0	175.0	121.0	110.0	144.0	83.3	68.7	46.8	30	33	1
92	150.0	87.2	80.4	143.0	592.0	727	282.0	147.0	138.0	83.0	165.0	88.6	50.5	57.8	30	33	2
93	311.0	390.0	250.0	454.0	625.0	1010	304.0	128.0	90.5	72.6	87.8	85.6	41.4	57.3	30	33	2
94	1170.0	826.0	416.0	268.0	279.0	301	146.0	102.0	94.0	95.1	137.0	74.8	62.6	84.0	30	33	1
95	267.0	260.0	489.0	568.0	642.0	866	221.0	122.0	103.0	146.0	118.0	86.2	58.3	72.0	30	33	2
96	284.0	379.0	250.0	417.0	907.0	532	195.0	159.0	155.0	168.0	129.0	118.0	101.0	95.8	30	33	1

Reference ID: 3227106

Obs	c21	c22	c23	c24	c25	c26	c27	c28	c29	c30	c31	c32	c33	c34	KE_FIRST	KE_LAST	trt
97	572.0	795.0	738.0	564.0	527.0	352	224.0	154.0	111.0	76.7	140.0	104.0	66.4	66.2	30	33	2
98	1090.0	822.0	986.0	577.0	369.0	276	194.0	143.0	123.0	118.0	137.0	93.7	88.9	90.2	30	33	1
99	240.0	807.0	1250.0	1100.0	996.0	489	360.0	229.0	119.0	69.1	208.0	81.9	71.9	65.8	30	33	1
100	101.0	95.3	140.0	309.0	737.0	637	676.0	262.0	181.0	109.0	143.0	80.9	76.6	66.0	30	33	2
101	337.0	485.0	267.0	243.0	137.0	125	90.8	69.7	61.0	65.9	106.0	88.5	37.8	48.1	30	33	2
102	226.0	144.0	112.0	79.5	74.0	104	67.5	34.1	42.0	65.7	78.8	38.4	29.8	39.4	30	33	1
103	189.0	263.0	279.0	258.0	279.0	231	169.0	74.0	81.2	113.0	93.2	60.2	53.2	47.5	30	33	1
104	208.0	174.0	164.0	218.0	361.0	361	224.0	101.0	56.8	94.0	108.0	65.5	54.7	59.2	30	33	2
105	496.0	561.0	253.0	236.0	377.0	365	78.2	104.0	96.1	180.0	102.0	150.0	41.8	41.4	30	33	1
106	685.0	369.0	513.0	795.0	404.0	491	132.0	83.0	136.0	127.0	109.0	71.9	51.6	61.4	30	33	2
107	666.0	636.0	505.0	571.0	1130.0	1130	265.0	302.0	136.0	232.0	266.0	135.0	83.9	102.0	30	33	1
108	1150.0	565.0	283.0	487.0	719.0	566	235.0	137.0	164.0	170.0	209.0	126.0	96.3	93.7	30	33	2
109	936.0	1100.0	652.0	453.0	245.0	358	96.4	70.3	74.0	74.7	98.1	67.8	44.4	47.0	30	33	2
110	587.0	486.0	289.0	338.0	217.0	239	99.4	72.7	72.9	143.0	92.6	65.7	62.0	50.5	30	33	1
111	304.0	786.0	611.0	521.0	1120.0	1200	436.0	191.0	137.0	250.0	233.0	91.1	71.1	91.8	30	33	2
112	303.0	775.0	390.0	256.0	298.0	484	606.0	140.0	133.0	350.0	228.0	90.7	109.0	174.0	30	33	1
113	656.0	426.0	680.0	897.0	1700.0	933	312.0	120.0	122.0	174.0	264.0	74.4	54.2	52.9	30	33	1
114	678.0	867.0	810.0	680.0	268.0	206	116.0	85.5	77.2	160.0	212.0	52.9	46.6	68.5	30	33	2
115	547.0	582.0	514.0	415.0	570.0	375	360.0	159.0	143.0	120.0	86.9	148.0	64.9	54.4	30	33	2
116	577.0	680.0	588.0	558.0	737.0	676	367.0	211.0	182.0	171.0	122.0	81.0	73.7	68.7	30	33	1
117	290.0	227.0	133.0	275.0	366.0	1280	222.0	83.5	67.6	113.0	147.0	159.0	37.4	38.7	30	33	2
118	25.5	23.1	18.5	24.6	65.8	246	334.0	144.0	97.0	175.0	113.0	130.0	36.9	40.1	30	33	1
119	1150.0	1140.0	773.0	646.0	477.0	377	158.0	98.3	140.0	151.0	224.0	103.0	77.5	72.7	30	33	1
120	1090.0	1100.0	518.0	450.0	519.0	421	225.0	167.0	179.0	152.0	249.0	119.0	131.0	124.0	30	33	2
121	44.1	98.9	603.0	668.0	897.0	369	254.0	181.0	104.0	90.3	111.0	66.2	52.5	46.8	30	33	1
122	386.0	788.0	1250.0	1520.0	979.0	481	142.0	104.0	89.2	130.0	162.0	79.9	67.6	69.1	30	33	2

Reference ID: 3227106

Obs	c21	c22	c23	c24	c25	c26	c27	c28	c29	c30	c31	c32	c33	c34	KE_FIRST	KE_LAST	trt
123	461.0	277.0	167.0	154.0	191.0	401	204.0	103.0	127.0	202.0	223.0	215.0	60.5	59.1	30	33	2
124	988.0	532.0	224.0	157.0	283.0	672	355.0	150.0	158.0	270.0	227.0	155.0	86.4	99.9	30	33	1
125	608.0	416.0	295.0	189.0	337.0	859	422.0	130.0	97.2	146.0	143.0	65.1	44.9	55.3	30	33	2
126	31.8	157.0	296.0	542.0	1120.0	983	446.0	145.0	103.0	169.0	191.0	99.5	49.3	53.2	30	33	1
127	348.0	901.0	635.0	230.0	229.0	491	435.0	167.0	177.0	124.0	178.0	91.2	70.5	60.8	30	33	1
128	308.0	486.0	282.0	282.0	729.0	785	589.0	208.0	192.0	127.0	141.0	105.0	67.8	80.2	30	33	2
129	958.0	757.0	481.0	499.0	291.0	423	138.0	92.8	99.2	89.8	136.0	64.5	51.3	66.6	30	33	2
130	238.0	399.0	176.0	112.0	192.0	796	406.0	147.0	143.0	150.0	193.0	104.0	48.7	71.4	30	33	1
131	602.0	861.0	209.0	346.0	365.0	667	164.0	202.0	127.0	92.2	179.0	143.0	88.7	73.9	30	33	2
132	222.0	150.0	103.0	151.0	224.0	228	68.3	76.3	117.0	113.0	112.0	75.2	53.3	44.9	30	33	1
133	1010.0	750.0	375.0	412.0	269.0	146	85.6	65.4	86.7	128.0	182.0	57.2	43.8	44.6	30	33	1
134	876.0	649.0	465.0	462.0	382.0	169	110.0	95.5	85.9	96.1	157.0	65.6	41.0	55.0	30	33	2
135	1270.0	368.0	554.0	331.0	367.0	458	97.0	69.8	81.8	249.0	122.0	174.0	55.4	44.0	30	33	1
136	891.0	564.0	300.0	385.0	559.0	453	92.9	128.0	156.0	174.0	116.0	111.0	50.3	55.8	30	33	2
137	298.0	252.0	573.0	350.0	355.0	538	317.0	110.0	85.7	73.6	164.0	68.4	58.8	58.2	30	33	1
138	340.0	337.0	238.0	157.0	138.0	223	157.0	102.0	81.1	93.3	160.0	72.6	57.3	66.4	30	33	2
139	1430.0	1250.0	458.0	410.0	394.0	371	138.0	97.2	117.0	94.2	148.0	85.9	37.8	45.8	30	33	2
140	1440.0	1100.0	554.0	452.0	460.0	342	156.0	129.0	148.0	143.0	202.0	113.0	91.5	78.5	30	33	1
141	1240.0	998.0	514.0	352.0	217.0	244	168.0	82.9	103.0	141.0	163.0	90.6	52.4	65.1	30	33	1
142	1150.0	453.0	278.0	202.0	229.0	254	129.0	167.0	111.0	140.0	179.0	119.0	97.4	64.8	30	33	2
143	511.0	605.0	688.0	526.0	745.0	560	169.0	146.0	112.0	149.0	125.0	89.9	57.6	61.9	30	33	1
144	407.0	420.0	344.0	420.0	694.0	370	134.0	156.0	164.0	99.9	114.0	87.1	71.5	71.8	30	33	2
145	282.0	374.0	497.0	881.0	1160.0	772	174.0	108.0	95.2	55.6	142.0	107.0	51.7	55.0	30	33	2
146	446.0	598.0	516.0	485.0	448.0	500	137.0	118.0	116.0	111.0	166.0	78.6	74.8	55.8	30	33	1
147	598.0	669.0	494.0	398.0	443.0	631	293.0	147.0	131.0	99.9	106.0	101.0	47.1	63.0	30	33	1
148	286.0	386.0	452.0	349.0	418.0	500	332.0	257.0	142.0	90.7	104.0	126.0	50.1	74.1	30	33	2

Obs	c21	c22	c23	c24	c25	c26	c27	c28	c29	c30	c31	c32	c33	c34	KE_FIRST	KE_LAST	trt
149	263.0	406.0	340.0	357.0	802.0	718	141.0	60.7	76.4	60.9	105.0	41.3	28.5	31.4	30	33	2
150	403.0	496.0	228.0	234.0	333.0	285	96.5	85.5	71.7	115.0	78.9	57.8	39.7	44.0	30	33	1
151	606.0	829.0	524.0	569.0	761.0	415	190.0	91.2	77.8	61.2	120.0	69.4	42.3	48.5	30	33	1
152	527.0	658.0	449.0	381.0	427.0	446	167.0	112.0	96.6	87.6	151.0	101.0	62.8	59.6	30	33	2
153	1950.0	1660.0	735.0	422.0	467.0	455	205.0	99.8	99.9	113.0	125.0	124.0	52.0	61.3	30	33	2
154	852.0	1510.0	793.0	457.0	409.0	288	247.0	130.0	121.0	142.0	184.0	65.5	67.2	64.1	30	33	1
155	404.0	523.0	633.0	734.0	783.0	624	151.0	112.0	184.0	151.0	120.0	130.0	67.3	60.5	30	33	2
156	674.0	720.0	403.0	355.0	371.0	319	133.0	156.0	152.0	150.0	88.0	82.6	52.7	60.9	30	33	1
157	691.0	815.0	572.0	231.0	360.0	340	170.0	82.9	71.0	157.0	104.0	76.2	49.2	55.9	30	33	1
158	634.0	384.0	183.0	343.0	572.0	569	277.0	126.0	131.0	195.0	124.0	96.5	53.5	63.3	30	33	2
159	829.0	1170.0	1050.0	680.0	688.0	656	253.0	168.0	129.0	159.0	214.0	118.0	82.7	85.8	30	33	1
160	685.0	1160.0	873.0	427.0	484.0	465	292.0	241.0	159.0	118.0	197.0	93.7	78.0	105.0	30	33	2

FED CONCENTRATION DATASET (FREE EPA): BASELINE-ADJUSTED

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14
1	1	2	1	B	1	0.0283	0.0108	0.0042	0.0047	0.2160	1.3607	0.7703	0.6538	0.5144	0.3420	0.3510	0.1071	0.0874	0.0585
2	1	2	2	A	1	0.0650	0.0331	0.0068	0.0000	0.0300	0.4314	0.6310	0.6781	0.3243	0.1570	0.2580	0.0922	0.0773	0.0180
3	2	1	1	A	1	0.0000	0.0000	0.0059	0.0218	0.1018	0.4210	0.6264	0.5176	0.3532	0.3543	0.3656	0.1639	0.1274	0.1345
4	2	1	2	B	1	0.0122	0.0218	0.2431	0.5944	1.1033	0.8783	0.5280	0.3764	0.1840	0.1684	0.2256	0.1252	0.1133	0.0581
5	3	2	1	B	1	0.0122	0.0050	0.0141	0.0555	0.2225	0.3878	0.5759	0.4775	0.5111	0.6991	0.6721	0.2079	0.0778	0.0410
6	3	2	2	A	1	0.0174	0.0110	0.0269	0.1271	0.1445	0.2650	0.4109	0.3966	0.4723	0.4280	0.2585	0.1859	0.1072	0.0827
7	4	1	1	A	1	0.0207	0.0000	0.0027	0.0147	0.1208	0.5870	0.9980	0.9335	0.6140	0.5761	0.6410	0.2628	0.1402	0.1173
8	4	1	2	B	1	0.0349	0.0315	0.0244	0.0165	0.0182	0.0069	0.1590	0.3796	0.4619	0.5317	0.5760	0.6106	0.3656	0.2227
9	5	2	1	B	1	0.0161	0.0138	0.0022	0.0233	0.1209	0.5622	1.1078	1.0645	0.7571	0.5025	0.4050	0.2226	0.1194	0.0766
10	5	2	2	A	1	0.0138	0.0221	0.0346	0.0326	0.1025	0.3148	0.8283	0.8342	0.7118	0.6732	0.6369	0.3225	0.1706	0.1224
11	6	1	1	A	1	0.0072	0.0396	0.1258	0.3444	0.9068	0.8212	0.5952	0.3339	0.2256	0.2232	0.2146	0.1307	0.0759	0.0797

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14
12	6	1	2	B	1	0.0279	0.0089	0.0712	0.2808	1.5780	1.1485	0.9341	0.3229	0.1703	0.1503	0.1877	0.1725	0.1191	0.0900
13	7	2	1	B	1	0.0243	0.0470	0.1454	0.3517	0.9284	1.4425	1.3912	0.9556	0.4591	0.3372	0.5397	0.1540	0.1214	0.1114
14	7	2	2	A	1	0.0190	0.0382	0.2301	0.7188	1.3650	1.3115	0.7887	0.8644	0.4039	0.3744	0.3698	0.2349	0.1412	0.0890
15	8	1	1	A	1	0.0300	0.0172	0.0078	0.0466	0.2512	1.3609	1.0597	0.4761	0.2608	0.1830	0.3170	0.1630	0.1161	0.1150
16	8	1	2	B	1	0.0520	0.1286	0.1492	0.2568	0.5171	0.7978	0.7613	0.3268	0.2275	0.1660	0.4640	0.2125	0.0940	0.0788
17	9	2	1	B	1	0.0000	0.0071	0.0249	0.0384	0.3128	0.8234	0.6247	0.5116	0.3335	0.2817	0.3791	0.1012	0.0808	0.1255
18	9	2	2	A	1	0.0000	0.0109	0.0136	0.0223	0.0442	0.4542	0.5093	0.5238	0.2610	0.2565	0.2169	0.1477	0.0859	0.0191
19	10	1	1	A	1	0.0000	0.0026	0.0095	0.0908	0.3513	0.5203	0.6389	0.5706	0.5729	0.5335	0.3789	0.2013	0.1578	0.1496
20	10	1	2	B	1	0.0084	0.0029	0.0485	0.1946	0.5585	0.5610	0.8977	0.7651	0.4853	0.3507	0.3129	0.2253	0.1609	0.0990
21	11	1	1	A	1	0.0214	0.0000	0.0056	0.2286	1.0007	1.3872	0.7158	0.4199	0.3090	0.4435	0.3620	0.1298	0.1091	0.1027
22	11	1	2	B	1	0.0551	0.0138	0.0185	0.1461	0.6474	1.5917	0.7374	0.4691	0.3989	0.1575	0.1835	0.1139	0.0978	0.1424
23	12	2	1	B	1	0.0219	0.0000	0.0036	0.0000	0.0063	0.2014	0.2537	0.4295	0.2602	0.4350	0.6192	0.5120	0.1467	0.1879
24	12	2	2	A	1	0.0688	0.0125	0.0000	0.0206	0.0070	0.0150	0.2146	0.5189	0.5794	0.8638	0.7320	0.4255	0.1735	0.1449
25	13	2	1	B	1	0.0000	0.0008	0.0056	0.0672	0.7025	0.9559	0.6593	0.2616	0.2552	0.1873	0.1270	0.0861	0.0671	0.0751
26	13	2	2	A	1	0.0897	0.0195	0.1826	0.0966	0.2366	0.1917	0.0957	0.0948	0.0111	0.1220	0.6405	1.0835	0.2393	0.1511
27	16	1	1	A	1	0.0099	0.0111	0.0194	0.1223	0.4025	1.5075	0.9725	0.6030	0.4020	0.4601	0.6069	0.2519	0.1279	0.1327
28	16	1	2	B	1	0.0020	0.0008	0.1350	0.1523	0.1930	1.0742	1.0152	0.9514	0.2910	0.5860	0.5290	0.3295	0.1246	0.1040
29	17	2	1	B	1	0.0283	0.0000	0.0103	0.0140	0.2330	0.4965	0.4800	0.6362	0.7190	0.6190	0.6490	0.1795	0.1065	0.0879
30	17	2	2	A	1	0.1778	0.0254	0.0543	0.1731	0.6380	1.0202	0.9594	0.5750	0.3128	0.2110	0.2550	0.1414	0.0570	0.0450
31	18	1	1	A	1	0.0544	0.0290	0.0107	0.0323	0.1286	0.6654	0.7084	0.2726	0.3957	0.5452	1.5650	0.1495	0.0917	0.0550
32	18	1	2	B	1	0.0394	0.0264	0.0249	0.0186	0.0796	0.6227	0.7472	0.4733	0.3238	0.2608	0.5650	0.1330	0.0574	0.0362
33	19	1	1	A	1	0.0020	0.0000	0.0100	0.0590	0.2269	0.7815	1.0309	0.9655	0.6482	0.3604	0.1489	0.1021	0.0793	0.0490
34	19	1	2	B	1	0.0111	0.0000	0.0015	0.0319	0.1366	0.8061	1.1257	1.0973	0.6068	0.5779	0.6938	0.1803	0.0869	0.0624
35	20	2	1	B	1	0.0335	0.0072	0.0268	0.2274	0.5470	0.6315	0.7092	0.5235	0.4229	0.2892	0.3991	0.1190	0.0774	0.0776
36	20	2	2	A	1	0.0704	0.0011	0.2826	0.6673	0.9045	0.9292	0.7664	0.5179	0.3204	0.2570	0.4390	0.1744	0.0969	0.0568
37	21	1	1	A	1	0.0510	0.0173	0.0087	0.0154	0.0000	0.1083	0.2329	0.1401	0.1523	0.2550	0.7230	0.6247	0.1933	0.0762

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14
38	21	1	2	B	1	0.0000	0.0337	0.0184	0.1546	0.1740	1.0786	0.7675	0.8358	0.2760	0.1730	0.0550	0.1142	0.0905	0.0433
39	22	2	1	B	1	0.0213	0.0000	0.0014	0.1526	0.5692	1.1713	0.9656	0.4061	0.3020	0.2471	0.2175	0.1488	0.0932	0.0580
40	22	2	2	A	1	0.0900	0.0098	0.0000	0.0000	0.2375	1.0234	1.1506	0.7239	0.3340	0.1590	0.2450	0.1671	0.1163	0.0710
41	23	1	1	A	1	0.0200	0.0000	0.0000	0.0333	0.1400	0.3351	0.4297	0.4813	0.6800	1.2810	0.7120	0.3711	0.1723	0.1291
42	23	1	2	B	1	0.0000	0.0760	0.1095	0.2678	0.5158	0.4654	0.4466	0.3276	0.3053	0.2200	0.2440	0.2862	0.1751	0.0987
43	24	2	1	B	1	0.0341	0.0081	0.0101	0.0207	0.0617	0.3393	1.0341	0.9854	0.4256	0.3710	0.4078	0.1851	0.0659	0.0322
44	24	2	2	A	1	0.0000	0.0200	0.0202	0.0112	0.0339	0.1802	0.4979	0.3866	0.1729	0.1870	0.3251	0.3052	0.0664	0.0573
45	25	1	1	A	1	0.0371	0.0110	0.0075	0.0599	0.1634	0.5613	0.4268	0.1340	0.1956	0.4235	0.7910	0.1632	0.0499	0.0625
46	25	1	2	B	1	0.0296	0.0265	0.0433	0.1312	0.8307	0.6690	0.4373	0.1314	0.0138	0.0010	0.0000	0.0898	0.0494	0.0354
47	26	2	1	B	1	0.0192	0.0000	0.0000	0.0008	0.1029	0.4324	0.5002	0.3640	0.3692	0.4068	0.3610	0.1187	0.0665	0.0486
48	26	2	2	A	1	0.0328	0.0127	0.0159	0.0049	0.1726	0.4054	0.3131	0.4169	0.3438	0.2136	0.1960	0.1547	0.0925	0.0639
49	27	2	1	B	1	0.0247	0.0070	0.0134	0.0595	0.1576	0.3283	0.2599	0.1956	0.3125	0.8251	0.9030	0.2285	0.0963	0.0928
50	27	2	2	A	1	0.0244	0.0140	0.0128	0.0080	0.1845	0.4279	0.5354	0.4841	0.2270	0.2562	0.4991	0.2557	0.1188	0.0942
51	28	1	1	A	1	0.0236	0.0016	0.0017	0.0117	0.0222	0.0414	0.0365	0.0460	0.0337	0.0460	0.0811	0.1221	0.0759	0.0389
52	28	1	2	B	1	0.0321	0.0190	0.0207	0.0200	0.0172	0.0194	0.0678	0.1917	0.3441	0.4052	0.3094	0.1690	0.0965	0.0793
53	29	2	1	B	1	0.0272	0.0000	0.0107	0.0184	0.1021	0.3715	0.4414	0.6242	0.3966	0.3880	0.4015	0.1252	0.0764	0.0574
54	29	2	2	A	1	0.0484	0.0003	0.0012	0.0386	0.0928	0.5111	0.6357	0.6261	0.3788	0.1976	0.1090	0.0823	0.0434	0.0427
55	30	2	1	B	1	0.0375	0.0199	0.0096	0.2371	0.9670	1.1948	0.9798	0.5245	0.3174	0.2784	0.2488	0.1769	0.0814	0.0767
56	30	2	2	A	1	0.0000	0.0062	0.0082	0.1900	0.5813	1.1406	1.2358	0.6446	0.3432	0.1430	0.1210	0.1486	0.0899	0.0849
57	31	1	1	A	1	0.0000	0.0062	0.0244	0.1373	0.2763	0.4049	0.1821	0.1384	0.2385	0.5855	1.5106	0.2453	0.1022	0.2344
58	31	1	2	B	1	0.0358	0.0078	0.0380	0.0000	0.1001	1.0843	0.9791	0.2773	0.2872	0.4820	0.7800	0.2330	0.0501	0.0560
59	32	1	1	A	1	0.0041	0.0051	0.0192	0.0344	0.0437	0.0748	0.0497	0.0224	0.0624	0.3124	1.0301	0.4093	0.1492	0.1708
60	32	1	2	B	1	0.0020	0.0000	0.0000	0.0678	0.2593	0.5112	0.4059	0.1153	0.0974	0.1679	0.8450	0.6966	0.2246	0.1084
61	33	2	1	B	1	0.0376	0.0245	0.0214	0.0053	0.2126	0.7295	1.2239	0.7163	0.4041	0.3482	0.1958	0.0845	0.0774	0.0630
62	33	2	2	A	1	0.0067	0.0110	0.0130	0.0618	0.2526	0.8353	0.7561	0.6397	0.4180	0.3912	0.4154	0.1389	0.0949	0.0598
63	34	1	1	A	1	0.0000	0.0000	0.0051	0.0006	0.0433	0.2039	0.2416	0.3080	0.3968	0.4926	0.2532	0.0728	0.0625	0.0170

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14
64	34	1	2	B	1	0.0075	0.0007	0.0017	0.0000	0.0953	0.2758	0.3826	0.1896	0.1327	0.1420	0.3865	0.0980	0.0544	0.0346
65	37	2	1	B	1	0.0050	0.0040	0.0211	0.1131	0.2510	0.4590	0.4081	0.3438	0.1947	0.3750	0.5610	0.3033	0.2733	0.1683
66	37	2	2	A	1	0.0000	0.0000	0.0290	0.2420	0.4770	0.5970	0.7670	0.5539	0.2560	0.2870	0.3930	0.3640	0.2389	0.2280
67	38	2	1	B	1	0.0127	0.0036	0.3800	0.6364	0.9706	0.6401	0.4773	0.4421	0.5289	0.4451	0.3846	0.1154	0.0848	0.0920
68	38	2	2	A	1	0.0000	0.0000	0.2848	0.4007	1.2707	0.5715	0.5671	0.5121	0.3058	0.3170	0.2380	0.0870	0.0472	0.0300
69	39	1	1	A	1	0.0250	0.0018	0.0024	0.1387	0.4144	0.9011	0.6979	0.5224	0.3177	0.6557	0.4430	0.2837	0.0685	0.1016
70	39	1	2	B	1	0.0000	0.0010	0.0000	0.0062	0.0250	0.3662	0.5670	0.5184	0.7300	0.8700	0.5360	0.3578	0.1363	0.0370
71	40	1	1	A	1	0.0326	0.0294	0.0193	0.0286	0.0745	0.7204	0.3737	0.1828	0.3466	0.9266	1.0451	0.4258	0.1446	0.0938
72	40	1	2	B	1	0.0650	0.0294	0.0221	0.1540	1.7785	1.0962	0.6238	0.2138	0.2971	0.5950	1.3890	0.4900	0.2088	0.0820
73	41	2	1	B	1	0.0459	0.0110	0.0440	0.1477	0.2927	1.3396	0.8242	0.2101	0.2161	0.1612	0.1965	0.1134	0.0562	0.0000
74	41	2	2	A	1	0.0633	0.0078	0.0543	0.0977	0.3668	1.0552	0.8117	0.2640	0.1523	0.4041	0.1683	0.1079	0.0418	0.0205
75	42	2	1	B	1	0.0011	0.0272	0.0195	0.1354	0.3409	1.0987	1.0438	0.5595	0.2641	0.4796	0.2908	0.1050	0.0467	0.0477
76	42	2	2	A	1	0.0325	0.0172	0.0985	0.1473	0.5702	0.5866	0.6853	0.3668	0.4628	0.3312	0.1810	0.0945	0.0802	0.0507
77	43	1	1	A	1	0.0057	0.0067	0.0000	0.0187	0.1248	0.4023	0.5636	0.4429	0.5916	0.6344	0.6171	0.2386	0.1000	0.0818
78	43	1	2	B	1	0.0000	0.0070	0.0195	0.1872	0.3067	0.7400	0.9877	0.5740	0.2808	0.1764	0.2058	0.1757	0.1167	0.0729
79	44	1	1	A	1	0.0123	0.0069	0.0142	0.0875	0.4982	0.6271	0.4232	0.2335	0.2967	0.2317	0.2687	0.1470	0.0660	0.0505
80	44	1	2	B	1	0.0033	0.0000	0.0246	0.2084	0.7941	0.7036	0.4282	0.1899	0.1200	0.2050	0.2087	0.1490	0.0772	0.0546
81	45	1	1	A	1	0.0352	0.0165	0.0119	0.0161	0.0338	0.1872	0.2630	0.3701	1.1443	1.6866	1.5883	0.2321	0.0820	0.0301
82	45	1	2	B	1	0.0203	0.0089	0.0463	0.1003	0.4911	1.3295	0.6448	0.3313	0.3829	0.5227	0.5390	0.1989	0.0906	0.0485
83	46	2	1	B	1	0.0409	0.0137	0.0107	0.0217	0.0855	1.2747	0.7724	0.3753	0.1896	0.3014	0.2491	0.0627	0.0336	0.0392
84	46	2	2	A	1	0.0318	0.0029	0.0108	0.0500	0.2735	1.2307	0.4835	0.3041	0.1636	0.2211	0.3787	0.0871	0.0555	0.0698
85	47	1	1	A	1	0.0000	0.0130	0.0647	0.2454	0.9494	1.6423	1.0559	0.5782	0.3199	0.3124	0.3300	0.1012	0.0376	0.0000
86	47	1	2	B	1	0.0502	0.0081	0.3047	0.6860	0.9840	1.2215	0.6553	0.4822	0.1675	0.1570	0.1210	0.0794	0.1021	0.0471
87	48	2	1	B	1	0.0254	0.0451	0.0316	0.1844	0.6635	0.9122	0.7624	0.3735	0.2337	0.4020	0.3401	0.0818	0.0756	0.0409
88	48	2	2	A	1	0.0276	0.0019	0.0046	0.1243	0.7803	1.1902	0.5918	0.2625	0.1518	0.1982	0.2720	0.1022	0.0726	0.0492
89	49	1	1	A	1	0.0205	0.0103	0.0152	0.0062	0.2311	0.6743	0.8534	0.3785	0.2757	0.4217	0.4867	0.1015	0.0494	0.0314

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14
90	49	1	2	B	1	0.0135	0.0037	0.0893	0.8502	2.4270	1.4971	0.5774	0.2968	0.2170	0.1517	0.1742	0.0703	0.0491	0.0611
91	50	1	1	A	1	0.0221	0.0096	0.0142	0.0100	0.0015	0.0204	0.0114	0.0121	0.0000	0.0109	0.1230	0.1732	0.1576	0.0920
92	50	1	2	B	1	0.0000	0.0224	0.0132	0.0108	0.0000	0.0959	0.0607	0.0425	0.0855	0.4973	0.6328	0.2575	0.1216	0.0813
93	51	2	1	B	1	0.0000	0.0000	0.0081	0.0158	0.0862	0.2975	0.3746	0.2306	0.4298	0.6024	0.9698	0.2894	0.1145	0.0772
94	51	2	2	A	1	0.0000	0.0075	0.0182	0.2829	0.7581	1.1482	0.8050	0.3943	0.2479	0.2544	0.2279	0.1224	0.0702	0.0680
95	52	2	1	B	1	0.0069	0.0012	0.0019	0.0057	0.0786	0.2509	0.2420	0.4663	0.5364	0.6032	0.8117	0.2014	0.1017	0.0661
96	52	2	2	A	1	0.0058	0.0124	0.0169	0.0811	0.2022	0.2500	0.3571	0.2290	0.3884	0.8647	0.4852	0.1635	0.1314	0.1256
97	53	2	1	B	1	0.0530	0.0098	0.0040	0.0048	0.0696	0.5536	0.7812	0.7216	0.5452	0.4991	0.3045	0.2105	0.1379	0.0710
98	53	2	2	A	1	0.0346	0.0088	0.0193	0.0631	0.4220	1.0448	0.7914	0.9533	0.5454	0.3258	0.2026	0.1520	0.1145	0.0779
99	54	1	1	A	1	0.0000	0.0127	0.0246	0.0234	0.0679	0.2267	0.8070	1.2395	1.0877	0.9713	0.4514	0.3408	0.2162	0.0988
100	54	1	2	B	1	0.0000	0.0143	0.0105	0.0076	0.0205	0.0786	0.0784	0.1241	0.2907	0.7147	0.5953	0.6594	0.2464	0.1538
101	55	2	1	B	1	0.0123	0.0392	0.0445	0.0967	0.1550	0.3122	0.4685	0.2478	0.2124	0.1046	0.0840	0.0794	0.0555	0.0419
102	55	2	2	A	1	0.0021	0.0847	0.1391	0.1905	0.2680	0.1826	0.1066	0.0784	0.0379	0.0089	0.0433	0.0319	0.0062	0.0008
103	56	1	1	A	1	0.0003	0.0041	0.0045	0.0082	0.0260	0.1577	0.2388	0.2547	0.2306	0.2178	0.1344	0.1481	0.0557	0.0534
104	56	1	2	B	1	0.0000	0.0040	0.0219	0.0153	0.0111	0.1637	0.1481	0.1441	0.1889	0.3079	0.2510	0.1953	0.0841	0.0279
105	57	1	1	A	1	0.0303	0.0197	0.0108	0.0592	0.1662	0.4719	0.5343	0.2214	0.1933	0.3110	0.2400	0.0487	0.0726	0.0448
106	57	1	2	B	1	0.1142	0.0000	0.0000	0.0596	0.2760	0.6361	0.3306	0.4685	0.7218	0.2680	0.2820	0.1040	0.0325	0.0050
107	58	1	1	A	1	0.0000	0.0000	0.0050	0.0404	0.4640	0.5640	0.5580	0.3750	0.4100	0.8930	0.9330	0.2075	0.2282	0.0448
108	58	1	2	B	1	0.0010	0.0100	0.0633	0.1362	0.7601	1.0750	0.4904	0.2055	0.3931	0.5680	0.3830	0.1751	0.0881	0.0837
109	59	2	1	B	1	0.0339	0.0024	0.0031	0.0324	0.2246	0.9154	1.0839	0.6293	0.4038	0.2048	0.3035	0.0814	0.0490	0.0334
110	59	2	2	A	1	0.0112	0.0490	0.2133	0.4366	0.7414	0.5602	0.4636	0.2667	0.3110	0.1941	0.1909	0.0786	0.0391	0.0183
111	60	2	1	B	1	0.0260	0.0137	0.0270	0.0135	0.0450	0.2445	0.7424	0.5639	0.4578	1.0361	1.0130	0.4001	0.1632	0.0853
112	60	2	2	A	1	0.0460	0.0097	0.0442	0.0229	0.0748	0.2128	0.7054	0.3423	0.2006	0.2097	0.3720	0.5487	0.0905	0.0778
113	61	1	1	A	1	0.0158	0.0047	0.0090	0.0133	0.0160	0.6114	0.4052	0.6589	0.8709	1.6670	0.8756	0.2896	0.0994	0.0924
114	61	1	2	B	1	0.0000	0.0115	0.0321	0.0159	0.0392	0.6432	0.8375	0.7862	0.6453	0.2425	0.1415	0.0976	0.0645	0.0292
115	62	2	1	B	1	0.0058	0.0023	0.0441	0.1111	0.3182	0.5215	0.5634	0.4901	0.3924	0.5336	0.3102	0.3392	0.1394	0.1181

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14
116	62	2	2	A	1	0.0000	0.0000	0.0499	0.2110	0.2969	0.5321	0.6530	0.5645	0.5319	0.6825	0.6150	0.3440	0.1901	0.1481
117	63	2	1	B	1	0.0464	0.0006	0.0103	0.0083	0.0094	0.2726	0.2085	0.1168	0.2537	0.3443	1.2247	0.2064	0.0671	0.0285
118	63	2	2	A	1	0.0013	0.0046	0.0144	0.0353	0.0132	0.0120	0.0111	0.0013	0.0000	0.0119	0.1360	0.3216	0.1300	0.0840
119	64	1	1	A	1	0.0490	0.0214	0.0417	0.2761	0.8952	1.0781	1.0811	0.7255	0.5636	0.4089	0.2380	0.1168	0.0552	0.0679
120	64	1	2	B	1	0.0000	0.0171	0.0399	0.2431	0.4473	0.9976	1.0258	0.4613	0.3964	0.4562	0.3180	0.1806	0.1220	0.1194
121	65	1	1	A	1	0.0000	0.0080	0.0008	0.0013	0.0000	0.0075	0.0750	0.5843	0.6459	0.8764	0.3272	0.2311	0.1620	0.0696
122	65	1	2	B	1	0.0064	0.0124	0.0067	0.0223	0.0384	0.3279	0.7582	1.2228	1.4630	0.8620	0.2890	0.1026	0.0760	0.0448
123	66	2	1	B	1	0.0411	0.0209	0.0164	0.0418	0.0807	0.4196	0.2487	0.1368	0.1221	0.1422	0.3014	0.1792	0.0829	0.0952
124	66	2	2	A	1	0.0500	0.0245	0.0333	0.0752	0.4954	0.9431	0.4978	0.1943	0.1147	0.1710	0.5570	0.2871	0.1197	0.0862
125	67	2	1	B	1	0.0000	0.0158	0.0120	0.0189	0.0743	0.5863	0.4001	0.2773	0.1705	0.3055	0.8051	0.4035	0.1138	0.0789
126	67	2	2	A	1	0.0000	0.0146	0.0180	0.0199	0.0068	0.0048	0.1387	0.2763	0.5178	1.0894	0.9050	0.4261	0.1274	0.0750
127	68	1	1	A	1	0.0000	0.0000	0.0038	0.0162	0.1068	0.3138	0.8742	0.6108	0.1858	0.1650	0.3880	0.3979	0.1467	0.1189
128	68	1	2	B	1	0.0000	0.0146	0.0095	0.0282	0.0880	0.2790	0.4599	0.2544	0.2481	0.6640	0.7002	0.5503	0.1860	0.1284
129	69	2	1	B	1	0.0414	0.0099	0.0074	0.0259	0.1292	0.9198	0.7286	0.4515	0.4566	0.2320	0.3485	0.1096	0.0638	0.0539
130	69	2	2	A	1	0.0071	0.0061	0.0221	0.0135	0.0006	0.1986	0.3731	0.1516	0.0527	0.1133	0.6820	0.3806	0.1236	0.1122
131	70	2	1	B	1	0.0198	0.0122	0.0160	0.0131	0.1621	0.5681	0.8376	0.1852	0.3249	0.3425	0.6292	0.1454	0.1813	0.0986
132	70	2	2	A	1	0.0171	0.0281	0.1814	0.2771	0.2053	0.1924	0.1298	0.0713	0.1183	0.1890	0.1870	0.0428	0.0517	0.0894
133	71	1	1	A	1	0.0010	0.0000	0.0026	0.0438	0.2385	0.9637	0.7098	0.3476	0.3737	0.2192	0.0730	0.0607	0.0417	0.0488
134	71	1	2	B	1	0.0408	0.0099	0.0084	0.0447	0.1743	0.8498	0.6284	0.4452	0.4409	0.3430	0.1262	0.0854	0.0740	0.0501
135	72	1	1	A	1	0.0000	0.0042	0.0169	0.1397	0.7160	1.2090	0.3330	0.5232	0.2905	0.3073	0.3798	0.0761	0.0410	0.0000
136	72	1	2	B	1	0.0246	0.0179	0.0067	0.1506	0.5050	0.8206	0.5331	0.2720	0.3327	0.4647	0.3569	0.0655	0.0974	0.0850
137	73	1	1	A	1	0.0046	0.0000	0.0042	0.0066	0.0120	0.2753	0.2323	0.5532	0.3249	0.2758	0.4000	0.2941	0.0974	0.0656
138	73	1	2	B	1	0.0224	0.0319	0.0593	0.3751	0.3082	0.3106	0.3102	0.2174	0.1337	0.1103	0.1678	0.1167	0.0850	0.0510
139	74	2	1	B	1	0.0065	0.0002	0.0161	0.0941	0.2721	1.3939	1.2250	0.4029	0.3733	0.3450	0.3084	0.1168	0.0734	0.0759
140	74	2	2	A	1	0.0350	0.0000	0.0632	0.3381	0.4793	1.3350	1.0374	0.4998	0.3611	0.3570	0.1760	0.0955	0.0747	0.0727
141	75	1	1	A	1	0.0077	0.0123	0.0207	0.0847	0.4555	1.2150	0.9763	0.4943	0.3251	0.1819	0.1905	0.1470	0.0595	0.0708

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14
142	75	1	2	B	1	0.0016	0.0000	0.0645	0.5338	1.0077	1.1050	0.4126	0.2458	0.1613	0.1636	0.1922	0.1043	0.1417	0.0675
143	77	1	1	A	1	0.0072	0.0185	0.0090	0.0172	0.1229	0.4827	0.5787	0.6642	0.4947	0.7170	0.5270	0.1472	0.1190	0.0822
144	77	1	2	B	1	0.0000	0.0010	0.0102	0.0032	0.1885	0.3792	0.3930	0.3088	0.3927	0.6684	0.3367	0.1073	0.1196	0.1190
145	78	2	1	B	1	0.0429	0.0000	0.0081	0.0101	0.0707	0.2480	0.3473	0.4669	0.8404	1.1086	0.7080	0.1541	0.0856	0.0594
146	78	2	2	A	1	0.0237	0.0047	0.0121	0.0125	0.0429	0.4179	0.5681	0.4880	0.4512	0.3763	0.4373	0.1122	0.0841	0.0780
147	79	1	1	A	1	0.0015	0.0000	0.0015	0.0215	0.0776	0.5731	0.6483	0.4697	0.3641	0.3793	0.5465	0.2758	0.1244	0.0823
148	79	1	2	B	1	0.0066	0.0027	0.0043	0.0197	0.0515	0.2610	0.3581	0.4220	0.3079	0.3596	0.4036	0.3033	0.2356	0.1107
149	80	2	1	B	1	0.0096	0.0031	0.0029	0.0127	0.0936	0.2481	0.3948	0.3213	0.3360	0.7545	0.6540	0.1306	0.0479	0.0613
150	80	2	2	A	1	0.0000	0.0000	0.0065	0.0394	0.2080	0.3797	0.4809	0.2158	0.2218	0.3109	0.2397	0.0857	0.0694	0.0467
151	81	1	1	A	1	0.0054	0.0137	0.0162	0.0149	0.0842	0.5845	0.8065	0.5059	0.5492	0.7351	0.3848	0.1755	0.0740	0.0630
152	81	1	2	B	1	0.0000	0.0119	0.0105	0.0105	0.0683	0.5034	0.6362	0.4241	0.3472	0.3871	0.4031	0.1474	0.0906	0.0635
153	82	2	1	B	1	0.0021	0.0307	0.2199	0.2247	0.6446	1.9005	1.6282	0.7039	0.3840	0.3836	0.3440	0.1720	0.0706	0.0307
154	82	2	2	A	1	0.0008	0.0120	0.0000	0.0103	0.0927	0.7932	1.4780	0.7673	0.4257	0.3698	0.2340	0.2178	0.1090	0.0808
155	83	2	1	B	1	0.0000	0.0000	0.0059	0.0047	0.0357	0.3642	0.4941	0.5988	0.6863	0.7029	0.5446	0.1229	0.0871	0.1310
156	83	2	2	A	1	0.0215	0.0053	0.0491	0.1979	0.4570	0.6384	0.6965	0.3763	0.3165	0.3150	0.2294	0.1086	0.1293	0.1025
157	84	1	1	A	1	0.0000	0.0083	0.0061	0.0000	0.0972	0.6626	0.7958	0.5570	0.2025	0.3272	0.2957	0.1531	0.0628	0.0400
158	84	1	2	B	1	0.0016	0.0083	0.0578	0.2974	0.3720	0.5974	0.3648	0.1659	0.3224	0.5212	0.5177	0.2508	0.1057	0.0919
159	86	1	1	A	1	0.0191	0.0177	0.0470	0.0707	0.1955	0.7878	1.1342	1.0231	0.6515	0.6544	0.6004	0.2303	0.1407	0.0909
160	86	1	2	B	1	0.0000	0.0119	0.0165	0.0767	0.1571	0.6345	1.1256	0.8447	0.3879	0.4273	0.3776	0.2607	0.2090	0.0929

Obs	c15	c16	c17	c18	c19	KE_FIRST	KE_LAST	trt
1	0.0738	0.1166	0.0610	0.0143	0.0327	13	16	2
2	0.0400	0.0640	0.0720	0.0000	0.0212	13	16	1
3	0.0376	0.0663	0.0908	0.0129	0.0184	13	16	1
4	0.0641	0.1232	0.1013	0.0610	0.0310	13	16	2
5	0.0602	0.0712	0.0445	0.0330	0.0291	13	16	2

Reference ID: 3227106

Obs	c15	c16	c17	c18	c19	KE_FIRST	KE_LAST	trt
6	0.0892	0.1322	0.0555	0.0276	0.0667	13	16	1
7	0.1675	0.1301	0.1038	0.0640	0.0488	13	16	1
8	0.2244	0.2569	0.2100	0.0659	0.1016	13	16	2
9	0.0855	0.0922	0.0779	0.0441	0.0450	13	16	2
10	0.1056	0.1689	0.1405	0.0858	0.0745	13	16	1
11	0.0804	0.0664	0.0503	0.0169	0.0360	13	16	1
12	0.0726	0.0693	0.0353	0.0334	0.0590	13	16	2
13	0.1697	0.1123	0.1844	0.0561	0.0668	13	16	2
14	0.1733	0.1370	0.1570	0.0619	0.1029	13	16	1
15	0.0793	0.0700	0.0652	0.0200	0.0640	13	16	1
16	0.0737	0.0470	0.0461	0.0427	0.0745	13	16	2
17	0.0569	0.1085	0.0728	0.0183	0.0544	13	16	2
18	0.0514	0.0924	0.0735	0.0083	0.0627	13	16	1
19	0.0990	0.1068	0.0853	0.0464	0.0518	13	16	1
20	0.0992	0.1538	0.0735	0.0460	0.0743	13	16	2
21	0.0860	0.0854	0.0013	0.0534	0.0530	13	16	1
22	0.0945	0.1091	0.0474	0.0489	0.0719	13	16	2
23	0.1470	0.1276	0.1054	0.0620	0.0655	13	16	2
24	0.1369	0.1388	0.1458	0.0534	0.0685	13	16	1
25	0.0000	0.0000	0.0168	0.0000	0.0080	13	16	2
26	0.0220	0.1067	0.0686	0.0075	0.0293	13	16	1
27	0.0709	0.1049	0.0675	0.0000	0.0547	13	16	1
28	0.1410	0.1780	0.0000	0.0000	0.0255	13	16	2
29	0.1471	0.0893	0.0170	0.0000	0.0375	13	16	2
30	0.1170	0.1268	0.1420	0.0138	0.0494	13	16	1
31	0.0985	0.0834	0.0496	0.0205	0.0325	13	16	1

Obs	c15	c16	c17	c18	c19	KE_FIRST	KE_LAST	trt
32	0.0203	0.0684	0.1046	0.0256	0.0312	13	16	2
33	0.0475	0.0437	0.0201	0.0100	0.0301	13	16	1
34	0.0589	0.0469	0.0468	0.0083	0.0320	13	16	2
35	0.1117	0.0578	0.0930	0.0201	0.0349	13	16	2
36	0.0810	0.0924	0.0615	0.0000	0.0545	13	16	1
37	0.0852	0.1010	0.0000	0.0000	0.0627	13	16	1
38	0.0226	0.0080	0.0000	0.0000	0.0357	13	16	2
39	0.0375	0.0213	0.0397	0.0000	0.0341	13	16	2
40	0.0320	0.0410	0.0395	0.0000	0.0024	13	16	1
41	0.0530	0.0290	0.0250	0.0000	0.0251	13	16	1
42	0.0664	0.1050	0.0378	0.0453	0.0492	13	16	2
43	0.0587	0.1447	0.0214	0.0236	0.0426	13	16	2
44	0.1167	0.1382	0.0189	0.0693	0.0000	13	16	1
45	0.0393	0.0496	0.0454	0.0000	0.0183	13	16	1
46	0.1583	0.0129	0.0000	0.0000	0.0110	13	16	2
47	0.0119	0.0102	0.0000	0.0184	0.0256	13	16	2
48	0.1151	0.0368	0.0188	0.0105	0.0335	13	16	1
49	0.0490	0.0947	0.0756	0.0129	0.0333	13	16	2
50	0.1085	0.0294	0.0558	0.0068	0.0274	13	16	1
51	0.0377	0.0188	0.0000	0.0137	0.0214	13	16	1
52	0.2355	0.0685	0.0467	0.0344	0.0423	13	16	2
53	0.0346	0.0518	0.0841	0.0269	0.0236	13	16	2
54	0.0292	0.0386	0.0358	0.0061	0.0293	13	16	1
55	0.0270	0.0725	0.0070	0.0390	0.0361	13	16	2
56	0.1034	0.0910	0.0843	0.0367	0.0484	13	16	1
57	0.0304	0.0369	0.0295	0.0197	0.0252	13	16	1

Obs	c15	c16	c17	c18	c19	KE_FIRST	KE_LAST	trt
58	0.0540	0.1298	0.2391	0.0214	0.0292	13	16	2
59	0.1006	0.1847	0.0302	0.0476	0.0503	13	16	1
60	0.1239	0.1992	0.1303	0.0729	0.0508	13	16	2
61	0.0112	0.0650	0.0406	0.0000	0.0337	13	16	2
62	0.0805	0.0447	0.0856	0.0351	0.0248	13	16	1
63	0.0654	0.0305	0.0149	0.0162	0.0244	13	16	1
64	0.0783	0.0270	0.0054	0.0124	0.0150	13	16	2
65	0.2006	0.0900	0.0350	0.0747	0.0365	13	16	2
66	0.2250	0.0470	0.0050	0.0250	0.0140	13	16	1
67	0.0593	0.0551	0.0756	0.0052	0.0236	13	16	2
68	0.0832	0.0574	0.0286	0.0202	0.0295	13	16	1
69	0.1440	0.0320	0.0474	0.0027	0.0468	13	16	1
70	0.2440	0.0130	0.0000	0.0440	0.0288	13	16	2
71	0.0570	0.0926	0.0885	0.0565	0.0609	13	16	1
72	0.1140	0.1070	0.0705	0.0000	0.0800	13	16	2
73	0.0605	0.0166	0.0274	0.0041	0.0273	13	16	2
74	0.0969	0.0482	0.0085	0.0205	0.0335	13	16	1
75	0.0345	0.1301	0.0423	0.0131	0.0369	13	16	2
76	0.1722	0.0410	0.0536	0.0178	0.0438	13	16	1
77	0.0050	0.0534	0.0538	0.0172	0.0389	13	16	1
78	0.1784	0.0449	0.0237	0.0193	0.0234	13	16	2
79	0.0942	0.0625	0.0502	0.0284	0.0573	13	16	1
80	0.0752	0.0392	0.0646	0.0278	0.0208	13	16	2
81	0.0810	0.1001	0.0000	0.0172	0.0449	13	16	1
82	0.1151	0.0938	0.0240	0.0220	0.0447	13	16	2
83	0.0242	0.0549	0.0499	0.0242	0.0401	13	16	2

Obs	c15	c16	c17	c18	c19	KE_FIRST	KE_LAST	trt
84	0.0353	0.0989	0.0695	0.0359	0.0221	13	16	1
85	0.0000	0.0073	0.0504	0.0000	0.0241	13	16	1
86	0.1088	0.1072	0.0000	0.0000	0.0473	13	16	2
87	0.0186	0.0525	0.0000	0.0028	0.0404	13	16	2
88	0.0628	0.0518	0.0207	0.0105	0.0430	13	16	1
89	0.0676	0.0534	0.0499	0.0061	0.0185	13	16	1
90	0.0362	0.0577	0.0000	0.0000	0.0294	13	16	2
91	0.0610	0.0674	0.0302	0.0161	0.0320	13	16	1
92	0.0486	0.0666	0.0000	0.0000	0.0333	13	16	2
93	0.0307	0.0344	0.0678	0.0172	0.0427	13	16	2
94	0.0616	0.0697	0.0529	0.0425	0.0604	13	16	1
95	0.0755	0.0769	0.0663	0.0267	0.0524	13	16	2
96	0.1278	0.0749	0.0862	0.0724	0.0643	13	16	1
97	0.0513	0.1001	0.0781	0.0476	0.0527	13	16	2
98	0.0449	0.0927	0.0637	0.0573	0.0482	13	16	1
99	0.0427	0.1660	0.0819	0.0596	0.0466	13	16	1
100	0.0829	0.0539	0.0624	0.0583	0.0494	13	16	2
101	0.0465	0.0367	0.0665	0.0072	0.0367	13	16	2
102	0.0259	0.0084	0.0000	0.0000	0.0038	13	16	1
103	0.0554	0.0504	0.0248	0.0258	0.0266	13	16	1
104	0.0549	0.0639	0.0312	0.0256	0.0305	13	16	2
105	0.1189	0.0293	0.0602	0.0000	0.0119	13	16	1
106	0.0293	0.0352	0.0000	0.0000	0.0334	13	16	2
107	0.1140	0.0000	0.0000	0.0000	0.0445	13	16	1
108	0.0120	0.0000	0.0381	0.0024	0.0338	13	16	2
109	0.0522	0.0565	0.0000	0.0000	0.0320	13	16	2

Obs	c15	c16	c17	c18	c19	KE_FIRST	KE_LAST	trt
110	0.0619	0.0279	0.0031	0.0350	0.0297	13	16	1
111	0.1767	0.1170	0.0387	0.0079	0.0559	13	16	2
112	0.1910	0.1280	0.0235	0.0536	0.1167	13	16	1
113	0.1086	0.1937	0.0354	0.0281	0.0305	13	16	1
114	0.0360	0.1070	0.0255	0.0119	0.0501	13	16	2
115	0.0769	0.0507	0.0992	0.0423	0.0336	13	16	2
116	0.1173	0.0814	0.0429	0.0476	0.0457	13	16	1
117	0.0202	0.0844	0.1143	0.0161	0.0231	13	16	2
118	0.1130	0.0374	0.1061	0.0113	0.0277	13	16	1
119	0.0684	0.0970	0.0332	0.0000	0.0315	13	16	1
120	0.0801	0.1200	0.0703	0.0774	0.0796	13	16	2
121	0.0465	0.0538	0.0303	0.0304	0.0239	13	16	1
122	0.0678	0.0841	0.0384	0.0106	0.0297	13	16	2
123	0.1325	0.1645	0.1357	0.0286	0.0343	13	16	2
124	0.1890	0.1200	0.0944	0.0441	0.0320	13	16	1
125	0.0934	0.0818	0.0395	0.0264	0.0368	13	16	2
126	0.1403	0.1181	0.0723	0.0251	0.0333	13	16	1
127	0.0759	0.0807	0.0470	0.0263	0.0237	13	16	1
128	0.0854	0.0690	0.0770	0.0339	0.0415	13	16	2
129	0.0000	0.0684	0.0017	0.0089	0.0382	13	16	2
130	0.1002	0.1362	0.0342	0.0000	0.0460	13	16	1
131	0.0616	0.1387	0.0991	0.0676	0.0553	13	16	2
132	0.0764	0.0658	0.0455	0.0206	0.0194	13	16	1
133	0.0663	0.0550	0.0097	0.0055	0.0197	13	16	1
134	0.0439	0.1099	0.0229	0.0199	0.0304	13	16	2
135	0.1340	0.0498	0.1210	0.0149	0.0231	13	16	1

Obs	c15	c16	c17	c18	c19	KE_FIRST	KE_LAST	trt
136	0.0811	0.0552	0.0000	0.0000	0.0284	13	16	2
137	0.0370	0.1035	0.0252	0.0337	0.0353	13	16	1
138	0.0542	0.0893	0.0298	0.0340	0.0261	13	16	2
139	0.0534	0.0804	0.0340	0.0011	0.0246	13	16	2
140	0.0270	0.0830	0.0173	0.0006	0.0180	13	16	1
141	0.1091	0.1124	0.0521	0.0255	0.0441	13	16	1
142	0.0746	0.1024	0.0667	0.0567	0.0401	13	16	2
143	0.1127	0.0803	0.0618	0.0263	0.0401	13	16	1
144	0.0463	0.0479	0.0496	0.0442	0.0451	13	16	2
145	0.0292	0.0849	0.0457	0.0111	0.0351	13	16	2
146	0.0619	0.0994	0.0273	0.0410	0.0310	13	16	1
147	0.0715	0.0564	0.0676	0.0132	0.0458	13	16	1
148	0.0414	0.0523	0.0958	0.0090	0.0454	13	16	2
149	0.0361	0.0782	0.0199	0.0075	0.0210	13	16	2
150	0.0493	0.0385	0.0228	0.0275	0.0332	13	16	1
151	0.0406	0.0799	0.0456	0.0225	0.0340	13	16	1
152	0.0330	0.0930	0.0734	0.0290	0.0400	13	16	2
153	0.0000	0.0539	0.0396	0.0140	0.0283	13	16	2
154	0.0760	0.1265	0.0072	0.0359	0.0349	13	16	1
155	0.0697	0.0581	0.0781	0.0196	0.0324	13	16	2
156	0.0712	0.0603	0.0496	0.0142	0.0365	13	16	1
157	0.1204	0.0709	0.0454	0.0207	0.0390	13	16	1
158	0.1293	0.0764	0.0625	0.0329	0.0371	13	16	2
159	0.0779	0.1487	0.0935	0.0542	0.0631	13	16	1
160	0.0799	0.1140	0.0588	0.0389	0.0737	13	16	2

FED CONCENTRATION DATASET (TOTAL EPA): BASELINE-NON-ADJUSTED

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19
1	1	2	1	B	1	21.70	22.40	22.50	23.40	23.60	22.90	22.50	22.30	23.50	23.20	23.30	22.90	23.30	22.30	20.70	22.30	24.30	24.00	24.10
2	1	2	2	A	1	57.30	57.80	56.50	55.90	53.90	51.80	52.80	52.50	54.90	53.30	52.40	48.50	50.70	47.10	44.10	48.20	48.90	50.10	47.10
3	2	1	1	A	1	8.64	8.57	8.58	8.61	9.04	9.19	8.83	8.71	8.79	8.62	8.87	8.48	8.33	8.13	7.56	7.49	8.05	8.62	9.38
4	2	1	2	B	1	8.93	8.99	8.80	8.30	8.70	8.67	8.98	8.96	9.19	9.90	9.20	9.58	9.96	9.81	9.44	9.28	9.35	18.00	74.00
5	3	2	1	B	1	8.06	7.68	7.49	8.00	7.70	8.45	8.45	8.48	8.74	9.04	9.05	8.48	8.17	8.16	8.11	7.58	7.27	7.82	10.10
6	3	2	2	A	1	10.70	10.10	10.30	10.90	11.40	11.00	11.00	10.60	11.60	11.60	11.80	11.60	11.60	11.10	10.30	9.64	9.88	10.20	17.00
7	4	1	1	A	1	16.80	16.60	16.20	17.00	17.10	17.00	16.70	17.40	16.00	15.30	15.10	15.30	15.10	14.70	13.80	12.60	13.00	13.30	13.60
8	4	1	2	B	1	19.20	19.40	20.10	19.30	20.00	19.30	18.50	18.00	17.20	17.60	18.30	16.90	16.20	16.70	16.30	15.20	15.00	14.90	15.10
9	5	2	1	B	1	15.00	14.90	16.20	15.70	15.10	15.50	16.90	16.70	17.30	16.30	16.10	15.60	16.80	16.40	14.10	13.60	14.30	14.90	15.40
10	5	2	2	A	1	16.60	16.50	16.30	16.80	17.10	15.80	17.20	16.80	17.00	17.20	17.20	16.50	15.90	15.50	15.70	16.30	18.10	18.70	22.40
11	6	1	1	A	1	3.68	3.54	3.57	3.82	3.62	4.13	3.88	3.74	3.75	3.78	3.65	3.37	3.71	3.72	3.30	3.19	4.28	9.33	20.10
12	6	1	2	B	1	5.01	4.45	4.44	4.45	4.83	4.64	4.81	4.58	4.45	4.54	4.79	4.86	4.31	4.30	3.92	3.93	3.97	8.19	10.20
13	7	2	1	B	1	5.94	6.16	5.98	6.91	5.97	6.24	6.19	6.88	5.88	5.83	5.60	5.75	6.15	5.83	4.91	5.49	6.47	16.80	27.50
14	7	2	2	A	1	11.60	12.80	12.70	13.20	13.20	12.90	12.50	12.80	12.10	15.10	10.50	10.80	12.80	12.40	10.60	10.80	11.90	30.70	93.00
15	8	1	1	A	1	14.10	15.10	13.80	12.90	14.70	14.20	14.20	14.50	15.20	13.20	12.80	13.90	12.90	12.30	12.40	12.10	11.70	12.30	12.10
16	8	1	2	B	1	10.30	11.20	12.90	12.50	12.30	11.60	12.70	12.60	11.90	11.30	17.20	11.80	11.60	11.60	9.96	11.00	12.90	31.20	34.50
17	9	2	1	B	1	10.40	10.40	9.95	9.53	11.30	12.80	11.50	11.90	13.10	12.90	12.40	11.00	11.30	13.10	11.60	11.70	12.00	12.90	14.40
18	9	2	2	A	1	14.80	14.30	14.30	16.80	15.00	16.70	17.90	17.40	15.70	15.20	12.40	14.90	14.90	15.00	14.00	14.40	15.70	17.60	16.30
19	10	1	1	A	1	6.17	6.04	6.23	5.60	6.09	5.47	6.36	6.02	6.23	5.46	6.44	6.41	6.15	5.50	6.52	6.07	6.60	6.34	8.98
20	10	1	2	B	1	12.90	12.20	13.20	13.10	12.70	13.70	12.30	13.50	15.20	12.70	13.20	14.20	12.80	16.10	14.30	12.40	12.90	13.30	68.60
21	11	1	1	A	1	12.50	12.90	12.80	13.50	12.90	11.80	12.60	11.80	13.10	11.60	11.60	11.40	13.50	11.20	10.90	10.50	10.60	10.10	19.80
22	11	1	2	B	1	14.40	14.70	14.40	14.70	13.60	13.30	15.00	12.60	15.10	12.70	14.50	14.60	13.70	13.90	12.50	13.40	13.60	13.50	18.30
23	12	2	1	B	1	7.78	7.59	7.92	7.49	8.21	8.46	8.61	8.47	9.53	8.65	8.28	7.30	9.46	7.79	7.67	8.60	8.93	8.59	10.20
24	12	2	2	A	1	12.70	12.70	11.80	12.70	14.70	14.40	15.60	13.70	14.20	11.60	14.10	13.60	14.20	13.90	13.70	13.80	14.40	12.80	12.10
25	13	2	1	B	1	20.20	23.90	21.70	19.60	18.90	20.40	21.00	19.70	21.10	18.50	22.00	18.70	20.40	18.20	16.80	18.60	16.80	17.80	17.30

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19
26	13	2	2	A	1	21.00	20.00	18.90	21.40	19.50	19.70	22.70	19.30	19.90	19.10	23.00	20.60	22.00	19.60	20.30	21.60	19.80	17.00	26.20
27	16	1	1	A	1	8.10	7.44	7.69	7.62	7.13	8.30	8.59	8.06	8.10	9.15	7.25	9.29	8.43	9.01	7.71	7.71	8.51	9.13	9.96
28	16	1	2	B	1	26.40	23.40	25.90	24.00	25.80	26.30	25.30	29.30	25.70	25.60	25.50	27.50	24.20	25.50	22.50	23.00	23.70	20.30	25.30
29	17	2	1	B	1	15.80	16.10	16.50	16.90	17.30	16.80	16.90	16.50	17.70	16.20	16.90	16.70	15.60	15.20	14.50	15.70	16.70	17.00	17.40
30	17	2	2	A	1	18.90	18.60	18.50	20.60	20.90	20.90	20.40	20.40	21.20	22.30	21.10	21.20	22.10	22.90	22.00	22.40	22.90	23.40	25.70
31	18	1	1	A	1	18.40	17.30	18.10	17.70	17.30	18.00	17.30	17.00	17.00	17.80	17.10	16.00	15.30	14.50	13.80	13.30	13.50	13.80	13.20
32	18	1	2	B	1	9.92	9.97	10.10	10.10	10.30	9.94	9.94	10.00	10.10	10.20	10.00	9.65	9.47	9.76	8.67	8.99	9.24	9.02	9.44
33	19	1	1	A	1	7.44	7.59	7.51	7.00	6.51	7.45	6.91	6.81	6.67	6.74	6.41	6.72	7.28	6.70	6.56	6.37	6.72	6.72	8.93
34	19	1	2	B	1	11.50	11.40	11.50	11.90	11.30	10.70	10.80	11.50	10.80	11.10	11.00	10.70	11.30	10.50	10.20	10.80	10.50	10.70	11.00
35	20	2	1	B	1	8.08	9.13	8.06	8.87	9.15	9.21	9.05	9.23	8.95	9.33	8.37	8.58	7.91	8.52	8.14	8.88	9.13	9.53	14.40
36	20	2	2	A	1	14.40	13.80	14.10	14.20	14.80	14.10	13.90	13.30	14.10	13.60	13.30	14.40	13.30	14.20	11.40	11.70	12.30	13.40	40.40
37	21	1	1	A	1	14.90	15.00	14.70	15.10	16.20	16.10	14.60	14.10	15.90	17.00	15.90	15.60	15.70	16.60	14.10	13.20	17.30	16.00	14.80
38	21	1	2	B	1	22.30	21.80	21.80	23.00	21.50	21.70	20.10	20.00	23.40	21.40	21.90	19.90	19.20	18.00	19.70	20.70	21.10	21.50	21.60
39	22	2	1	B	1	9.19	9.30	8.53	8.02	8.01	7.64	7.66	8.08	8.07	7.54	7.57	7.37	7.09	7.82	6.93	6.72	7.02	6.80	7.75
40	22	2	2	A	1	22.80	23.30	23.20	23.20	21.30	21.00	23.60	20.40	20.90	21.10	20.00	19.90	19.50	17.40	15.70	16.50	13.80	15.00	14.80
41	23	1	1	A	1	23.90	24.70	24.90	25.50	24.80	26.10	26.40	26.50	25.80	25.60	25.10	24.70	24.40	24.80	21.20	23.10	21.40	22.60	23.30
42	23	1	2	B	1	17.30	17.10	17.70	17.80	19.00	17.70	18.90	17.60	18.20	17.80	17.80	17.50	16.60	18.50	17.90	16.20	17.40	20.80	53.70
43	24	2	1	B	1	8.13	8.28	7.76	7.99	7.27	8.01	7.97	8.20	8.23	8.20	8.82	7.92	7.33	7.30	7.18	6.30	6.70	6.79	7.11
44	24	2	2	A	1	13.50	13.30	13.30	13.20	13.20	12.80	12.80	13.20	13.30	13.30	12.80	13.00	12.10	12.70	12.70	11.30	11.40	13.50	14.50
45	25	1	1	A	1	9.38	8.87	8.87	8.30	8.31	8.31	8.94	8.51	8.34	8.87	9.01	8.03	7.83	7.08	6.57	6.58	7.37	8.18	8.18
46	25	1	2	B	1	14.60	14.30	14.40	13.70	13.90	14.10	14.60	14.30	13.20	14.30	13.90	13.60	12.70	12.50	10.90	11.20	12.40	13.00	11.90
47	26	2	1	B	1	15.00	14.90	14.40	14.90	15.70	16.40	15.30	15.50	14.60	15.10	15.90	15.20	13.20	14.00	13.70	13.70	13.60	13.50	14.60
48	26	2	2	A	1	26.30	25.70	24.40	24.10	26.00	26.50	26.40	25.50	26.40	26.40	26.60	26.20	23.80	26.20	24.90	26.00	25.20	24.90	25.40
49	27	2	1	B	1	15.30	14.80	15.20	14.60	14.80	15.80	15.30	17.10	16.00	15.70	14.70	14.00	15.90	14.00	12.50	13.40	14.20	16.20	16.40
50	27	2	2	A	1	15.80	15.20	13.80	16.60	14.80	16.30	16.70	16.10	16.70	18.20	15.90	13.80	17.50	17.80	14.70	16.30	17.30	17.00	16.40
51	28	1	1	A	1	8.88	8.75	8.92	9.55	9.78	9.42	9.04	10.00	9.47	10.20	11.40	9.79	11.20	11.50	10.90	9.75	9.85	10.00	11.40

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19
52	28	1	2	B	1	15.20	13.40	15.80	14.50	13.00	15.40	13.40	13.50	15.70	14.70	15.90	13.70	14.20	13.80	15.60	13.60	15.40	14.30	15.60
53	29	2	1	B	1	14.80	13.60	13.30	12.90	12.70	12.40	12.30	12.20	11.90	12.10	12.20	12.30	12.40	12.00	12.30	12.00	12.30	11.60	12.30
54	29	2	2	A	1	12.20	12.10	11.70	10.80	11.40	11.50	11.40	11.00	10.90	11.30	11.40	11.10	10.80	10.60	10.90	9.72	10.10	9.81	9.75
55	30	2	1	B	1	16.50	15.60	16.40	15.20	15.80	15.30	15.70	15.80	15.50	15.50	16.20	15.00	14.40	13.60	13.90	15.10	15.00	14.60	15.50
56	30	2	2	A	1	17.10	17.90	17.30	18.20	17.10	15.90	17.10	17.00	17.20	16.30	16.30	16.50	16.90	15.70	16.90	16.10	16.90	16.50	16.30
57	31	1	1	A	1	4.84	4.50	4.55	4.86	4.45	4.80	4.57	4.66	5.06	4.87	5.42	5.38	4.96	5.08	5.24	4.56	5.94	6.03	6.62
58	31	1	2	B	1	7.40	7.40	7.31	7.52	7.51	7.21	6.96	7.22	7.64	8.68	7.83	7.13	6.77	6.95	7.48	6.69	6.99	7.18	7.51
59	32	1	1	A	1	4.92	4.55	4.34	4.20	4.38	4.71	4.57	4.56	4.67	4.80	4.86	4.70	4.60	4.58	3.89	4.45	4.18	4.95	5.01
60	32	1	2	B	1	14.80	9.78	10.10	9.04	8.95	9.15	9.57	10.30	9.53	8.54	9.26	9.07	8.88	8.33	7.71	7.58	7.85	8.08	9.10
61	33	2	1	B	1	12.00	12.30	13.00	12.80	12.40	12.80	13.00	12.50	12.70	12.60	12.80	12.00	13.30	11.80	11.60	11.20	12.50	12.80	12.80
62	33	2	2	A	1	19.10	20.40	20.20	20.70	20.20	21.70	20.80	22.20	20.70	21.20	20.80	20.90	20.10	20.00	19.10	19.40	19.90	21.20	20.90
63	34	1	1	A	1	8.74	8.31	7.97	8.82	8.36	8.21	8.31	8.18	8.59	8.94	8.28	7.91	7.96	8.43	6.96	7.84	7.69	7.68	7.97
64	34	1	2	B	1	11.50	11.80	11.00	11.80	11.80	11.40	11.90	11.50	11.90	10.90	11.50	10.60	10.80	10.90	9.66	10.10	9.90	9.93	10.70
65	37	2	1	B	1	23.70	23.70	24.20	25.60	24.70	26.50	24.50	25.50	25.30	26.50	27.00	26.90	26.00	24.90	28.90	28.30	30.60	31.80	34.70
66	37	2	2	A	1	62.90	61.50	62.30	59.60	64.50	57.70	57.10	55.10	54.90	55.20	54.40	52.70	54.50	55.10	50.30	49.60	49.90	50.00	63.10
67	38	2	1	B	1	5.57	5.53	5.21	5.60	5.78	5.61	6.01	5.68	5.72	5.66	5.44	5.70	5.76	5.47	4.97	4.88	5.24	14.70	71.60
68	38	2	2	A	1	13.50	13.20	12.90	13.80	13.00	13.20	12.60	12.30	12.00	11.60	11.90	12.00	12.00	10.60	9.53	9.67	9.80	16.10	62.90
69	39	1	1	A	1	7.59	7.44	8.27	7.82	8.30	8.61	8.20	8.17	8.07	8.11	7.79	7.94	8.03	7.65	6.85	7.12	7.07	7.90	7.60
70	39	1	2	B	1	33.30	32.80	35.10	34.40	33.20	30.40	30.70	30.30	31.20	29.90	29.00	26.70	27.40	27.80	22.50	22.20	21.70	25.00	23.30
71	40	1	1	A	1	6.90	7.42	7.49	6.96	7.45	7.09	6.92	6.94	7.39	7.41	6.96	7.60	7.43	7.91	7.79	7.29	8.30	9.14	9.17
72	40	1	2	B	1	15.40	14.30	13.40	14.30	13.50	13.80	14.00	13.90	14.50	13.40	13.60	13.50	13.60	12.90	12.30	10.00	12.20	12.00	11.50
73	41	2	1	B	1	6.28	6.38	6.76	6.95	6.75	6.92	6.46	6.93	7.14	6.65	6.95	6.60	6.37	6.26	6.16	6.29	5.96	6.87	10.40
74	41	2	2	A	1	12.70	12.60	13.10	12.70	12.70	12.40	12.20	11.70	12.30	12.20	11.50	12.10	11.80	11.10	8.39	10.50	10.70	11.50	18.00
75	42	2	1	B	1	6.93	7.47	7.16	7.50	7.56	8.02	7.70	8.19	7.61	8.38	7.59	7.92	7.19	7.75	7.41	7.40	7.91	8.37	11.70
76	42	2	2	A	1	10.40	10.20	9.98	11.20	11.00	10.10	12.10	11.50	11.60	11.40	12.40	11.50	11.40	10.00	10.60	10.00	10.60	11.40	21.20
77	43	1	1	A	1	7.74	7.63	7.63	7.30	7.67	7.74	7.86	7.70	7.74	7.62	7.81	7.63	7.77	7.40	7.04	7.04	6.83	7.13	6.37

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19
78	43	1	2	B	1	9.79	10.10	9.91	10.20	10.10	9.97	10.10	9.48	9.87	9.78	10.10	10.10	9.60	10.50	9.62	8.64	10.30	10.20	13.10
79	44	1	1	A	1	3.87	3.95	4.08	3.85	4.04	4.34	4.11	4.55	4.39	4.38	4.37	4.28	4.30	4.18	3.81	4.23	4.33	4.61	4.72
80	44	1	2	B	1	11.10	9.86	9.15	9.18	9.38	9.32	9.58	9.29	9.31	9.50	9.58	9.74	9.61	9.30	8.39	8.92	8.66	10.30	11.00
81	45	1	1	A	1	4.45	4.93	4.29	4.90	4.86	4.78	5.14	4.98	4.71	4.87	4.89	5.23	5.08	4.95	4.98	5.10	5.19	5.69	5.77
82	45	1	2	B	1	11.40	10.90	9.89	10.80	10.40	10.70	10.30	11.00	10.00	10.40	11.00	10.00	10.40	9.87	9.20	9.03	9.79	10.20	11.90
83	46	2	1	B	1	11.00	11.90	12.30	10.80	12.10	10.60	11.40	11.60	11.60	11.60	11.40	11.10	10.30	10.80	9.96	9.95	10.00	11.00	9.67
84	46	2	2	A	1	11.20	11.00	11.50	9.68	10.70	10.10	10.80	11.80	10.60	10.20	9.60	10.00	9.32	9.62	10.40	10.30	9.12	10.50	10.10
85	47	1	1	A	1	16.90	18.30	18.10	17.10	17.00	18.50	17.20	17.40	17.90	16.30	18.30	15.70	16.70	15.60	14.50	14.90	15.90	21.60	34.40
86	47	1	2	B	1	24.00	25.40	24.40	24.00	24.70	23.40	22.60	24.10	24.30	24.60	24.30	21.30	21.90	21.70	18.70	19.50	21.00	43.60	85.00
87	48	2	1	B	1	7.30	6.78	7.26	7.87	8.03	7.47	8.62	7.41	7.59	7.42	7.34	7.68	7.09	7.76	6.57	6.96	6.94	10.90	11.60
88	48	2	2	A	1	9.43	9.46	9.18	8.82	9.02	9.69	9.59	9.45	9.85	9.65	9.11	8.93	9.12	8.96	7.89	7.78	8.04	8.46	8.51
89	49	1	1	A	1	7.38	7.63	8.00	6.47	7.18	7.20	6.91	6.57	7.14	6.72	7.96	7.26	6.55	6.67	7.17	6.84	7.83	7.14	7.24
90	49	1	2	B	1	5.76	5.99	5.85	5.70	6.07	6.89	7.33	5.71	6.31	6.52	6.77	6.63	6.46	6.79	6.35	6.48	7.02	6.72	22.90
91	50	1	1	A	1	9.15	9.42	10.10	9.71	9.06	10.40	9.77	8.62	9.47	10.10	9.72	9.67	9.60	9.45	9.56	9.81	10.70	12.30	11.70
92	50	1	2	B	1	14.50	14.40	14.10	13.40	13.70	15.40	14.60	13.90	15.20	13.90	14.20	13.40	14.10	14.60	14.50	13.90	14.10	14.40	14.00
93	51	2	1	B	1	4.96	5.14	5.04	5.39	5.24	5.30	5.20	5.16	5.22	5.15	5.40	5.36	5.55	5.26	5.68	5.98	6.29	6.76	6.82
94	51	2	2	A	1	10.20	9.81	9.58	9.87	9.59	9.57	9.96	9.61	9.72	9.92	9.88	9.15	10.20	9.67	9.49	9.75	9.96	10.00	10.60
95	52	2	1	B	1	10.70	10.80	10.70	11.20	10.60	10.90	11.10	11.60	11.40	10.90	10.70	10.90	11.00	11.20	10.50	10.90	11.00	10.90	10.30
96	52	2	2	A	1	13.10	13.40	13.80	13.70	15.00	16.00	15.60	15.30	15.80	16.90	15.80	14.90	14.90	15.90	14.30	15.10	15.50	16.80	16.80
97	53	2	1	B	1	6.74	6.85	7.09	6.89	7.11	7.06	7.09	7.36	7.40	7.15	7.14	6.87	7.01	7.25	6.93	6.98	7.51	8.12	8.65
98	53	2	2	A	1	4.04	17.00	17.90	17.40	18.60	19.40	18.10	17.90	28.00	27.40	18.30	19.30	16.10	16.20	16.60	18.60	20.40	49.70	142.00
99	54	1	1	A	1	2.39	2.38	2.40	2.44	2.57	2.70	2.60	2.63	2.58	2.71	2.78	2.56	2.60	2.58	2.59	2.61	2.79	2.85	3.01
100	54	1	2	B	1	16.20	3.67	4.11	4.12	4.02	4.21	3.81	3.83	4.02	3.86	3.78	3.60	3.75	3.78	4.16	3.90	3.73	3.98	4.14
101	55	2	1	B	1	4.24	4.02	3.99	4.26	4.12	4.05	4.16	4.17	4.33	4.22	4.11	4.18	4.24	4.44	3.93	4.19	4.23	11.00	16.20
102	55	2	2	A	1	7.52	7.29	7.60	7.48	7.71	7.07	7.59	7.68	7.81	7.83	7.62	6.83	6.67	6.08	6.18	6.14	6.59	17.70	18.70
103	56	1	1	A	1	9.72	9.29	10.10	9.81	10.30	10.20	10.30	10.30	10.50	10.70	11.30	10.60	10.40	10.90	10.40	9.65	10.50	10.50	11.00

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19
104	56	1	2	B	1	11.30	10.50	11.20	11.60	11.50	11.70	12.20	12.10	11.90	12.40	13.00	12.10	12.60	13.20	12.60	12.30	12.50	13.10	12.40
105	57	1	1	A	1	17.40	17.40	17.60	16.80	17.40	16.80	16.30	15.90	17.10	16.60	16.90	16.20	15.90	15.40	14.80	14.50	13.80	14.50	14.10
106	57	1	2	B	1	21.30	20.80	21.40	20.30	21.90	21.50	22.20	20.30	19.30	21.70	20.80	19.20	18.40	18.80	19.20	16.70	17.10	17.10	17.20
107	58	1	1	A	1	32.60	34.00	32.40	30.00	31.00	30.00	32.20	30.70	31.40	30.20	29.60	28.90	28.10	27.00	23.10	23.90	24.30	24.60	23.10
108	58	1	2	B	1	30.20	30.40	30.50	29.60	31.30	29.80	29.90	30.00	29.80	28.80	30.90	27.80	28.20	26.70	24.60	23.60	24.30	24.00	23.90
109	59	2	1	B	1	4.11	4.35	4.22	4.27	4.28	4.29	4.35	4.61	4.31	4.18	4.28	4.28	4.18	3.99	3.89	3.86	4.08	4.16	4.29
110	59	2	2	A	1	7.59	7.63	7.75	7.79	7.61	7.96	7.85	7.97	7.73	7.72	7.50	7.48	7.14	6.64	6.49	6.35	7.87	20.60	41.60
111	60	2	1	B	1	13.60	14.10	13.50	14.20	13.80	13.50	14.40	14.40	14.30	14.70	15.30	14.60	13.90	14.30	13.00	12.80	13.30	13.00	13.10
112	60	2	2	A	1	27.80	27.40	27.20	27.70	26.30	27.70	27.60	28.40	28.30	27.50	28.50	28.00	27.30	26.60	23.50	23.00	23.10	23.00	23.80
113	61	1	1	A	1	10.00	10.00	10.00	9.90	10.00	9.62	9.96	10.10	9.90	9.79	9.62	9.32	9.33	8.74	8.04	7.97	7.84	8.18	7.98
114	61	1	2	B	1	11.30	10.80	10.90	10.60	10.70	10.40	11.20	11.00	10.50	10.80	10.70	10.10	10.10	10.20	9.52	9.56	9.63	9.95	9.53
115	62	2	1	B	1	8.39	8.31	8.64	8.25	9.10	9.13	9.39	9.13	9.32	8.86	8.90	9.17	8.68	8.20	7.60	6.95	7.06	7.42	9.95
116	62	2	2	A	1	12.30	11.80	10.90	11.40	12.30	11.90	12.10	11.50	11.90	12.10	10.90	11.30	11.10	10.70	9.40	9.10	9.83	10.50	26.30
117	63	2	1	B	1	8.99	9.29	9.19	9.69	9.36	9.03	9.31	9.56	9.42	9.43	9.24	9.83	9.00	8.94	9.22	9.68	10.40	10.10	10.40
118	63	2	2	A	1	9.11	8.57	8.88	8.85	8.58	9.31	8.95	9.39	9.45	8.93	9.57	8.93	8.75	8.66	9.10	10.10	10.60	10.60	10.50
119	64	1	1	A	1	14.70	15.60	15.90	16.50	16.70	16.50	17.30	16.80	16.70	16.10	16.80	16.40	16.90	16.30	15.40	14.80	15.50	15.70	39.80
120	64	1	2	B	1	21.60	22.70	24.50	25.70	26.00	25.70	27.90	27.20	27.20	27.60	25.20	26.80	25.90	26.40	24.30	23.10	25.10	25.10	35.90
121	65	1	1	A	1	9.75	10.30	9.42	10.20	10.60	10.50	11.10	10.70	11.20	11.40	11.50	11.40	10.90	10.90	10.70	10.80	11.80	11.00	11.90
122	65	1	2	B	1	21.10	19.30	21.10	20.40	20.50	20.60	19.90	21.50	19.90	18.90	18.30	20.80	19.00	19.30	18.10	18.10	17.10	18.10	17.70
123	66	2	1	B	1	9.36	9.13	9.26	9.15	10.00	9.70	10.10	10.40	10.00	9.46	9.46	9.07	8.74	9.32	8.60	8.79	10.00	11.80	12.50
124	66	2	2	A	1	16.60	15.10	15.70	14.90	15.30	15.90	16.20	15.60	16.10	16.30	16.60	15.80	14.40	13.70	14.90	14.10	13.90	14.00	16.00
125	67	2	1	B	1	6.33	6.63	6.24	6.34	6.45	6.52	6.93	6.25	6.10	6.39	6.36	6.79	6.43	6.24	6.82	6.53	6.82	6.86	7.40
126	67	2	2	A	1	6.94	6.62	7.15	6.89	7.06	6.98	7.61	7.24	7.18	7.72	7.63	7.34	6.81	7.47	7.12	7.38	6.91	7.97	7.53
127	68	1	1	A	1	11.40	12.00	12.00	11.20	11.80	11.90	12.20	13.00	13.50	13.30	11.90	12.40	10.60	11.80	11.20	10.40	11.10	11.40	11.60
128	68	1	2	B	1	12.80	11.50	12.80	13.50	11.80	12.00	12.80	14.20	12.50	13.00	14.10	12.50	12.70	11.90	11.60	11.70	12.80	11.40	11.20
129	69	2	1	B	1	14.60	14.50	15.10	15.50	14.90	14.40	15.40	15.80	16.50	16.50	15.60	15.30	15.40	15.30	14.40	14.40	15.90	17.10	17.00

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19
130	69	2	2	A	1	13.10	13.50	13.10	14.70	14.70	14.40	14.90	14.30	15.10	15.20	15.10	13.90	14.50	14.50	13.40	13.60	13.70	14.80	14.80
131	70	2	1	B	1	11.80	12.40	12.40	13.10	14.60	13.80	13.40	13.90	15.00	13.70	14.30	14.20	14.10	13.80	13.10	12.60	13.70	14.20	15.40
132	70	2	2	A	1	11.40	11.60	10.80	11.00	11.60	12.30	12.00	10.80	11.90	11.90	11.60	11.60	10.90	11.10	10.60	10.40	11.90	43.20	59.30
133	71	1	1	A	1	23.10	23.80	22.10	24.80	22.90	24.10	24.80	23.20	22.50	21.90	20.80	20.90	21.30	20.10	17.60	16.20	17.40	17.20	18.00
134	71	1	2	B	1	12.50	15.00	15.90	16.00	16.20	16.80	15.60	16.70	17.10	16.30	13.60	14.80	15.50	15.60	12.70	14.20	15.20	15.60	16.00
135	72	1	1	A	1	17.80	17.20	17.90	17.50	17.60	17.60	16.60	17.30	16.70	16.10	17.20	15.20	15.80	15.80	14.80	13.80	14.70	14.80	19.40
136	72	1	2	B	1	22.20	22.20	23.30	24.60	23.30	22.10	22.90	23.30	23.80	22.50	23.30	23.20	21.30	20.90	21.30	21.70	22.60	22.20	21.80
137	73	1	1	A	1	6.85	6.85	6.52	6.90	7.07	7.47	7.08	7.21	6.95	6.85	6.93	6.86	6.48	6.67	6.01	6.38	6.73	6.91	6.85
138	73	1	2	B	1	11.20	11.50	11.70	11.30	11.50	11.70	11.70	11.30	11.30	11.60	11.00	11.30	9.84	10.50	10.10	10.20	10.90	10.60	40.30
139	74	2	1	B	1	7.05	6.85	7.02	6.99	7.45	6.88	7.24	7.06	7.19	7.26	7.48	6.71	6.44	6.63	6.21	6.01	5.94	6.19	6.74
140	74	2	2	A	1	21.30	20.30	19.30	19.40	19.20	19.90	18.00	18.10	18.10	17.90	18.40	17.20	16.10	15.70	15.50	14.20	13.30	13.30	18.30
141	75	1	1	A	1	7.26	7.58	7.33	7.60	7.57	7.64	8.50	7.59	8.22	7.61	7.51	7.44	8.08	7.59	7.16	7.23	8.08	8.55	9.78
142	75	1	2	B	1	11.60	12.10	12.10	11.60	11.70	12.90	13.00	12.10	11.70	12.20	11.00	10.70	12.10	10.90	9.80	10.30	10.10	10.80	27.90
143	77	1	1	A	1	9.06	9.61	9.40	9.85	9.64	9.43	9.78	9.90	9.66	9.45	9.28	9.34	9.11	9.04	8.48	8.87	9.51	9.84	10.40
144	77	1	2	B	1	10.80	10.60	10.90	10.40	10.50	10.50	11.00	10.30	10.20	9.86	10.30	10.20	10.70	9.80	9.87	10.10	10.60	10.60	10.50
145	78	2	1	B	1	14.30	13.50	14.10	13.50	14.50	15.30	14.50	15.80	14.30	13.90	12.60	12.50	14.00	13.50	11.80	12.80	12.30	12.90	13.20
146	78	2	2	A	1	12.70	13.50	13.60	15.20	13.70	13.80	12.90	15.50	15.50	15.80	14.90	14.60	14.80	15.80	13.10	13.10	13.40	14.50	15.50
147	79	1	1	A	1	6.21	6.66	7.00	8.30	7.83	8.94	8.87	9.64	8.69	9.55	7.96	7.53	8.66	8.71	8.06	9.07	10.90	11.60	12.10
148	79	1	2	B	1	13.20	12.00	13.50	15.30	13.90	14.80	15.30	15.00	16.20	15.70	15.50	6.89	15.70	17.80	13.70	13.90	17.30	18.80	19.70
149	80	2	1	B	1	4.31	4.56	4.41	4.60	4.40	4.70	5.00	4.54	4.40	4.45	4.56	4.49	4.68	4.47	4.06	4.09	4.30	4.43	4.55
150	80	2	2	A	1	7.53	7.58	6.90	6.83	6.81	6.71	6.43	6.93	6.65	7.57	6.93	6.92	6.85	6.52	6.79	6.65	6.65	6.07	6.51
151	81	1	1	A	1	8.01	7.58	7.63	8.02	8.14	8.96	9.08	8.42	9.19	8.54	8.31	8.10	8.93	8.14	7.39	6.56	7.44	6.95	8.01
152	81	1	2	B	1	14.10	13.90	14.80	14.90	14.80	16.20	14.90	15.30	15.30	15.30	13.70	14.10	13.90	12.70	12.00	12.20	12.70	13.00	13.40
153	82	2	1	B	1	10.70	11.10	11.20	10.20	10.20	10.60	10.00	10.40	10.40	10.00	10.50	10.00	9.91	10.20	9.81	9.30	9.40	16.00	13.10
154	82	2	2	A	1	5.38	9.42	9.90	9.66	10.10	10.80	11.20	10.80	11.30	11.00	10.80	9.83	9.80	9.99	9.78	10.00	10.20	10.50	9.98
155	83	2	1	B	1	8.86	8.58	8.84	8.82	8.83	8.56	8.47	8.89	9.01	9.16	8.46	8.62	8.13	7.83	8.22	7.57	7.80	8.35	8.12

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19
156	83	2	2	A	1	7.32	7.30	7.90	7.41	7.14	7.52	8.13	8.34	8.29	8.07	7.66	7.76	7.86	7.46	7.79	7.64	7.12	12.20	24.30
157	84	1	1	A	1	3.78	3.88	3.94	4.06	4.09	4.41	4.37	4.34	4.47	4.33	4.41	4.26	4.22	4.20	4.10	4.09	4.13	4.21	4.34
158	84	1	2	B	1	7.96	7.45	7.98	7.87	7.58	7.80	7.76	8.06	7.93	7.67	7.97	14.20	7.69	7.37	7.42	7.11	7.67	7.89	26.20
159	86	1	1	A	1	7.80	8.01	8.45	8.44	8.52	8.89	8.89	9.21	9.08	9.22	9.04	9.36	9.32	10.00	9.38	8.92	11.00	15.40	21.30
160	86	1	2	B	1	10.70	11.20	11.30	11.40	12.00	11.90	12.00	11.50	12.50	12.50	12.30	11.60	12.40	12.60	11.30	11.40	11.60	12.70	15.90

Obs	c20	c21	c22	c23	c24	c25	c26	c27	c28	c29	c30	c31	c32	c33	c34	KE_FIRST	KE_LAST	trt
1	28.00	125.00	146.00	101.00	75.40	74.2	76.4	78.0	67.7	63.8	55.3	54.8	57.2	53.1	50.30	30	33	2
2	48.00	84.50	126.00	112.00	86.50	81.1	85.2	85.6	82.6	75.1	66.0	67.0	64.8	63.0	55.70	30	33	1
3	9.42	26.80	55.00	44.90	33.20	32.0	30.5	38.9	32.8	31.2	25.9	23.3	23.1	21.2	19.10	30	33	1
4	105.00	123.00	102.00	57.30	44.20	42.5	36.7	40.0	35.0	34.7	27.3	25.6	26.3	23.9	20.20	30	33	2
5	21.90	68.30	88.10	70.60	53.80	49.3	45.5	44.8	35.5	34.4	32.9	27.7	26.9	25.8	22.90	30	33	2
6	34.20	81.00	112.00	124.00	111.00	91.0	71.8	56.8	48.4	45.1	39.8	34.4	32.8	29.4	26.00	30	33	1
7	25.40	111.00	145.00	133.00	117.00	101.0	84.3	68.4	55.9	51.5	41.3	41.0	42.4	36.2	31.50	30	33	1
8	15.50	18.60	41.70	87.70	114.00	137.0	145.0	160.0	139.0	117.0	83.4	49.6	50.0	44.6	39.20	30	33	2
9	25.50	57.40	120.00	124.00	87.40	61.4	51.3	49.6	47.1	40.0	39.0	33.4	34.6	29.7	27.50	30	33	2
10	25.10	63.30	117.00	147.00	127.00	98.3	69.2	67.2	51.1	54.4	46.6	39.6	39.0	35.6	33.90	30	33	1
11	48.70	90.30	58.60	36.70	37.10	36.4	34.6	37.8	32.8	30.9	26.7	24.8	23.3	22.3	20.00	30	33	1
12	68.40	128.00	91.80	38.90	36.70	35.0	34.9	37.4	32.7	29.1	25.0	21.8	22.3	19.9	19.70	30	33	2
13	48.60	111.00	111.00	83.60	68.10	46.5	45.5	44.0	39.8	38.3	33.4	32.8	32.3	29.5	24.50	30	33	2
14	104.00	139.00	135.00	117.00	91.50	76.8	58.2	59.6	53.7	46.5	41.1	42.8	39.7	34.8	29.30	30	33	1
15	16.40	94.10	76.00	50.00	41.40	41.1	41.2	41.1	41.9	36.4	31.6	31.7	31.5	29.1	27.60	30	33	1
16	55.40	110.00	103.00	64.60	50.20	39.3	41.5	42.9	38.5	37.5	33.4	33.0	29.2	26.6	25.40	30	33	2
17	30.70	121.00	127.00	98.70	61.30	42.3	41.5	40.0	30.0	31.9	28.5	24.6	29.1	24.3	20.00	30	33	2
18	17.80	74.60	93.70	72.40	59.90	49.1	46.3	42.4	37.4	38.8	29.8	31.8	31.1	31.4	30.40	30	33	1
19	23.40	67.60	65.10	67.40	63.30	72.0	51.8	58.6	48.1	44.8	40.3	37.9	31.6	31.9	30.00	30	33	1

Reference ID: 3227106

Obs	c20	c21	c22	c23	c24	c25	c26	c27	c28	c29	c30	c31	c32	c33	c34	KE_FIRST	KE_LAST	trt
20	77.70	85.50	91.70	88.80	84.00	64.3	67.2	65.1	55.6	41.4	49.1	40.2	35.7	33.3	30.40	30	33	2
21	46.90	108.00	93.40	63.60	51.50	41.0	43.8	44.2	39.8	36.0	28.3	31.0	30.5	28.6	27.30	30	33	1
22	41.40	128.00	102.00	77.60	57.80	52.1	47.3	47.1	44.1	49.8	35.2	33.4	32.5	31.0	31.00	30	33	2
23	9.11	12.70	40.80	41.90	47.80	50.4	45.3	71.4	54.5	55.3	39.5	40.6	39.6	33.6	34.50	30	33	2
24	12.90	14.40	15.20	41.20	61.90	98.6	76.3	68.2	60.4	48.5	44.8	46.4	42.6	37.2	38.50	30	33	1
25	17.80	46.50	77.70	70.00	56.00	49.2	48.8	53.7	48.0	45.0	43.9	39.4	37.3	36.4	33.10	30	33	2
26	29.80	37.60	34.50	33.80	28.40	32.9	55.2	99.1	66.2	51.6	47.7	39.8	39.8	42.9	42.00	30	33	1
27	21.80	103.00	80.60	58.60	53.70	37.6	37.6	46.9	34.4	32.9	30.5	25.5	23.7	23.5	23.60	30	33	1
28	34.20	122.00	128.00	101.00	75.80	56.4	49.7	60.2	52.4	43.9	38.8	37.0	38.2	33.6	30.80	30	33	2
29	27.60	53.60	66.70	59.30	57.80	51.0	48.4	50.2	47.5	44.9	42.9	40.4	43.9	37.6	36.10	30	33	2
30	42.80	98.10	87.80	68.20	54.90	58.1	54.7	55.6	53.1	50.7	52.1	42.1	43.0	40.3	38.00	30	33	1
31	18.00	61.00	64.40	41.70	44.30	40.8	44.7	43.1	44.0	38.0	39.4	34.6	35.4	31.3	28.30	30	33	1
32	9.71	65.10	65.90	38.50	32.90	30.9	32.7	32.7	31.9	27.9	27.8	24.9	27.9	24.5	22.30	30	33	2
33	18.90	98.30	106.00	80.40	48.70	39.3	34.7	41.4	37.4	32.6	29.8	31.0	29.6	27.3	25.20	30	33	1
34	11.90	108.00	147.00	115.00	67.90	43.9	40.3	37.2	37.9	33.7	31.5	30.3	31.2	26.9	26.20	30	33	2
35	47.40	97.10	91.90	66.30	46.70	38.4	34.7	43.6	38.1	38.5	32.6	30.5	32.2	26.3	26.30	30	33	2
36	73.30	112.00	89.20	66.30	47.00	44.9	40.7	50.2	41.8	40.7	31.5	31.7	31.1	28.7	27.00	30	33	1
37	15.20	22.00	34.00	25.10	20.90	31.9	38.6	70.4	46.1	46.2	37.8	38.3	36.8	35.4	36.30	30	33	1
38	22.20	104.00	99.60	64.50	49.20	43.9	42.3	47.2	40.1	39.0	36.3	36.8	40.3	37.0	33.50	30	33	2
39	23.50	60.60	66.80	42.40	34.70	32.2	28.2	35.1	33.4	32.0	25.6	25.6	21.7	20.2	21.80	30	33	2
40	16.30	51.00	54.30	52.50	43.30	39.0	37.4	40.6	37.9	38.2	30.3	28.4	31.0	25.2	23.60	30	33	1
41	19.80	48.20	60.50	59.60	70.30	78.9	58.2	59.5	56.2	51.0	45.8	43.0	46.7	38.6	35.50	30	33	1
42	70.90	85.50	87.90	96.90	85.60	74.7	66.5	59.2	52.6	49.8	44.0	41.7	42.1	37.8	33.70	30	33	2
43	7.14	22.30	84.40	61.00	39.50	37.8	35.1	38.1	33.7	32.3	29.2	25.3	26.3	23.6	21.70	30	33	2
44	13.60	46.40	65.70	47.70	35.40	38.3	36.6	57.9	44.1	41.8	37.0	31.3	31.3	29.5	26.60	30	33	1
45	10.10	9.20	60.60	57.60	31.50	35.7	44.3	43.9	41.2	37.4	33.2	32.1	29.8	25.7	23.70	30	33	1

Reference ID: 3227106

Obs	c20	c21	c22	c23	c24	c25	c26	c27	c28	c29	c30	c31	c32	c33	c34	KE_FIRST	KE_LAST	trt
46	37.90	114.00	72.50	53.20	45.20	41.2	43.4	43.2	40.3	36.3	34.0	35.1	34.1	31.7	30.00	30	33	2
47	18.00	56.20	81.90	82.30	62.70	65.7	53.4	57.2	53.9	51.6	51.8	48.0	50.9	46.3	43.00	30	33	2
48	26.80	84.30	124.00	136.00	103.00	90.1	73.4	71.4	58.9	65.4	59.4	57.8	61.9	54.5	48.50	30	33	1
49	25.00	58.50	65.60	45.70	43.00	57.3	60.6	67.0	60.1	57.2	46.3	43.5	46.2	38.9	38.10	30	33	2
50	19.00	72.70	101.00	92.00	76.50	74.0	74.6	72.1	65.9	53.6	51.0	43.9	48.8	40.4	40.10	30	33	1
51	12.90	18.60	25.20	22.60	22.60	22.6	22.0	44.2	42.1	39.6	36.8	35.9	42.7	39.4	41.30	30	33	1
52	15.80	18.30	21.70	35.20	62.70	73.6	59.2	74.9	71.1	68.7	61.2	59.5	65.5	53.1	48.10	30	33	2
53	19.10	107.00	122.00	78.20	57.30	49.2	46.8	44.9	42.2	41.5	41.3	35.7	35.2	34.3	30.80	30	33	2
54	14.80	129.00	136.00	81.00	48.80	43.2	38.8	35.9	35.7	30.6	32.6	28.2	27.6	26.9	25.20	30	33	1
55	33.50	90.70	110.00	59.30	51.00	45.5	43.3	50.2	45.1	40.3	37.4	38.6	36.7	35.3	34.40	30	33	2
56	25.90	106.00	114.00	66.50	54.70	49.6	51.7	54.7	50.2	43.1	47.5	41.9	39.6	36.5	35.90	30	33	1
57	9.03	30.90	19.60	21.60	26.50	30.3	34.3	42.2	36.3	30.3	26.9	26.0	27.1	23.4	24.50	30	33	1
58	8.06	26.30	35.40	26.90	27.40	32.0	31.9	39.8	34.0	30.4	29.6	25.1	27.0	22.9	20.80	30	33	2
59	6.74	8.29	8.08	7.09	7.29	24.8	44.0	35.6	37.4	34.4	33.8	30.8	32.7	28.1	24.60	30	33	1
60	18.80	33.70	33.00	26.80	25.20	25.5	52.8	66.1	51.0	44.2	36.9	38.9	37.2	33.0	29.00	30	33	2
61	15.30	54.30	97.20	71.10	45.10	38.0	36.2	37.3	36.9	35.6	27.7	28.5	26.9	24.0	23.20	30	33	2
62	30.90	120.00	139.00	105.00	82.10	67.8	60.2	54.1	51.4	46.2	43.1	38.1	35.2	33.7	30.10	30	33	1
63	8.70	24.40	46.80	41.50	59.00	48.8	40.7	47.1	44.7	41.4	39.8	36.7	38.1	34.7	32.40	30	33	1
64	11.50	41.40	63.30	49.50	37.40	39.9	42.0	46.5	43.0	39.2	38.7	34.7	31.2	30.7	30.60	30	33	2
65	62.00	128.00	217.00	224.00	215.00	217.0	226.0	218.0	187.0	136.0	112.0	98.4	85.1	75.9	63.40	30	33	2
66	120.00	233.00	283.00	308.00	279.00	270.0	237.0	249.0	237.0	201.0	127.0	97.6	87.4	74.6	73.00	30	33	1
67	89.20	118.00	113.00	93.00	81.00	70.3	56.2	53.6	42.6	37.6	28.2	24.6	25.1	22.8	22.20	30	33	2
68	99.60	127.00	127.00	109.00	82.50	67.8	60.2	56.5	49.7	42.3	35.0	33.1	32.3	27.5	25.00	30	33	1
69	21.60	87.50	97.20	74.90	46.60	45.2	38.3	45.5	35.4	39.0	31.6	32.0	29.3	26.8	24.50	30	33	1
70	22.50	58.60	70.50	61.50	66.50	58.6	53.3	60.1	53.9	51.8	41.8	38.0	37.1	37.9	32.90	30	33	2
71	8.56	39.60	31.90	23.80	31.90	67.4	63.0	73.1	56.7	46.9	45.8	42.5	42.0	38.0	34.10	30	33	1

Reference ID: 3227106

Obs	c20	c21	c22	c23	c24	c25	c26	c27	c28	c29	c30	c31	c32	c33	c34	KE_FIRST	KE_LAST	trt
72	34.90	54.30	43.70	32.70	34.80	39.0	58.6	62.3	55.0	52.3	45.9	44.9	42.3	36.1	35.20	30	33	2
73	17.80	82.70	46.50	31.10	28.40	27.8	28.6	32.6	26.9	27.6	25.1	24.4	22.6	21.6	20.30	30	33	2
74	19.70	91.20	85.30	46.70	40.90	36.3	35.8	43.5	36.5	34.8	32.3	29.3	27.5	24.8	23.70	30	33	1
75	22.10	118.00	114.00	65.00	54.60	45.0	47.5	46.3	43.4	37.3	36.0	33.6	33.0	30.6	29.80	30	33	2
76	45.00	93.60	124.00	79.80	60.30	55.0	55.9	54.8	50.8	50.6	44.2	39.7	40.1	35.8	34.60	30	33	1
77	8.11	62.40	60.70	41.80	44.10	43.5	43.4	59.8	43.5	42.9	34.9	30.5	27.2	25.5	23.50	30	33	1
78	21.80	123.00	106.00	56.50	42.00	36.4	35.6	41.9	36.8	34.0	30.8	27.1	24.6	23.0	21.50	30	33	2
79	27.00	77.70	67.40	45.90	46.40	43.0	37.4	46.7	43.1	40.9	30.8	30.6	31.0	26.3	24.70	30	33	1
80	47.40	86.30	67.80	44.20	44.70	46.8	41.9	47.1	42.8	38.3	34.6	30.8	29.5	26.0	22.80	30	33	2
81	5.90	15.90	22.30	28.50	43.20	40.9	43.0	51.7	47.3	38.2	35.1	32.1	30.5	25.8	24.10	30	33	1
82	26.60	75.60	69.70	44.90	43.80	44.6	42.0	45.2	36.2	37.5	35.9	28.3	32.1	25.1	23.40	30	33	2
83	13.80	103.00	78.10	52.40	38.50	36.7	31.6	32.1	36.1	30.6	30.4	26.7	26.5	23.1	23.40	30	33	2
84	29.20	111.00	95.60	73.40	54.40	55.3	46.7	42.0	41.0	34.6	30.6	30.1	27.9	29.3	23.50	30	33	1
85	64.70	147.00	103.00	69.60	54.80	48.3	47.3	50.2	45.5	41.8	25.3	35.1	35.8	32.5	30.60	30	33	1
86	121.00	185.00	126.00	90.70	67.80	62.2	56.3	58.8	56.5	46.1	45.8	42.3	40.0	37.2	33.40	30	33	2
87	27.90	104.00	87.10	54.80	48.40	41.3	39.3	39.0	36.0	37.2	36.6	31.3	30.5	28.1	25.40	30	33	2
88	30.10	108.00	72.30	50.00	44.40	42.5	41.6	39.6	39.8	39.3	36.5	29.0	29.8	29.1	27.40	30	33	1
89	7.78	70.30	51.90	34.80	30.40	30.0	32.0	32.5	30.3	25.7	24.3	23.8	22.4	19.9	18.10	30	33	1
90	47.20	79.80	53.50	42.70	38.10	37.1	33.1	34.0	29.6	26.1	25.0	23.6	20.7	18.1	17.60	30	33	2
91	11.00	11.60	12.50	13.70	13.40	15.8	29.1	50.6	49.5	42.2	37.8	32.2	35.6	35.1	35.60	30	33	1
92	13.90	22.40	25.20	23.60	25.40	34.4	43.3	62.4	52.7	52.3	39.8	40.5	39.6	39.0	31.40	30	33	2
93	7.16	19.00	24.80	25.80	30.30	41.2	49.0	53.7	47.5	42.9	32.6	32.4	30.6	27.1	25.20	30	33	2
94	44.10	77.50	57.60	50.40	47.30	52.6	50.9	49.8	47.4	44.3	36.9	34.4	31.3	29.1	25.00	30	33	1
95	10.70	42.00	43.30	38.30	47.00	51.8	53.5	59.0	57.5	55.4	50.4	46.8	43.1	38.5	37.40	30	33	2
96	33.00	75.60	106.00	93.90	81.10	67.9	69.6	67.3	73.3	62.2	54.3	51.6	52.9	45.0	43.50	30	33	1
97	9.79	43.90	85.20	93.50	86.20	80.6	56.7	47.6	45.3	41.5	35.1	36.2	36.9	34.5	30.80	30	33	2

Reference ID: 3227106

Obs	c20	c21	c22	c23	c24	c25	c26	c27	c28	c29	c30	c31	c32	c33	c34	KE_FIRST	KE_LAST	trt
98	45.30	124.00	105.00	83.10	67.00	70.1	64.9	63.2	65.7	62.3	52.4	50.9	52.0	48.2	43.20	30	33	1
99	2.88	7.15	18.30	33.90	44.40	43.2	35.5	41.0	45.3	40.2	36.9	34.6	35.4	29.7	26.60	30	33	1
100	4.51	7.97	9.37	10.90	18.70	24.5	24.4	52.2	39.4	39.9	33.4	31.3	33.1	30.7	27.10	30	33	2
101	15.30	35.50	39.90	32.80	31.00	28.6	28.0	32.0	26.5	25.8	24.0	21.8	20.2	18.1	17.80	30	33	2
102	22.30	28.30	20.90	18.90	16.60	16.0	15.8	15.6	13.7	13.8	13.9	12.7	11.4	10.8	9.92	30	33	1
103	11.10	24.70	61.20	65.80	54.60	42.0	41.4	48.5	42.5	36.8	32.9	28.2	29.1	28.6	24.40	30	33	1
104	13.40	25.60	53.90	59.80	54.00	53.5	48.3	56.6	46.0	43.1	38.5	37.8	38.5	33.2	29.30	30	33	2
105	17.50	62.50	73.20	60.20	48.90	42.4	36.8	45.8	41.7	39.6	35.6	33.8	33.8	31.7	30.70	30	33	1
106	24.70	59.10	55.30	61.80	56.50	56.7	52.7	57.2	47.7	51.3	44.3	42.3	39.8	38.0	35.40	30	33	2
107	36.20	66.30	66.10	55.90	51.00	57.7	57.0	61.9	57.5	53.5	47.5	48.8	46.2	41.1	41.00	30	33	1
108	42.90	74.70	78.60	61.50	56.80	55.1	54.1	59.2	55.4	53.7	49.5	45.3	42.7	40.2	35.90	30	33	2
109	11.30	113.00	91.60	51.60	34.10	28.7	27.3	28.1	25.8	21.9	20.1	18.8	17.4	15.8	14.60	30	33	2
110	43.40	89.80	78.10	45.30	33.70	29.9	28.4	30.1	27.1	24.5	20.9	21.0	20.2	17.8	16.60	30	33	1
111	13.70	19.00	41.80	42.70	40.20	48.2	52.1	69.7	55.9	52.8	44.8	41.4	40.5	39.8	39.50	30	33	2
112	23.70	29.00	53.90	56.70	51.00	50.0	53.7	79.9	67.8	66.2	56.6	51.4	49.9	51.0	48.80	30	33	1
113	8.83	29.80	35.50	51.20	76.90	79.9	66.3	88.2	52.7	45.6	43.4	40.5	40.9	35.2	30.80	30	33	1
114	9.40	36.60	53.10	59.80	53.20	51.6	44.2	42.8	40.7	35.5	35.3	31.7	32.1	28.0	25.00	30	33	2
115	46.90	128.00	181.00	176.00	149.00	126.0	92.6	56.5	57.1	51.3	40.7	37.5	39.8	35.1	31.00	30	33	2
116	65.80	182.00	276.00	262.00	222.00	206.0	165.0	114.0	82.1	59.6	50.3	45.1	46.7	41.6	38.00	30	33	1
117	9.73	21.00	29.40	24.70	24.90	29.9	50.9	49.5	43.7	41.7	37.2	36.6	35.7	33.4	29.70	30	33	2
118	10.40	10.90	11.00	10.90	11.50	11.7	12.9	46.8	37.6	41.8	39.2	35.8	36.0	32.6	29.50	30	33	1
119	96.60	145.00	112.00	99.60	82.60	66.7	57.4	52.2	47.0	46.3	37.9	36.9	39.2	33.0	30.00	30	33	1
120	57.90	138.00	142.00	125.00	116.00	103.0	85.9	78.3	72.9	66.6	56.9	50.3	60.6	53.2	47.20	30	33	2
121	12.60	13.50	15.60	26.20	73.80	74.0	56.3	63.1	58.7	57.4	44.7	46.4	45.0	43.0	37.10	30	33	1
122	17.70	36.10	63.20	111.00	117.00	97.4	73.7	59.1	58.9	50.7	45.6	44.7	46.4	42.0	36.40	30	33	2
123	15.80	38.50	39.00	34.60	30.40	33.2	54.1	54.0	41.4	39.0	52.8	41.2	43.2	38.6	35.70	30	33	2

Reference ID: 3227106

Obs	c20	c21	c22	c23	c24	c25	c26	c27	c28	c29	c30	c31	c32	c33	c34	KE_FIRST	KE_LAST	trt
124	34.10	66.30	54.50	44.50	38.00	45.8	74.0	81.5	67.7	62.0	54.5	50.9	49.5	47.3	41.50	30	33	1
125	7.71	30.20	29.60	29.60	24.20	30.3	33.4	49.2	40.6	41.6	32.5	28.9	29.9	27.4	24.20	30	33	2
126	7.83	7.62	10.70	22.40	33.50	42.1	41.4	45.7	45.3	42.1	37.6	37.0	32.2	31.5	26.80	30	33	1
127	12.90	36.60	91.60	46.50	37.20	36.0	43.1	65.8	51.6	49.8	37.2	44.7	44.1	40.5	36.30	30	33	1
128	11.90	27.30	44.50	33.90	30.00	31.9	59.3	64.6	46.4	46.3	41.4	39.7	37.6	37.0	32.90	30	33	2
129	18.40	72.00	60.80	58.00	52.60	47.7	44.3	47.2	44.4	41.6	38.2	36.2	35.3	33.3	30.50	30	33	2
130	13.50	24.20	37.60	24.70	27.60	29.8	61.4	63.6	53.6	50.2	48.8	42.0	41.4	35.5	34.20	30	33	1
131	25.10	84.90	104.00	66.90	63.00	71.2	88.6	88.4	90.8	81.2	67.8	69.0	72.5	57.6	48.80	30	33	2
132	61.20	59.30	49.00	38.40	39.40	42.6	42.3	41.6	40.6	34.9	39.9	35.2	37.9	31.8	31.70	30	33	1
133	36.30	115.00	117.00	93.80	71.60	55.6	52.8	49.1	47.3	41.8	41.5	37.5	39.2	36.1	33.80	30	33	1
134	30.70	114.00	147.00	115.00	81.50	72.1	63.2	63.1	54.1	47.7	41.6	41.4	42.3	35.9	34.10	30	33	2
135	53.30	110.00	82.20	67.30	54.90	47.5	43.9	43.5	41.9	39.2	32.2	35.0	32.7	31.3	27.80	30	33	1
136	57.50	114.00	93.20	69.00	57.50	51.7	53.8	52.0	55.9	48.6	39.2	41.4	41.3	35.0	35.50	30	33	2
137	7.09	18.80	21.10	33.30	36.30	34.5	31.6	44.0	35.8	32.3	27.1	27.1	27.3	24.4	21.30	30	33	1
138	39.90	51.50	61.60	53.90	44.20	38.9	37.4	42.0	36.8	35.0	32.5	29.6	27.3	24.1	22.00	30	33	2
139	9.16	83.00	70.90	35.90	27.60	25.5	25.1	29.1	26.2	24.2	22.2	20.5	20.1	19.0	17.80	30	33	2
140	23.40	75.30	61.00	42.10	38.20	37.8	39.1	41.8	39.3	39.8	34.6	31.8	30.0	28.3	27.10	30	33	1
141	26.20	74.00	77.90	55.50	49.00	43.8	39.2	46.1	42.8	40.6	36.1	33.1	34.2	27.1	25.90	30	33	1
142	71.50	110.00	72.40	50.30	48.40	46.5	44.2	45.0	44.7	40.9	34.6	34.1	33.7	29.5	27.90	30	33	2
143	12.00	55.00	70.10	72.60	71.70	58.7	50.2	45.4	44.0	37.9	33.8	31.3	34.1	30.2	28.20	30	33	1
144	11.30	48.50	60.50	59.00	67.40	58.4	43.0	37.4	38.6	36.2	30.8	29.3	30.8	27.7	27.70	30	33	2
145	17.90	42.90	61.10	64.90	71.90	76.3	50.7	58.7	49.6	43.9	39.1	38.7	38.8	33.8	31.80	30	33	2
146	15.40	41.40	104.00	92.70	74.10	58.0	58.2	61.4	55.4	46.5	45.2	46.6	41.2	37.1	36.30	30	33	1
147	14.10	60.90	77.60	73.00	42.60	63.5	82.6	77.8	67.0	48.6	41.0	38.0	47.4	41.2	34.50	30	33	1
148	20.50	52.20	92.40	92.40	75.50	74.6	63.4	89.8	76.1	62.5	43.1	41.6	48.6	44.2	43.70	30	33	2
149	9.99	34.40	40.70	33.60	60.20	41.0	37.7	35.6	32.7	30.3	28.5	23.5	25.3	21.8	20.10	30	33	2

Reference ID: 3227106

Obs	c20	c21	c22	c23	c24	c25	c26	c27	c28	c29	c30	c31	c32	c33	c34	KE_FIRST	KE_LAST	trt
150	12.50	72.80	55.70	29.50	34.80	37.7	34.7	38.2	35.6	31.8	30.4	27.2	25.5	22.5	20.10	30	33	1
151	9.99	54.80	71.20	63.50	77.10	62.9	46.8	48.1	44.6	42.4	35.5	35.8	40.1	33.3	32.60	30	33	1
152	19.10	67.40	93.30	82.30	75.10	61.7	60.5	53.2	52.8	46.4	42.0	38.6	40.7	36.2	34.20	30	33	2
153	29.00	113.00	80.10	45.40	36.50	33.7	31.2	34.4	30.4	28.2	24.2	23.0	22.6	21.5	20.20	30	33	2
154	13.70	85.30	96.30	73.00	47.40	40.6	34.4	41.1	34.4	34.4	30.7	29.3	27.9	26.2	24.10	30	33	1
155	8.44	26.20	47.20	49.70	54.80	45.6	39.6	38.3	36.2	32.0	26.3	24.1	25.1	22.9	21.00	30	33	2
156	45.40	84.40	77.40	54.90	49.60	41.0	36.5	35.1	33.8	29.3	24.5	22.4	23.1	19.9	18.40	30	33	1
157	6.61	79.20	70.50	54.90	35.20	35.6	39.5	41.8	34.6	31.9	30.1	25.9	26.7	22.3	21.30	30	33	1
158	39.80	82.20	71.80	48.00	49.40	55.4	43.9	53.7	46.6	39.8	37.7	31.7	31.8	26.5	26.60	30	33	2
159	19.90	67.50	120.00	123.00	99.30	82.3	63.9	60.0	53.4	41.7	30.3	33.9	36.8	32.6	29.50	30	33	1
160	24.00	69.70	135.00	110.00	78.50	68.0	56.8	64.6	51.5	47.6	40.2	38.5	39.8	33.2	30.40	30	33	2

FED CONCENTRATION DATASET (TOTAL EPA): BASELINE-ADJUSTED

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
1	1	2	1	B	1	0.60	1.90	1.50	0.70	4.40	102.10	123.50	78.70	51.90	51.00	53.10	55.10	44.40	41.50	34.60
2	1	2	2	A	1	0.00	0.00	0.00	0.00	0.00	32.70	73.20	59.50	31.60	27.80	32.80	37.10	31.90	28.00	21.90
3	2	1	1	A	1	0.00	0.00	0.04	0.77	0.38	17.61	46.17	36.19	24.41	23.38	21.63	30.42	24.47	23.07	18.34
4	2	1	2	B	1	0.35	0.36	9.20	65.70	96.30	114.33	93.02	48.34	35.01	32.60	27.50	30.42	25.04	24.89	17.86
5	3	2	1	B	1	0.00	0.00	0.33	2.10	14.20	59.85	79.65	62.12	45.06	40.26	36.45	36.32	27.33	26.24	24.79
6	3	2	2	A	1	0.00	0.00	0.00	6.10	22.80	70.00	101.00	113.40	99.40	79.40	60.00	45.20	36.80	34.00	29.50
7	4	1	1	A	1	0.00	0.00	0.00	0.00	8.30	94.00	128.30	115.60	101.00	85.70	69.20	53.10	40.80	36.80	27.50
8	4	1	2	B	1	0.00	0.00	0.00	0.00	0.00	0.00	23.20	69.70	96.80	119.40	126.70	143.10	122.80	100.30	67.10
9	5	2	1	B	1	0.00	0.00	0.00	0.00	10.40	41.90	103.10	107.30	70.10	45.10	35.20	34.00	30.30	23.60	24.90
10	5	2	2	A	1	0.00	1.60	2.40	5.60	8.00	47.50	99.80	130.20	110.00	81.10	52.00	50.70	35.20	38.90	30.90
11	6	1	1	A	1	0.00	0.74	5.76	16.28	45.08	86.17	54.72	32.96	33.35	32.62	30.95	34.43	29.09	27.18	23.40

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
12	6	1	2	B	1	0.00	0.00	3.75	5.75	63.57	123.36	86.99	34.32	32.25	30.46	30.11	32.54	28.39	24.80	21.08
13	7	2	1	B	1	0.00	0.31	10.82	20.59	42.63	104.76	104.81	76.72	62.22	40.67	39.90	38.25	33.65	32.47	28.49
14	7	2	2	A	1	0.00	0.00	18.00	79.80	90.80	126.10	122.50	104.20	79.40	61.70	47.70	48.80	40.90	34.10	30.50
15	8	1	1	A	1	0.00	0.00	0.00	0.00	1.70	79.90	61.80	35.50	26.20	27.90	28.40	27.20	29.00	24.10	19.20
16	8	1	2	B	1	0.70	1.70	18.30	22.00	43.10	98.40	90.30	52.00	38.30	28.00	24.30	31.10	26.90	25.90	23.44
17	9	2	1	B	1	1.30	1.60	2.95	4.87	19.40	108.20	115.50	86.80	48.20	29.40	29.10	29.00	18.70	18.80	16.90
18	9	2	2	A	1	0.00	1.40	3.30	0.00	2.80	57.90	75.80	55.00	44.20	33.90	33.90	27.50	22.50	23.80	15.80
19	10	1	1	A	1	0.00	0.56	0.11	3.38	17.31	62.13	58.74	61.38	57.07	66.54	45.36	52.19	41.95	39.30	33.78
20	10	1	2	B	1	0.00	0.70	0.10	55.50	65.00	71.80	79.40	75.30	68.80	51.60	54.00	50.90	42.80	25.30	34.80
21	11	1	1	A	1	0.00	0.00	0.00	6.30	34.00	96.20	80.80	51.80	38.40	29.40	32.20	32.80	26.30	24.80	17.40
22	11	1	2	B	1	0.00	0.00	0.00	3.60	27.80	114.70	87.00	65.00	42.70	39.40	32.80	32.50	30.40	35.90	22.70
23	12	2	1	B	1	0.82	1.34	0.67	2.71	0.90	4.24	32.19	33.43	38.27	41.75	37.02	64.10	45.04	47.51	31.83
24	12	2	2	A	1	1.10	1.70	1.00	0.00	0.00	0.00	0.00	27.50	47.70	87.00	62.20	54.60	46.20	34.60	31.10
25	13	2	1	B	1	0.00	0.00	0.00	0.00	0.00	26.10	56.70	50.30	34.90	30.70	26.80	35.00	27.60	26.80	27.10
26	13	2	2	A	1	0.60	0.00	0.00	4.80	10.30	17.90	11.80	14.50	8.50	13.80	32.20	78.50	44.20	32.00	27.40
27	16	1	1	A	1	0.00	1.07	1.44	2.34	14.67	94.70	72.01	50.54	45.60	28.45	30.35	37.61	25.97	23.89	22.79
28	16	1	2	B	1	0.00	0.30	0.00	1.30	8.40	95.70	102.70	71.70	50.10	30.80	24.20	32.70	28.20	18.40	16.30
29	17	2	1	B	1	0.00	0.60	0.50	0.50	10.30	36.80	49.80	42.80	40.10	34.80	31.50	33.50	31.90	29.70	28.40
30	17	2	2	A	1	3.50	4.30	4.90	5.10	21.90	77.20	67.40	47.80	33.70	35.80	33.60	34.40	31.00	27.80	30.10
31	18	1	1	A	1	0.00	0.00	0.00	0.00	0.70	43.00	47.10	24.70	27.30	23.00	27.60	27.10	28.70	23.50	25.60
32	18	1	2	B	1	0.00	0.00	0.00	0.00	0.00	55.16	55.96	28.50	22.80	20.70	22.70	23.05	22.43	18.14	19.13
33	19	1	1	A	1	0.00	0.00	0.00	1.93	12.39	90.85	99.09	73.59	42.03	32.56	28.29	34.68	30.12	25.90	23.24
34	19	1	2	B	1	0.00	0.00	0.00	0.00	0.60	97.30	136.20	103.50	57.10	32.80	29.30	26.50	26.60	23.20	21.30
35	20	2	1	B	1	0.80	0.00	1.47	5.53	38.25	87.89	82.85	57.07	37.75	29.07	26.33	35.02	30.19	29.98	24.46
36	20	2	2	A	1	0.00	0.00	0.00	26.20	58.50	97.90	75.30	53.00	32.90	31.30	27.40	35.80	28.50	26.50	20.10
37	21	1	1	A	1	0.00	2.30	1.30	0.00	0.00	5.90	19.40	11.00	5.00	14.90	22.70	54.80	30.40	29.60	23.70

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
38	21	1	2	B	1	0.00	0.00	0.00	0.00	0.70	82.30	79.50	44.50	25.80	22.50	20.40	27.30	20.90	21.00	16.60
39	22	2	1	B	1	0.00	0.00	0.00	0.00	15.49	52.96	59.14	34.32	26.63	24.66	20.63	27.73	26.31	24.18	18.67
40	22	2	2	A	1	0.00	0.00	0.00	0.00	0.00	30.00	30.70	32.10	22.40	17.90	17.40	20.70	18.40	20.80	14.60
41	23	1	1	A	1	0.00	0.00	0.00	0.00	0.00	22.10	34.10	33.10	44.50	53.30	33.10	34.80	31.80	26.20	24.60
42	23	1	2	B	1	0.00	0.30	3.10	35.90	51.90	67.80	69.00	79.30	67.40	56.90	48.70	41.70	36.00	31.30	26.10
43	24	2	1	B	1	0.00	0.00	0.00	0.00	0.00	14.29	76.43	52.80	31.27	29.60	26.28	30.18	26.37	25.00	22.02
44	24	2	2	A	1	0.00	0.00	0.20	1.30	0.40	33.60	52.90	34.50	22.10	25.00	23.80	44.90	32.00	29.10	24.30
45	25	1	1	A	1	0.00	0.00	0.00	0.00	1.79	0.89	51.66	49.09	23.16	26.83	35.29	35.87	33.37	30.32	26.63
46	25	1	2	B	1	0.00	0.00	0.00	0.00	24.00	99.90	57.90	38.90	32.00	26.90	29.50	29.60	27.60	23.80	23.10
47	26	2	1	B	1	0.00	0.00	0.00	0.00	2.30	39.80	66.60	66.80	48.10	50.60	37.50	42.00	40.70	37.60	38.10
48	26	2	2	A	1	0.00	0.00	0.50	1.30	0.80	57.80	97.60	110.50	76.60	63.70	46.80	45.20	35.10	39.20	34.50
49	27	2	1	B	1	0.00	0.00	1.00	1.80	10.20	42.70	50.30	28.60	27.00	41.60	45.90	53.00	44.20	43.20	33.80
50	27	2	2	A	1	0.50	2.10	3.20	0.00	4.20	56.40	84.30	75.90	59.80	55.80	58.70	58.30	48.40	35.80	36.30
51	28	1	1	A	1	0.87	1.10	1.08	1.85	3.12	9.18	16.16	12.60	13.13	12.40	10.60	34.41	30.90	28.10	25.90
52	28	1	2	B	1	0.00	2.00	0.00	1.10	2.80	2.90	8.30	21.70	47.00	58.90	43.30	61.20	56.90	54.90	45.60
53	29	2	1	B	1	0.00	0.00	0.00	0.00	6.40	94.60	109.70	66.00	45.40	37.10	34.60	32.60	29.80	29.50	29.00
54	29	2	2	A	1	0.00	0.00	0.00	0.00	3.40	117.50	124.60	70.00	37.90	31.90	27.40	24.80	24.90	20.00	21.70
55	30	2	1	B	1	0.00	0.00	0.00	0.30	17.70	75.40	94.30	43.50	35.50	30.00	27.10	35.20	30.70	26.70	23.50
56	30	2	2	A	1	0.00	0.00	0.00	0.00	8.80	90.10	96.90	49.50	37.50	33.30	35.40	38.20	33.30	27.40	30.60
57	31	1	1	A	1	0.00	1.44	1.48	1.76	4.58	26.10	15.03	16.94	21.44	25.43	28.88	36.82	31.34	25.22	21.66
58	31	1	2	B	1	0.00	0.00	0.00	0.00	0.55	19.09	28.44	19.68	19.76	23.32	24.07	32.67	27.23	23.45	22.12
59	32	1	1	A	1	0.00	0.00	0.61	0.81	2.36	3.58	3.51	2.53	2.62	20.00	39.14	30.90	32.80	29.82	29.91
60	32	1	2	B	1	0.00	0.00	0.00	0.06	9.85	24.55	23.43	16.50	15.67	16.96	43.54	57.03	42.12	35.87	29.19
61	33	2	1	B	1	0.00	0.20	0.00	0.00	2.90	41.50	84.20	58.60	32.40	25.40	23.40	25.30	23.60	23.80	16.10
62	33	2	2	A	1	0.30	0.00	1.00	0.20	10.70	98.30	118.20	82.80	61.40	46.60	39.40	33.20	31.30	26.20	24.00
63	34	1	1	A	1	0.00	0.00	0.00	0.00	0.34	16.19	38.49	33.32	50.41	39.86	32.42	39.19	36.74	32.97	32.84

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
64	34	1	2	B	1	0.00	0.00	0.00	0.00	0.00	30.00	51.40	38.00	25.50	29.00	30.50	35.90	32.20	28.30	29.04
65	37	2	1	B	1	4.60	6.90	7.60	9.10	37.30	101.50	192.50	198.50	189.70	190.50	199.00	191.10	161.00	111.10	83.10
66	37	2	2	A	1	0.00	0.00	0.00	3.50	55.50	175.30	225.90	252.90	224.10	214.80	182.60	196.30	182.50	145.90	76.70
67	38	2	1	B	1	0.00	0.00	9.49	66.00	83.42	112.39	106.99	87.32	75.28	64.64	50.76	47.90	36.84	32.13	23.23
68	38	2	2	A	1	0.00	0.00	3.20	49.10	86.60	113.80	114.40	96.70	70.50	56.20	48.30	44.50	37.70	31.70	25.47
69	39	1	1	A	1	0.00	0.00	0.00	0.00	13.30	78.89	89.00	66.73	38.53	37.09	30.51	37.56	27.37	31.35	24.75
70	39	1	2	B	1	0.00	0.00	0.00	0.00	0.00	28.20	39.80	31.20	35.30	28.70	24.30	33.40	26.50	24.00	19.30
71	40	1	1	A	1	0.39	0.88	1.65	2.21	1.11	32.51	24.98	16.86	24.51	59.99	56.04	65.50	49.27	38.99	38.01
72	40	1	2	B	1	0.00	0.00	0.00	0.00	21.40	40.50	29.70	18.80	20.30	25.60	45.00	48.80	41.40	39.40	33.60
73	41	2	1	B	1	0.01	0.00	0.11	3.45	11.05	75.78	40.04	24.17	21.26	21.15	21.65	26.00	20.53	21.34	18.94
74	41	2	2	A	1	0.00	0.00	0.00	5.30	7.00	78.80	73.10	35.00	28.60	24.10	24.30	31.40	24.70	23.70	23.91
75	42	2	1	B	1	0.47	0.44	1.21	4.20	14.54	109.98	106.30	56.81	46.99	36.62	39.91	38.38	36.21	29.55	28.59
76	42	2	2	A	1	0.00	0.40	1.42	10.00	34.00	83.50	111.90	68.30	48.70	43.60	43.50	43.30	39.40	40.60	33.60
77	43	1	1	A	1	0.00	0.00	0.00	0.00	0.44	54.66	52.84	34.10	36.36	35.88	35.59	52.17	35.73	35.50	27.86
78	43	1	2	B	1	0.00	0.20	0.29	2.90	11.70	113.03	95.90	47.02	32.13	26.62	25.50	31.80	27.20	23.50	21.18
79	44	1	1	A	1	0.36	0.38	0.53	0.87	22.96	73.36	63.29	41.35	42.01	38.62	33.03	42.42	38.80	36.72	26.99
80	44	1	2	B	1	0.00	0.00	1.15	1.82	38.02	76.98	58.22	34.91	35.39	37.30	32.32	37.36	33.19	29.00	26.21
81	45	1	1	A	1	0.65	0.26	1.40	0.87	1.04	11.12	17.16	23.52	38.49	36.03	38.11	46.47	42.22	33.25	30.12
82	45	1	2	B	1	0.00	0.00	0.31	1.10	16.20	64.90	59.40	33.90	33.80	34.20	31.00	35.20	25.80	27.63	26.70
83	46	2	1	B	1	0.00	0.00	0.00	0.00	1.70	92.40	66.70	40.80	26.90	25.10	20.20	21.00	25.80	19.80	20.44
84	46	2	2	A	1	0.00	0.00	0.00	0.42	18.50	100.90	84.80	61.60	43.80	45.10	37.10	32.00	31.68	24.98	20.20
85	47	1	1	A	1	0.00	0.00	3.50	17.30	47.70	128.50	85.80	52.20	36.90	32.00	29.00	34.50	28.80	26.20	10.80
86	47	1	2	B	1	0.00	0.00	19.20	61.00	96.30	161.60	103.40	66.60	43.50	37.60	32.00	37.50	34.60	24.40	27.10
87	48	2	1	B	1	0.00	0.16	3.64	3.73	19.87	96.53	78.48	47.39	40.81	33.88	31.96	31.32	28.91	29.44	30.03
88	48	2	2	A	1	0.00	0.00	0.00	0.00	21.08	98.31	62.71	40.55	34.55	32.85	32.49	30.67	30.68	30.34	28.61
89	49	1	1	A	1	0.00	0.20	0.00	0.77	0.60	63.10	44.99	28.23	23.26	23.28	24.04	25.24	23.75	19.03	17.13

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
90	49	1	2	B	1	0.72	1.03	0.87	17.20	41.13	72.91	46.17	36.99	31.79	30.58	26.33	27.37	23.14	19.31	18.65
91	50	1	1	A	1	0.66	1.28	2.20	1.99	1.94	1.20	2.73	5.08	3.93	5.70	19.38	40.93	39.90	32.75	28.24
92	50	1	2	B	1	0.00	0.00	0.30	0.60	0.20	7.00	10.60	9.70	10.20	20.50	29.10	49.00	38.60	37.70	25.30
93	51	2	1	B	1	1.02	1.15	1.72	1.43	1.92	13.70	19.60	20.64	25.08	36.05	43.60	48.34	41.95	37.64	26.92
94	51	2	2	A	1	0.00	0.15	0.42	0.73	34.51	67.93	47.64	40.79	37.58	42.68	41.02	40.65	37.20	34.63	27.41
95	52	2	1	B	1	0.20	0.20	0.20	0.00	0.10	31.10	32.20	26.70	35.60	40.90	42.80	48.10	46.50	44.20	39.90
96	52	2	2	A	1	2.00	2.10	3.00	3.10	18.00	59.60	90.40	78.60	65.30	51.00	53.80	52.40	58.40	46.30	40.00
97	53	2	1	B	1	0.24	0.66	1.03	1.76	2.68	36.84	78.11	86.14	78.80	73.45	49.56	40.73	38.29	34.25	28.17
98	53	2	2	A	1	14.56	3.40	31.80	124.60	26.70	104.60	86.90	65.20	39.00	42.70	46.60	43.90	49.60	46.10	35.80
99	54	1	1	A	1	0.22	0.41	0.45	0.57	0.31	4.45	15.70	31.27	41.82	40.49	32.72	38.44	42.70	37.62	34.31
100	54	1	2	B	1	0.00	0.06	0.00	0.02	0.49	3.76	5.56	7.07	14.68	20.64	20.62	48.60	35.65	36.12	29.24
101	55	2	1	B	1	0.00	0.21	7.01	11.94	11.18	31.45	35.74	28.63	26.67	24.38	23.89	27.82	22.26	21.36	20.07
102	55	2	2	A	1	0.00	0.00	10.10	11.22	14.59	21.23	13.31	11.22	8.79	8.17	8.18	8.77	7.03	7.72	7.72
103	56	1	1	A	1	0.00	1.21	0.40	1.19	0.80	14.50	50.90	55.50	44.10	31.30	30.10	37.90	32.10	25.90	22.50
104	56	1	2	B	1	1.00	2.00	1.90	0.80	1.90	13.90	41.70	47.70	42.10	41.10	35.30	44.50	33.40	29.90	25.90
105	57	1	1	A	1	0.00	0.00	0.00	0.00	0.10	45.70	56.90	44.30	31.80	25.80	19.90	29.60	25.80	24.20	20.80
106	57	1	2	B	1	0.00	0.00	0.00	0.00	2.80	37.60	33.10	41.50	37.20	35.00	31.90	38.00	29.30	32.50	25.10
107	58	1	1	A	1	0.00	0.00	0.00	0.00	5.20	36.30	33.90	25.20	19.60	27.50	27.40	33.00	29.40	26.50	24.40
108	58	1	2	B	1	0.00	0.00	0.00	0.00	11.60	44.90	48.70	31.50	27.00	26.30	23.20	31.40	27.20	27.00	24.90
109	59	2	1	B	1	0.00	0.00	0.00	0.02	7.02	108.71	87.25	46.99	29.79	24.52	23.02	23.82	21.62	17.91	16.21
110	59	2	2	A	1	0.00	0.24	12.85	33.81	35.79	81.84	70.25	37.33	25.97	22.18	20.90	22.62	19.96	17.86	14.41
111	60	2	1	B	1	0.00	0.00	0.00	0.00	0.00	5.50	27.40	28.30	25.90	33.50	36.80	55.10	42.00	38.50	31.80
112	60	2	2	A	1	0.00	0.00	0.00	0.00	0.00	1.30	26.30	28.30	22.70	22.50	25.20	51.90	40.50	39.60	33.10
113	61	1	1	A	1	0.00	0.00	0.00	0.00	0.00	20.18	25.54	41.10	67.00	70.11	56.68	78.88	43.37	36.86	35.36
114	61	1	2	B	1	0.00	0.00	0.00	0.00	0.00	26.20	41.90	48.80	42.70	40.80	33.50	32.70	30.60	25.30	25.78
115	62	2	1	B	1	0.00	0.00	0.00	1.70	37.80	118.87	171.61	166.87	139.68	117.14	83.70	47.33	48.42	43.10	33.10

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
116	62	2	2	A	1	0.00	0.00	0.00	14.90	53.50	170.10	263.90	250.50	210.10	193.90	154.10	102.70	71.00	48.90	40.90
117	63	2	1	B	1	0.69	1.11	0.91	0.71	0.37	11.97	20.09	15.14	15.48	20.47	41.66	39.67	34.70	32.76	27.98
118	63	2	2	A	1	0.99	2.03	1.72	1.65	1.82	1.59	2.05	1.51	2.05	2.77	3.33	37.87	28.85	33.14	30.10
119	64	1	1	A	1	0.10	0.00	0.00	23.30	79.90	128.50	94.70	82.80	65.90	50.60	40.60	35.80	30.10	30.00	22.50
120	64	1	2	B	1	1.50	2.40	0.60	10.20	31.90	112.30	114.10	97.80	88.80	75.40	60.70	51.50	47.00	40.20	32.60
121	65	1	1	A	1	1.05	1.50	1.58	1.70	2.00	3.00	4.50	15.50	62.60	62.60	44.80	51.70	47.80	46.50	34.00
122	65	1	2	B	1	0.00	0.00	0.00	0.00	0.00	15.50	43.30	89.50	97.10	78.50	55.40	38.30	39.90	31.40	27.50
123	66	2	1	B	1	0.00	0.87	2.54	3.35	5.80	28.80	28.90	24.20	20.40	23.74	44.64	44.93	32.66	29.68	44.20
124	66	2	2	A	1	0.00	0.00	0.00	1.10	18.80	50.40	38.30	28.90	21.90	29.50	57.40	65.70	53.30	48.30	39.60
125	67	2	1	B	1	0.20	0.19	0.62	1.06	1.26	23.68	22.67	23.35	18.10	23.91	27.04	42.41	34.17	35.36	25.68
126	67	2	2	A	1	0.44	0.29	0.82	0.64	0.77	0.64	3.09	15.16	26.32	34.38	33.77	38.36	38.49	34.63	30.48
127	68	1	1	A	1	0.00	0.00	0.00	0.40	1.10	24.70	79.40	33.50	23.70	22.70	31.20	53.40	41.00	38.00	26.00
128	68	1	2	B	1	0.00	1.30	0.00	0.00	0.10	15.30	31.70	19.70	17.50	18.90	45.20	52.10	33.70	34.40	29.80
129	69	2	1	B	1	0.00	1.40	2.00	1.50	3.50	57.60	45.40	42.20	36.10	31.20	28.70	31.90	29.00	26.30	23.80
130	69	2	2	A	1	0.50	0.20	1.70	0.10	0.00	9.80	22.70	10.40	12.50	14.60	46.30	49.70	39.10	35.70	35.40
131	70	2	1	B	1	0.80	1.30	1.80	2.30	10.50	71.10	90.60	53.00	48.00	57.50	74.30	74.20	76.70	67.40	54.70
132	70	2	2	A	1	0.00	0.30	32.40	48.30	49.60	47.00	37.00	27.60	27.50	30.70	30.70	30.00	29.70	23.80	29.30
133	71	1	1	A	1	0.00	0.00	0.00	0.00	13.40	90.90	92.20	70.60	49.10	33.70	32.00	28.20	26.00	21.70	23.90
134	71	1	2	B	1	1.70	0.20	0.00	0.00	14.50	97.20	131.40	98.30	64.40	55.80	49.60	48.30	38.60	32.10	28.90
135	72	1	1	A	1	0.00	0.00	0.00	1.90	35.70	92.40	65.60	50.00	38.20	31.40	26.70	28.30	26.10	23.40	17.40
136	72	1	2	B	1	0.00	0.40	0.00	0.00	34.20	91.90	70.30	45.70	33.70	29.20	30.50	28.80	34.60	27.70	17.90
137	73	1	1	A	1	0.00	0.00	0.39	0.00	0.02	11.33	14.02	26.09	29.35	27.65	24.67	37.14	29.32	25.63	21.09
138	73	1	2	B	1	0.00	0.00	0.00	29.00	28.40	39.80	49.90	42.60	32.90	27.30	26.40	30.70	26.96	24.50	22.40
139	74	2	1	B	1	0.00	0.00	0.00	0.00	1.71	76.12	63.66	28.84	20.41	18.24	17.62	22.39	19.76	17.57	15.99
140	74	2	2	A	1	0.00	0.00	0.00	0.00	4.20	55.40	43.00	24.00	20.10	19.90	20.70	24.60	23.20	24.10	19.10
141	75	1	1	A	1	0.00	0.50	1.22	2.18	18.63	66.36	69.40	47.91	40.78	36.19	31.69	38.66	34.72	33.01	28.94

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Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
142	75	1	2	B	1	0.00	0.00	0.00	16.30	59.80	97.10	59.40	38.20	36.70	34.30	33.20	34.30	32.60	30.00	24.80
143	77	1	1	A	1	0.00	0.00	0.44	0.55	2.36	45.57	60.32	62.70	62.04	49.25	40.92	36.06	34.89	28.86	25.32
144	77	1	2	B	1	0.00	0.00	0.00	0.10	0.80	38.00	49.50	48.70	57.20	48.54	32.70	27.20	27.90	26.40	20.93
145	78	2	1	B	1	0.00	0.00	0.00	0.00	3.40	27.60	46.60	49.10	57.60	62.40	38.10	46.20	35.60	30.40	27.30
146	78	2	2	A	1	0.40	0.00	0.90	0.30	1.70	27.60	91.10	77.20	58.60	42.20	43.30	46.80	40.60	30.70	32.10
147	79	1	1	A	1	2.86	4.24	4.60	3.80	6.27	51.96	68.73	63.36	33.91	53.95	74.64	70.27	58.34	39.89	32.94
148	79	1	2	B	1	0.70	5.30	5.30	4.40	6.60	37.40	77.10	77.40	59.30	58.90	47.90	82.91	60.40	44.70	29.40
149	80	2	1	B	1	0.00	0.00	0.02	0.00	5.59	29.70	35.70	29.06	55.80	36.55	33.14	31.11	28.02	25.83	24.44
150	80	2	2	A	1	0.00	0.00	0.00	0.00	5.69	66.09	49.27	22.57	28.15	30.13	27.77	31.28	28.75	25.28	23.61
151	81	1	1	A	1	0.00	0.00	0.00	0.00	1.85	45.84	62.12	55.08	67.91	54.36	38.49	40.00	35.67	34.26	28.11
152	81	1	2	B	1	0.00	0.00	0.00	0.00	4.30	51.20	78.40	67.00	59.80	46.40	46.80	39.10	38.90	33.70	30.00
153	82	2	1	B	1	0.00	0.00	4.80	2.90	18.80	102.40	70.10	35.00	26.10	23.70	20.70	24.40	20.49	18.00	14.39
154	82	2	2	A	1	4.62	0.78	0.60	0.32	3.60	74.50	85.10	62.20	36.10	29.60	23.60	31.27	24.60	24.41	20.92
155	83	2	1	B	1	0.00	0.00	0.00	0.00	0.00	17.64	38.73	40.81	45.79	36.44	31.14	29.68	28.07	24.17	18.08
156	83	2	2	A	1	0.32	0.00	4.30	16.89	38.26	76.88	69.27	46.56	41.31	32.93	28.84	27.34	25.94	21.84	16.71
157	84	1	1	A	1	0.31	0.25	0.27	0.28	2.52	74.79	66.13	50.56	30.73	31.27	35.09	37.54	30.38	27.70	26.00
158	84	1	2	B	1	0.00	0.22	0.00	18.33	32.22	74.40	64.04	39.94	41.47	47.73	35.93	39.50	38.91	32.43	30.28
159	86	1	1	A	1	1.12	2.99	6.95	12.86	11.38	58.61	111.11	113.79	90.22	73.08	54.86	50.64	44.08	31.70	20.92
160	86	1	2	B	1	0.70	0.40	1.40	4.50	12.00	57.80	123.00	98.50	66.00	55.50	44.50	53.00	39.10	35.00	28.90

Obs	c16	c17	c18	c19	KE_FIRST	KE_LAST	trt
1	33.10	33.60	29.60	27.40	16	19	2
2	9.70	10.90	8.10	7.20	16	19	1
3	14.66	14.06	12.41	10.62	16	19	1
4	16.67	17.60	14.71	10.62	16	19	2
5	19.64	19.20	17.06	14.42	16	19	2

Obs	c16	c17	c18	c19	KE_FIRST	KE_LAST	trt
6	23.70	21.40	17.80	14.40	16	19	1
7	24.20	25.30	20.20	16.20	16	19	1
8	30.40	30.00	27.40	22.30	16	19	2
9	18.40	19.50	12.40	11.90	16	19	2
10	23.00	21.90	18.60	17.40	16	19	1
11	21.12	19.68	18.55	16.63	16	19	1
12	16.79	17.47	15.45	14.84	16	19	2
13	26.86	26.33	23.62	18.75	16	19	2
14	31.20	26.50	22.70	18.50	16	19	1
15	17.60	16.80	13.90	13.70	16	19	1
16	22.70	16.90	14.70	13.60	16	19	2
17	14.20	17.80	11.20	9.00	16	19	2
18	17.00	16.10	15.70	15.50	16	19	1
19	31.73	25.51	25.67	23.59	16	19	1
20	27.30	23.00	18.10	16.20	16	19	2
21	18.50	17.60	15.50	15.90	16	19	1
22	19.00	18.90	15.90	16.40	16	19	2
23	32.82	31.39	24.07	27.20	16	19	2
24	33.70	27.90	23.00	24.90	16	19	1
25	19.20	18.40	15.30	14.40	16	19	2
26	18.80	20.30	23.00	21.40	16	19	1
27	17.40	16.57	15.40	14.31	16	19	1
28	10.60	12.40	7.90	3.30	16	19	2
29	24.60	26.60	19.90	19.40	16	19	2
30	23.20	22.10	19.10	16.80	16	19	1
31	16.20	18.10	14.30	12.30	16	19	1

Obs	c16	c17	c18	c19	KE_FIRST	KE_LAST	trt
32	14.98	17.60	14.40	12.65	16	19	2
33	23.56	23.09	20.63	18.48	16	19	1
34	18.80	19.90	16.10	15.50	16	19	2
35	22.42	23.05	17.35	17.72	16	19	2
36	17.30	16.30	14.60	12.60	16	19	1
37	23.40	20.60	19.50	20.70	16	19	1
38	14.50	18.80	13.60	13.60	16	19	2
39	16.41	13.69	12.13	14.43	16	19	2
40	5.60	9.70	4.30	3.70	16	19	1
41	19.10	21.90	12.80	10.80	16	19	1
42	24.40	23.10	19.60	16.20	16	19	2
43	17.17	19.03	15.37	13.78	16	19	2
44	17.80	18.10	16.20	13.60	16	19	1
45	22.72	21.49	17.36	15.67	16	19	1
46	20.50	20.20	18.50	16.40	16	19	2
47	33.00	35.20	31.70	27.80	16	19	2
48	31.50	35.90	28.10	22.30	16	19	1
49	28.20	31.40	22.90	24.10	16	19	2
50	28.10	34.00	23.70	26.30	16	19	1
51	27.02	32.92	29.93	31.51	16	19	1
52	44.30	52.50	37.40	34.40	16	19	2
53	20.90	22.50	22.40	18.50	16	19	2
54	16.00	16.20	16.00	14.10	16	19	1
55	22.10	20.90	19.80	19.40	16	19	2
56	24.80	22.50	19.30	19.40	16	19	1
57	21.16	22.65	18.34	19.12	16	19	1

Obs	c16	c17	c18	c19	KE_FIRST	KE_LAST	trt
58	17.70	19.49	15.26	13.67	16	19	2
59	25.88	28.32	23.43	19.90	16	19	1
60	24.10	28.25	23.47	19.93	16	19	2
61	16.50	14.50	11.30	11.20	16	19	2
62	19.00	15.00	13.00	9.20	16	19	1
63	27.96	29.74	26.11	24.49	16	19	1
64	23.20	19.40	18.80	20.00	16	19	2
65	74.70	60.40	50.60	36.50	16	19	2
66	34.70	22.90	19.70	20.30	16	19	1
67	19.03	19.32	17.08	16.50	16	19	2
68	19.60	19.30	15.50	13.00	16	19	1
69	24.41	21.00	18.73	16.56	16	19	1
70	4.70	3.90	6.70	6.20	16	19	2
71	35.60	34.55	30.61	26.50	16	19	1
72	29.50	28.80	21.60	21.70	16	19	2
73	18.12	15.85	14.46	13.70	16	19	2
74	16.60	14.80	12.50	11.60	16	19	1
75	26.67	25.44	22.99	21.88	16	19	2
76	29.30	29.10	24.20	23.10	16	19	1
77	22.76	19.53	17.76	15.87	16	19	1
78	17.31	14.50	13.13	11.40	16	19	2
79	26.73	26.96	21.91	20.42	16	19	1
80	19.70	20.12	16.69	13.06	16	19	2
81	27.65	25.64	21.09	18.87	16	19	1
82	16.90	21.70	15.10	13.40	16	19	2
83	15.70	14.40	11.50	12.30	16	19	2

Obs	c16	c17	c18	c19	KE_FIRST	KE_LAST	trt
84	18.90	17.20	18.70	13.50	16	19	1
85	18.20	18.80	14.60	14.90	16	19	1
86	18.30	15.30	12.90	12.10	16	19	2
87	24.00	22.47	20.51	17.72	16	19	2
88	19.57	20.78	19.25	18.47	16	19	1
89	16.42	15.22	12.76	10.84	16	19	1
90	17.84	14.63	11.79	10.97	16	19	2
91	23.05	26.54	25.63	25.93	16	19	1
92	26.00	25.90	23.80	18.00	16	19	2
93	27.44	25.36	21.88	19.84	16	19	2
94	24.20	21.71	19.38	15.85	16	19	1
95	36.10	32.50	27.10	26.50	16	19	2
96	38.50	37.90	29.20	28.60	16	19	1
97	29.46	29.79	27.10	23.93	16	19	2
98	46.86	33.40	20.20	23.90	16	19	1
99	32.21	32.83	27.12	24.04	16	19	1
100	15.10	29.08	26.68	23.50	16	19	2
101	17.56	16.08	13.77	13.62	16	19	2
102	5.18	3.69	2.99	3.09	16	19	1
103	18.48	18.80	18.10	13.80	16	19	1
104	26.50	27.00	21.30	17.20	16	19	2
105	16.40	16.40	14.60	14.50	16	19	1
106	21.00	17.90	18.70	16.20	16	19	2
107	16.20	15.20	9.70	12.10	16	19	1
108	15.10	11.40	10.40	8.10	16	19	2
109	14.69	13.12	11.49	10.32	16	19	2

Reference ID: 3227106

Obs	c16	c17	c18	c19	KE_FIRST	KE_LAST	trt
110	13.41	12.59	10.07	9.12	16	19	1
111	27.80	26.70	25.50	24.90	16	19	2
112	23.60	23.60	22.70	20.80	16	19	1
113	30.50	30.90	25.30	21.48	16	19	1
114	20.40	21.40	17.50	14.90	16	19	2
115	29.11	30.70	25.78	21.83	16	19	2
116	32.80	34.40	29.70	26.70	16	19	1
117	27.61	26.34	23.98	19.87	16	19	2
118	26.69	27.42	23.15	20.57	16	19	1
119	22.20	22.50	16.30	13.60	16	19	1
120	28.70	34.60	26.00	20.40	16	19	2
121	36.65	34.40	31.80	25.70	16	19	1
122	23.60	25.90	22.10	15.60	16	19	2
123	31.84	33.20	28.60	26.63	16	19	2
124	34.30	34.20	31.20	25.70	16	19	1
125	22.57	23.45	21.30	17.41	16	19	2
126	30.06	25.14	24.32	19.46	16	19	1
127	33.30	32.30	27.00	23.90	16	19	1
128	26.90	25.80	24.50	20.40	16	19	2
129	21.60	20.40	16.80	15.20	16	19	2
130	28.90	26.70	20.40	20.30	16	19	1
131	57.20	57.90	42.60	34.60	16	19	2
132	23.80	26.30	19.90	20.10	16	19	1
133	14.40	16.30	13.60	12.90	16	19	1
134	28.90	26.10	18.80	19.30	16	19	2
135	17.20	15.10	14.60	12.60	16	19	1

Obs	c16	c17	c18	c19	KE_FIRST	KE_LAST	trt
136	19.20	18.00	11.20	12.30	16	19	2
137	20.25	20.23	17.45	14.44	16	19	1
138	18.40	15.80	12.80	10.70	16	19	2
139	13.45	12.65	11.81	11.09	16	19	2
140	10.50	10.80	10.20	9.90	16	19	1
141	25.84	26.63	18.88	18.46	16	19	1
142	22.50	22.00	17.80	17.20	16	19	2
143	22.24	24.46	20.54	18.86	16	19	1
144	18.50	20.30	17.50	17.50	16	19	2
145	24.40	24.30	19.50	19.30	16	19	2
146	33.90	27.50	21.60	21.70	16	19	1
147	31.79	39.57	32.51	26.97	16	19	1
148	28.40	34.70	28.00	36.81	16	19	2
149	19.19	20.90	17.40	15.61	16	19	2
150	19.67	18.69	15.85	13.18	16	19	1
151	27.79	31.96	24.11	24.50	16	19	1
152	24.50	25.90	20.90	20.10	16	19	2
153	12.30	12.40	11.10	10.20	16	19	2
154	23.92	17.80	14.90	14.27	16	19	1
155	15.24	16.27	13.89	12.38	16	19	2
156	15.08	15.96	11.61	10.64	16	19	1
157	22.12	22.61	17.83	17.04	16	19	1
158	23.74	24.22	18.57	12.40	16	19	2
159	26.10	28.28	23.52	20.14	16	19	1
160	27.80	27.80	20.70	18.80	16	19	2

Reference ID: 3227106

FED CONCENTRATION DATASET (FREE DHA): BASELINE-NON-ADJUSTED

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	c20
1	1	2	1	B	1	411	276.0	221.0	369.0	636	313	184.0	242.0	334.0	721	937	142.0	237.0	367.0	360	464	347	252	516	1190
2	1	2	2	A	1	382	260.0	280.0	396.0	638	291	199.0	210.0	305.0	410	521	241.0	237.0	444.0	550	729	567	391	636	911
3	2	1	1	A	1	375	215.0	155.0	171.0	225	294	174.0	165.0	269.0	306	503	214.0	165.0	397.0	303	329	251	305	422	616
4	2	1	2	B	1	151	125.0	135.0	142.0	220	224	163.0	241.0	230.0	261	277	181.0	174.0	578.0	271	296	318	527	1840	3360
5	3	2	1	B	1	363	148.0	144.0	195.0	266	260	245.0	173.0	390.0	688	521	159.0	272.0	494.0	388	427	204	249	408	1030
6	3	2	2	A	1	357	174.0	192.0	256.0	423	305	195.0	239.0	282.0	570	665	164.0	134.0	209.0	373	524	275	250	456	659
7	4	1	1	A	1	530	349.0	260.0	254.0	291	388	251.0	285.0	312.0	516	794	423.0	343.0	316.0	369	825	430	372	445	803
8	4	1	2	B	1	338	249.0	230.0	232.0	306	516	340.0	388.0	365.0	436	731	353.0	233.0	269.0	481	811	682	631	504	520
9	5	2	1	B	1	458	312.0	203.0	219.0	274	309	315.0	238.0	328.0	464	474	204.0	164.0	308.0	321	556	458	335	388	757
10	5	2	2	A	1	286	318.0	213.0	255.0	336	388	196.0	158.0	209.0	262	270	277.0	256.0	264.0	347	467	459	426	414	598
11	6	1	1	A	1	290	170.0	133.0	261.0	438	241	172.0	189.0	295.0	525	621	175.0	277.0	381.0	328	424	356	488	1100	3050
12	6	1	2	B	1	320	159.0	126.0	200.0	453	329	185.0	265.0	367.0	505	521	230.0	264.0	284.0	305	577	243	493	739	3340
13	7	2	1	B	1	960	547.0	473.0	555.0	830	714	489.0	505.0	593.0	764	861	255.0	389.0	505.0	461	1090	698	1040	1730	3510
14	7	2	2	A	1	1080	808.0	612.0	545.0	1150	707	736.0	414.0	512.0	552	909	430.0	349.0	670.0	447	1240	789	1270	2720	5723
15	8	1	1	A	1	1280	537.0	319.0	326.0	462	553	380.0	395.0	586.0	1190	1650	253.0	320.0	582.0	628	1390	764	486	819	1160
16	8	1	2	B	1	992	573.0	401.0	385.0	776	637	323.0	305.0	330.0	894	545	303.0	346.0	553.0	498	1320	782	907	1150	2080
17	9	2	1	B	1	643	369.0	211.0	273.0	270	286	203.0	206.0	266.0	535	368	212.0	202.0	428.0	453	253	403	314	438	1220
18	9	2	2	A	1	557	300.0	192.0	125.0	259	240	260.0	268.0	380.0	273	590	196.0	242.0	617.0	448	472	312	301	335	349
19	10	1	1	A	1	501	166.0	161.0	137.0	301	163	131.0	152.0	152.0	182	215	155.0	155.0	150.0	223	329	231	203	425	1320
20	10	1	2	B	1	512	275.0	145.0	160.0	305	276	228.0	152.0	259.0	186	204	157.0	183.0	372.0	297	567	282	342	716	1930
21	11	1	1	A	1	356	257.0	184.0	325.0	593	378	182.0	148.0	187.0	376	771	134.0	155.0	282.0	666	595	237	243	747	2860
22	11	1	2	B	1	403	204.0	181.0	210.0	448	362	217.0	162.0	171.0	204	232	183.0	194.0	299.0	500	783	335	329	566	2040
23	12	2	1	B	1	585	231.0	154.0	290.0	404	208	147.0	168.0	215.0	266	525	186.0	276.0	238.0	415	730	230	203	296	658
24	12	2	2	A	1	400	216.0	209.0	259.0	339	162	246.0	251.0	280.0	664	829	140.0	223.0	251.0	540	835	316	230	371	528
25	13	2	1	B	1	775	248.0	323.0	369.0	278	253	301.0	488.0	411.0	692	238	322.0	474.0	554.0	1050	321	384	498	564	1870

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	c20
26	13	2	2	A	1	225	155.0	184.0	297.0	227	276	226.0	388.0	721.0	899	249	272.0	452.0	225.0	762	1020	285	423	763	1300
27	16	1	1	A	1	695	386.0	312.0	291.0	412	380	294.0	227.0	378.0	476	387	222.0	201.0	264.0	397	562	493	503	535	1490
28	16	1	2	B	1	715	399.0	610.0	340.0	714	461	388.0	263.0	634.0	759	633	277.0	240.0	391.0	487	510	475	634	982	959
29	17	2	1	B	1	594	350.0	441.0	540.0	1420	584	287.0	373.0	481.0	783	1060	264.0	257.0	311.0	294	691	354	624	623	1460
30	17	2	2	A	1	452	273.0	238.0	447.0	727	525	362.0	317.0	459.0	563	598	267.0	407.0	579.0	590	1210	428	486	812	2290
31	18	1	1	A	1	537	215.0	171.0	216.0	569	296	257.0	230.0	262.0	550	811	148.0	222.0	392.0	377	961	562	405	737	986
32	18	1	2	B	1	679	254.0	151.0	165.0	268	246	157.0	154.0	230.0	759	1040	159.0	207.0	387.0	572	905	582	476	424	789
33	19	1	1	A	1	372	298.0	188.0	210.0	418	383	254.0	284.0	483.0	545	687	236.0	217.0	443.0	208	353	261	286	601	1150
34	19	1	2	B	1	605	416.0	283.0	299.0	277	417	440.0	441.0	566.0	777	710	247.0	235.0	602.0	306	696	341	310	493	796
35	20	2	1	B	1	464	180.0	133.0	223.0	432	252	189.0	221.0	314.0	537	664	135.0	107.0	187.0	667	667	267	332	874	1640
36	20	2	2	A	1	449	221.0	204.0	285.0	391	297	168.0	195.0	428.0	695	868	150.0	165.0	274.0	727	1020	244	446	1540	2800
37	21	1	1	A	1	933	384.0	294.0	490.0	726	514	294.0	286.0	602.0	796	1330	241.0	219.0	456.0	483	1240	601	451	746	854
38	21	1	2	B	1	1090	406.0	462.0	319.0	1260	460	241.0	255.0	611.0	668	1650	222.0	217.0	488.0	526	765	683	647	1040	1520
39	22	2	1	B	1	979	440.0	274.0	234.0	282	217	229.0	276.0	649.0	714	886	198.0	253.0	336.0	711	1210	541	355	522	1670
40	22	2	2	A	1	906	349.0	294.0	339.0	558	562	343.0	379.0	527.0	696	1240	242.0	262.0	384.0	832	1740	602	523	588	1100
41	23	1	1	A	1	1770	1180.0	1260.0	658.0	876	914	763.0	690.0	991.0	1070	1440	742.0	506.0	763.0	906	1850	1070	839	1050	1120
42	23	1	2	B	1	1230	813.0	565.0	464.0	729	712	609.0	456.0	597.0	843	1340	537.0	473.0	613.0	820	1050	1020	1030	1630	2870
43	24	2	1	B	1	663	393.0	363.0	273.0	453	412	312.0	276.0	327.0	539	909	361.0	256.0	522.0	974	923	661	541	646	800
44	24	2	2	A	1	733	499.0	377.0	629.0	865	702	428.0	220.0	211.0	220	635	476.0	280.0	420.0	458	617	763	612	784	850
45	25	1	1	A	1	393	217.0	161.0	158.0	491	230	230.0	279.0	515.0	745	1030	165.0	169.0	283.0	650	730	370	257	758	979
46	25	1	2	B	1	601	247.0	233.0	151.0	637	522	495.0	553.0	733.0	946	1110	256.0	171.0	454.0	495	816	550	714	551	2320
47	26	2	1	B	1	610	226.0	166.0	251.0	726	417	190.0	153.0	252.0	400	754	149.0	157.0	411.0	646	748	229	165	251	569
48	26	2	2	A	1	573	237.0	117.0	196.0	383	260	155.0	161.0	270.0	495	861	154.0	131.0	260.0	448	818	385	330	281	568
49	27	2	1	B	1	307	177.0	156.0	244.0	558	327	196.0	280.0	371.0	658	986	147.0	207.0	315.0	476	533	242	281	428	867
50	27	2	2	A	1	473	158.0	104.0	325.0	328	183	183.0	186.0	396.0	555	800	175.0	166.0	389.0	402	655	281	238	461	845
51	28	1	1	A	1	711	353.0	281.0	291.0	725	338	241.0	255.0	265.0	591	958	158.0	161.0	424.0	794	1010	392	294	360	811

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	c20
52	28	1	2	B	1	663	358.0	218.0	149.0	306	144	126.0	137.0	230.0	388	648	159.0	137.0	330.0	578	1040	689	587	492	716
53	29	2	1	B	1	382	268.0	143.0	176.0	304	230	260.0	199.0	224.0	324	302	143.0	148.0	160.0	426	595	234	243	256	644
54	29	2	2	A	1	397	151.0	116.0	162.0	284	184	124.0	233.0	292.0	526	824	94.0	177.0	168.0	409	734	192	182	258	699
55	30	2	1	B	1	697	201.0	188.0	351.0	739	337	160.0	205.0	169.0	228	619	193.0	213.0	248.0	705	952	389	292	597	2040
56	30	2	2	A	1	863	348.0	199.0	274.0	371	212	154.0	186.0	287.0	713	982	162.0	178.0	180.0	450	756	447	314	537	1200
57	31	1	1	A	1	542	224.0	82.8	147.0	392	175	121.0	108.0	162.0	188	484	148.0	181.0	276.0	788	475	200	280	625	1140
58	31	1	2	B	1	441	227.0	204.0	842.0	660	172	100.0	99.3	184.0	911	1270	137.0	212.0	816.0	520	619	331	634	696	685
59	32	1	1	A	1	533	266.0	211.0	232.0	397	192	155.0	118.0	163.0	312	467	129.0	196.0	186.0	259	527	353	631	801	1000
60	32	1	2	B	1	546	272.0	173.0	130.0	261	171	139.0	141.0	133.0	378	632	172.0	157.0	398.0	476	459	286	227	442	1110
61	33	2	1	B	1	465	199.0	163.0	236.0	440	438	175.0	192.0	269.0	485	596	140.0	168.0	216.0	535	698	457	374	366	766
62	33	2	2	A	1	627	343.0	164.0	189.0	425	406	255.0	225.0	263.0	353	478	153.0	150.0	270.0	280	726	492	360	491	951
63	34	1	1	A	1	430	117.0	85.3	204.0	289	177	113.0	115.0	132.0	289	547	70.0	92.1	555.0	169	340	118	158	266	458
64	34	1	2	B	1	337	130.0	125.0	163.0	299	129	131.0	136.0	256.0	429	539	119.0	102.0	256.0	242	390	163	144	198	392
65	37	2	1	B	1	996	683.0	495.0	390.0	871	767	526.0	430.0	524.0	871	1290	411.0	282.0	265.0	612	1060	718	577	656	1200
66	37	2	2	A	1	1060	859.0	644.0	550.0	921	929	570.0	364.0	370.0	619	1180	603.0	362.0	665.0	871	1070	794	716	1110	2170
67	38	2	1	B	1	230	98.5	142.0	304.0	538	263	159.0	217.0	259.0	422	520	116.0	137.0	310.0	214	307	129	522	1950	3530
68	38	2	2	A	1	518	229.0	207.0	239.0	423	251	161.0	198.0	294.0	521	710	109.0	232.0	483.0	479	360	203	434	1350	4230
69	39	1	1	A	1	1150	481.0	352.0	541.0	773	566	352.0	368.0	689.0	679	1130	332.0	370.0	663.0	855	1340	477	377	813	1710
70	39	1	2	B	1	1310	664.0	560.0	590.0	1310	752	429.0	515.0	583.0	917	1020	488.0	455.0	686.0	1010	1070	787	627	885	1410
71	40	1	1	A	1	762	295.0	302.0	203.0	353	210	277.0	312.0	237.0	234	458	260.0	227.0	274.0	1140	1100	595	518	627	542
72	40	1	2	B	1	913	392.0	458.0	251.0	435	241	260.0	278.0	618.0	1350	1400	244.0	313.0	494.0	1570	1440	775	872	1040	4593
73	41	2	1	B	1	558	191.0	160.0	335.0	626	597	312.0	189.0	321.0	805	979	249.0	185.0	1110.0	350	1060	336	308	764	1220
74	41	2	2	A	1	372	295.0	252.0	332.0	681	443	173.0	137.0	246.0	513	810	177.0	198.0	604.0	745	978	400	468	643	1370
75	42	2	1	B	1	342	104.0	89.3	195.0	517	250	162.0	146.0	343.0	380	687	106.0	215.0	154.0	468	324	269	222	427	905
76	42	2	2	A	1	439	184.0	150.0	106.0	263	181	223.0	323.0	330.0	724	828	189.0	131.0	356.0	207	740	323	319	473	2010
77	43	1	1	A	1	312	138.0	125.0	203.0	259	218	152.0	151.0	176.0	341	376	102.0	119.0	154.0	440	330	194	183	229	552

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	c20
78	43	1	2	B	1	535	114.0	122.0	156.0	230	177	133.0	129.0	187.0	255	326	81.0	114.0	180.0	268	314	179	190	508	866
79	44	1	1	A	1	251	81.3	59.1	66.5	140	129	73.1	87.7	71.0	131	153	77.2	116.0	91.9	143	328	179	149	221	1320
80	44	1	2	B	1	418	214.0	81.1	83.7	112	124	138.0	138.0	168.0	272	407	161.0	137.0	273.0	222	472	212	221	382	1800
81	45	1	1	A	1	393	198.0	174.0	207.0	428	247	130.0	214.0	245.0	548	650	131.0	268.0	362.0	368	773	350	282	358	708
82	45	1	2	B	1	565	331.0	227.0	251.0	328	256	128.0	182.0	201.0	369	779	160.0	248.0	209.0	428	752	429	567	815	1590
83	46	2	1	B	1	315	187.0	150.0	148.0	334	382	239.0	124.0	143.0	358	443	107.0	121.0	250.0	242	654	355	321	375	580
84	46	2	2	A	1	363	261.0	172.0	254.0	287	461	294.0	163.0	252.0	379	493	113.0	136.0	257.0	262	677	323	349	433	1340
85	47	1	1	A	1	651	229.0	149.0	202.0	404	312	129.0	148.0	221.0	398	523	95.6	211.0	499.0	290	539	322	379	824	2840
86	47	1	2	B	1	484	242.0	138.0	247.0	510	264	132.0	138.0	317.0	749	1330	116.0	114.0	459.0	279	770	315	739	2010	3280
87	48	2	1	B	1	526	226.0	172.0	269.0	716	295	274.0	215.0	442.0	568	850	149.0	189.0	592.0	457	798	409	388	768	2240
88	48	2	2	A	1	443	295.0	178.0	213.0	571	256	227.0	272.0	253.0	571	1100	138.0	187.0	351.0	321	705	336	311	619	2550
89	49	1	1	A	1	456	159.0	98.7	151.0	229	173	155.0	153.0	237.0	305	439	126.0	114.0	192.0	205	648	302	305	273	827
90	49	1	2	B	1	294	216.0	134.0	182.0	560	292	110.0	128.0	356.0	507	488	101.0	142.0	264.0	295	352	256	301	1630	6093
91	50	1	1	A	1	690	302.0	113.0	148.0	465	166	172.0	177.0	362.0	503	833	91.4	105.0	235.0	314	807	385	262	258	547
92	50	1	2	B	1	759	497.0	300.0	192.0	651	287	157.0	200.0	293.0	723	630	121.0	105.0	340.0	230	610	684	439	323	374
93	51	2	1	B	1	568	227.0	146.0	144.0	174	151	161.0	190.0	241.0	296	384	116.0	147.0	123.0	376	475	186	237	392	598
94	51	2	2	A	1	569	157.0	119.0	125.0	161	136	157.0	161.0	150.0	153	541	160.0	181.0	184.0	296	290	296	323	606	1930
95	52	2	1	B	1	349	193.0	87.4	91.8	133	102	103.0	148.0	211.0	245	373	107.0	115.0	251.0	485	366	207	151	190	353
96	52	2	2	A	1	388	113.0	91.0	111.0	220	195	107.0	103.0	156.0	256	275	182.0	122.0	152.0	231	444	156	185	261	703
97	53	2	1	B	1	503	242.0	165.0	192.0	357	242	139.0	162.0	234.0	345	549	136.0	181.0	361.0	243	953	451	301	409	459
98	53	2	2	A	1	469	394.0	291.0	205.0	209	349	207.0	203.0	199.0	280	591	324.0	162.0	407.0	644	652	478	435	539	1530
99	54	1	1	A	1	575	216.0	94.8	108.0	114	188	127.0	137.0	180.0	357	439	276.0	172.0	302.0	414	455	397	382	415	472
100	54	1	2	B	1	743	145.0	118.0	162.0	222	261	171.0	186.0	191.0	257	416	170.0	151.0	312.0	256	647	333	290	271	465
101	55	2	1	B	1	966	351.0	372.0	215.0	362	446	283.0	323.0	532.0	539	556	168.0	214.0	312.0	332	1190	510	529	815	1270
102	55	2	2	A	1	734	340.0	317.0	335.0	419	495	382.0	402.0	484.0	772	698	417.0	320.0	415.0	391	813	620	848	949	1460
103	56	1	1	A	1	364	175.0	110.0	144.0	298	298	183.0	196.0	214.0	518	779	149.0	112.0	201.0	451	354	240	189	229	306

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	c20
104	56	1	2	B	1	307	120.0	91.8	162.0	259	354	197.0	132.0	199.0	442	793	134.0	88.8	179.0	268	240	156	230	350	229
105	57	1	1	A	1	531	217.0	273.0	408.0	594	166	156.0	206.0	356.0	512	947	183.0	224.0	422.0	442	768	448	451	613	935
106	57	1	2	B	1	552	307.0	504.0	401.0	891	368	227.0	313.0	517.0	919	1220	168.0	299.0	861.0	658	1300	325	536	722	1450
107	58	1	1	A	1	1340	677.0	475.0	408.0	754	548	380.0	587.0	782.0	1010	988	213.0	327.0	429.0	505	1160	774	693	558	1680
108	58	1	2	B	1	1110	433.0	273.0	361.0	405	360	361.0	360.0	398.0	694	758	188.0	185.0	348.0	763	1100	567	681	808	2520
109	59	2	1	B	1	418	186.0	211.0	440.0	676	200	134.0	206.0	485.0	420	438	128.0	173.0	452.0	189	757	235	322	451	918
110	59	2	2	A	1	512	364.0	203.0	305.0	573	206	154.0	178.0	202.0	159	430	172.0	282.0	487.0	668	622	497	950	1760	2810
111	60	2	1	B	1	917	419.0	351.0	313.0	384	580	402.0	413.0	460.0	636	1370	291.0	202.0	297.0	566	1060	619	690	546	751
112	60	2	2	A	1	584	504.0	278.0	226.0	373	571	406.0	214.0	271.0	524	691	260.0	222.0	288.0	1030	870	650	682	470	970
113	61	1	1	A	1	630	286.0	157.0	174.0	345	470	174.0	157.0	211.0	222	469	166.0	158.0	207.0	431	688	370	350	460	270
114	61	1	2	B	1	802	305.0	115.0	96.5	215	306	181.0	170.0	310.0	203	497	99.8	134.0	453.0	802	677	490	578	343	343
115	62	2	1	B	1	428	242.0	181.0	168.0	610	354	262.0	291.0	236.0	388	733	218.0	183.0	255.0	440	511	273	249	299	1080
116	62	2	2	A	1	385	240.0	133.0	157.0	356	491	266.0	225.0	214.0	543	654	203.0	170.0	324.0	524	369	222	256	479	941
117	63	2	1	B	1	778	252.0	142.0	228.0	574	234	190.0	173.0	256.0	249	660	162.0	167.0	477.0	1040	1260	248	313	365	636
118	63	2	2	A	1	857	201.0	109.0	112.0	226	104	119.0	171.0	260.0	622	1160	120.0	129.0	138.0	738	813	257	342	704	570
119	64	1	1	A	1	966	611.0	493.0	441.0	504	641	519.0	380.0	679.0	465	980	279.0	341.0	591.0	665	1360	901	769	1120	3070
120	64	1	2	B	1	893	538.0	404.0	357.0	346	752	539.0	409.0	366.0	419	584	284.0	277.0	414.0	474	553	659	722	1350	1940
121	65	1	1	A	1	692	313.0	220.0	222.0	368	488	287.0	194.0	240.0	197	427	238.0	174.0	419.0	464	590	407	258	268	324
122	65	1	2	B	1	740	276.0	198.0	262.0	336	604	247.0	197.0	482.0	1050	1600	314.0	180.0	339.0	593	785	479	351	614	717
123	66	2	1	B	1	702	338.0	238.0	320.0	837	552	303.0	315.0	313.0	523	1020	223.0	172.0	376.0	750	1090	549	447	590	987
124	66	2	2	A	1	1110	421.0	281.0	414.0	581	360	249.0	202.0	350.0	1030	1190	551.0	209.0	601.0	818	1580	808	821	1030	2500
125	67	2	1	B	1	599	207.0	134.0	184.0	233	252	151.0	154.0	211.0	302	469	162.0	160.0	144.0	541	588	404	392	588	518
126	67	2	2	A	1	615	224.0	142.0	178.0	282	262	167.0	168.0	223.0	288	641	174.0	133.0	275.0	270	535	388	373	581	435
127	68	1	1	A	1	904	415.0	235.0	225.0	414	372	267.0	250.0	426.0	584	954	343.0	181.0	551.0	381	629	358	323	472	683
128	68	1	2	B	1	625	260.0	215.0	249.0	248	245	247.0	231.0	325.0	638	784	340.0	168.0	640.0	371	506	410	349	627	648
129	69	2	1	B	1	600	298.0	189.0	263.0	475	324	196.0	184.0	277.0	528	552	187.0	168.0	294.0	787	949	452	345	544	1070

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	c20
130	69	2	2	A	1	439	193.0	114.0	168.0	439	320	168.0	141.0	347.0	593	909	157.0	129.0	223.0	373	547	267	345	303	543
131	70	2	1	B	1	506	198.0	122.0	246.0	503	425	175.0	225.0	191.0	247	354	148.0	146.0	273.0	282	706	378	316	333	958
132	70	2	2	A	1	482	221.0	166.0	204.0	258	336	157.0	257.0	281.0	293	390	197.0	206.0	205.0	287	600	371	646	995	763
133	71	1	1	A	1	1040	387.0	185.0	223.0	365	376	279.0	176.0	250.0	329	535	125.0	132.0	277.0	458	1040	412	310	443	998
134	71	1	2	B	1	313	286.0	114.0	207.0	398	215	159.0	130.0	155.0	362	370	193.0	146.0	349.0	426	766	411	242	295	868
135	72	1	1	A	1	459	141.0	106.0	151.0	367	456	212.0	182.0	241.0	385	560	109.0	156.0	614.0	689	366	174	225	480	2040
136	72	1	2	B	1	352	155.0	119.0	140.0	673	426	108.0	118.0	191.0	623	533	89.0	125.0	440.0	540	441	321	161	578	1590
137	73	1	1	A	1	599	269.0	177.0	143.0	416	265	158.0	168.0	289.0	670	964	188.0	98.1	125.0	302	627	281	255	292	432
138	73	1	2	B	1	569	276.0	142.0	141.0	370	298	183.0	148.0	165.0	217	459	367.0	110.0	230.0	296	731	631	323	978	1110
139	74	2	1	B	1	542	257.0	196.0	508.0	443	330	181.0	475.0	312.0	396	526	174.0	216.0	279.0	236	596	281	401	727	1140
140	74	2	2	A	1	828	446.0	329.0	486.0	746	785	453.0	313.0	759.0	811	1150	421.0	358.0	471.0	851	1130	576	752	1880	2220
141	75	1	1	A	1	415	220.0	127.0	170.0	339	219	134.0	124.0	198.0	272	354	111.0	123.0	160.0	204	442	348	359	487	1720
142	75	1	2	B	1	493	318.0	132.0	177.0	328	272	178.0	159.0	223.0	411	362	103.0	98.1	263.0	394	511	293	302	1310	2970
143	77	1	1	A	1	228	76.2	74.7	114.0	151	161	97.6	96.8	151.0	160	205	69.4	102.0	120.0	176	227	322	181	378	632
144	77	1	2	B	1	362	88.3	66.2	123.0	124	119	101.0	110.0	114.0	110	134	91.2	164.0	154.0	216	313	116	157	149	337
145	78	2	1	B	1	571	254.0	172.0	203.0	518	317	224.0	231.0	356.0	417	504	137.0	172.0	360.0	229	956	236	261	309	625
146	78	2	2	A	1	599	208.0	128.0	183.0	322	233	199.0	176.0	248.0	587	495	138.0	239.0	300.0	351	732	276	254	335	533
147	79	1	1	A	1	440	167.0	171.0	223.0	313	201	164.0	181.0	286.0	483	556	108.0	121.0	292.0	180	340	141	234	554	722
148	79	1	2	B	1	348	168.0	138.0	127.0	218	126	145.0	172.0	247.0	353	633	236.0	90.5	152.0	277	346	153	192	333	467
149	80	2	1	B	1	286	135.0	100.0	133.0	208	162	110.0	195.0	211.0	423	576	79.3	108.0	146.0	210	338	176	147	229	388
150	80	2	2	A	1	345	145.0	89.0	128.0	269	176	92.3	76.3	92.3	190	379	72.4	120.0	190.0	497	295	121	219	216	916
151	81	1	1	A	1	495	187.0	118.0	150.0	270	270	257.0	200.0	197.0	353	388	131.0	185.0	185.0	206	544	394	364	422	412
152	81	1	2	B	1	560	205.0	163.0	201.0	204	182	153.0	186.0	322.0	388	411	122.0	156.0	312.0	528	415	380	386	383	462
153	82	2	1	B	1	536	351.0	313.0	405.0	529	448	267.0	243.0	298.0	601	744	268.0	216.0	437.0	620	571	568	1060	890	2000
154	82	2	2	A	1	489	328.0	443.0	314.0	474	576	325.0	233.0	188.0	335	443	273.0	170.0	317.0	540	440	525	587	579	519
155	83	2	1	B	1	708	419.0	235.0	350.0	522	496	419.0	360.0	503.0	807	842	243.0	251.0	679.0	723	570	382	389	505	753

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	c20
156	83	2	2	A	1	258	292.0	266.0	250.0	347	425	240.0	228.0	391.0	387	852	212.0	191.0	611.0	848	444	301	415	877	1620
157	84	1	1	A	1	317	178.0	152.0	250.0	291	340	221.0	150.0	306.0	304	438	161.0	175.0	313.0	376	378	401	331	349	591
158	84	1	2	B	1	411	318.0	176.0	275.0	316	376	156.0	136.0	166.0	499	421	111.0	146.0	376.0	667	500	452	582	1430	1470
159	86	1	1	A	1	547	393.0	175.0	157.0	169	472	330.0	181.0	192.0	227	452	173.0	196.0	302.0	623	668	412	430	558	739
160	86	1	2	B	1	606	368.0	203.0	196.0	198	439	237.0	168.0	241.0	411	646	185.0	173.0	607.0	250	441	521	380	503	721

Obs	c21	c22	c23	c24	c25	c26	c27	c28	c29	c30	c31	c32	c33	c34	KE_FIRST	KE_LAST	trt
1	3780	2530	1670	1600	1400	1620	290	343	268	431	647	594	226.0	161	30	33	2
2	1680	1860	1840	1000	666	1060	375	284	251	451	519	863	201.0	265	30	33	1
3	1360	2000	1400	1020	1100	1410	551	425	656	222	422	441	170.0	179	30	33	1
4	3080	1400	866	583	498	845	322	346	566	307	552	439	423.0	194	30	33	2
5	1440	1910	1570	1690	2490	2410	519	269	262	391	402	320	246.0	251	30	33	2
6	1090	1520	1520	1580	1570	969	443	309	260	474	668	364	279.0	290	30	33	1
7	2010	3130	3000	1790	1800	2700	875	523	514	931	897	555	461.0	491	30	33	1
8	463	767	1390	1770	1840	2130	1630	1030	705	937	1230	888	479.0	548	30	33	2
9	1990	3260	3160	2120	1780	1430	653	425	394	455	633	430	328.0	301	30	33	2
10	1310	2690	2650	2540	2390	2270	999	559	427	470	764	685	477.0	363	30	33	1
11	2810	1770	1020	758	905	1050	362	274	397	459	408	385	128.0	238	30	33	1
12	3380	2600	849	524	540	714	457	282	358	379	343	250	222.0	356	30	33	2
13	4970	4560	3250	1600	1410	2460	476	412	481	832	821	1280	399.0	380	30	33	2
14	4910	2860	3040	1540	1670	1570	863	531	508	951	1210	1350	512.0	791	30	33	1
15	4780	3460	1370	848	973	2100	563	466	615	583	1040	548	323.0	402	30	33	1
16	2970	2600	848	625	848	2150	628	369	434	676	708	520	308.0	558	30	33	2
17	2910	2290	1570	1130	1030	1640	342	267	826	418	752	382	174.0	367	30	33	2
18	1520	2010	1770	1030	1360	976	434	295	244	468	723	416	193.0	468	30	33	1
19	1980	2100	1740	2060	1800	1360	534	349	296	297	562	332	187.0	164	30	33	1

Obs	c21	c22	c23	c24	c25	c26	c27	c28	c29	c30	c31	c32	c33	c34	KE_FIRST	KE_LAST	trt
20	1950	2860	2460	1560	1040	760	509	461	338	422	863	461	234.0	250	30	33	2
21	4830	2370	1030	897	1500	1510	380	248	391	664	537	275	258.0	237	30	33	1
22	5393	2300	1140	961	522	574	321	283	413	545	621	357	241.0	383	30	33	2
23	618	770	1190	794	1350	2330	948	385	453	534	607	538	187.0	225	30	33	2
24	331	563	1410	2010	2610	2520	922	337	459	694	644	622	231.0	274	30	33	1
25	3240	1810	792	844	870	516	374	473	617	554	399	241	227.0	202	30	33	2
26	932	534	558	375	715	1770	2660	694	444	432	615	471	382.0	289	30	33	1
27	4720	2430	1400	1090	1380	1920	610	339	774	368	702	435	238.0	379	30	33	1
28	3110	2440	2020	967	2090	1940	868	411	648	679	1040	499	424.0	341	30	33	2
29	2220	1850	2030	3200	2900	3290	539	383	403	615	730	1130	218.0	295	30	33	2
30	3570	3710	2220	1260	986	1240	447	418	430	828	848	1220	305.0	363	30	33	1
31	2650	2260	787	1140	2130	4533	414	263	414	585	684	604	180.0	225	30	33	1
32	1830	1740	1140	1010	1080	2510	384	229	217	405	663	718	231.0	235	30	33	2
33	2710	3610	3160	2130	1480	691	370	336	351	257	358	238	227.0	224	30	33	1
34	2630	3680	3550	2080	2290	2780	675	339	548	394	524	351	280.0	265	30	33	2
35	2180	1920	1400	1250	950	1430	315	227	305	818	488	600	233.0	201	30	33	2
36	3140	1730	1430	962	1090	1830	549	305	311	754	634	483	234.0	321	30	33	1
37	886	1240	758	720	1120	2560	1580	542	446	609	1060	371	258.0	463	30	33	1
38	3600	2190	1950	1120	912	1080	397	342	362	389	745	722	178.0	324	30	33	2
39	4120	3180	1010	967	1120	1230	461	348	325	554	687	315	222.0	266	30	33	2
40	4080	4170	2720	1250	845	1550	606	539	463	631	958	798	258.0	267	30	33	1
41	2550	2160	2610	3090	4733	3820	1680	1160	1110	867	1620	801	594.0	677	30	33	1
42	2640	2600	1870	1600	1430	1680	1570	1170	819	785	1600	588	805.0	603	30	33	2
43	1480	3840	3510	1620	1570	2100	779	309	334	745	1070	308	326.0	487	30	33	2
44	1140	2080	1430	757	778	1800	1450	344	429	803	1120	522	365.0	273	30	33	1
45	2160	1310	457	801	1850	3690	575	206	380	664	441	654	249.0	215	30	33	1

Obs	c21	c22	c23	c24	c25	c26	c27	c28	c29	c30	c31	c32	c33	c34	KE_FIRST	KE_LAST	trt
46	2450	1460	543	341	584	634	482	295	458	996	493	389	304.0	247	30	33	2
47	1230	1680	1080	1180	1470	1920	360	268	391	367	327	371	176.0	205	30	33	2
48	1200	983	1320	1240	866	1050	498	393	319	817	515	321	153.0	247	30	33	1
49	1610	963	765	878	2570	3600	523	288	340	409	437	592	179.0	191	30	33	2
50	1510	1700	1480	909	1230	2040	644	414	224	543	310	335	183.0	205	30	33	1
51	519	366	337	337	398	699	304	221	282	488	531	163	132.0	147	30	33	1
52	253	309	753	1200	1470	1220	369	267	270	1350	674	216	183.0	230	30	33	2
53	1300	1700	2170	1330	1500	1530	367	247	252	350	454	592	198.0	167	30	33	2
54	1820	2180	2120	1420	916	873	229	226	237	263	414	367	220.0	200	30	33	1
55	3120	2530	947	689	797	1180	506	296	330	485	722	539	191.0	232	30	33	2
56	3030	3120	1640	871	739	997	386	294	226	578	759	619	329.0	298	30	33	1
57	1590	562	409	755	1710	4450	609	246	1030	515	403	276	132.0	168	30	33	1
58	3010	2040	661	860	1880	3160	545	160	615	434	687	1420	187.0	182	30	33	2
59	726	430	223	263	994	3020	864	439	600	369	859	220	197.0	157	30	33	1
60	1540	1090	353	327	565	2420	1470	424	366	732	910	634	357.0	257	30	33	2
61	2190	3550	1930	1190	1460	1080	292	345	396	333	604	460	171.0	254	30	33	2
62	2730	2690	2130	1570	1490	1650	481	316	276	500	616	633	357.0	227	30	33	1
63	532	686	882	1260	1780	1450	204	285	309	354	359	236	102.0	127	30	33	1
64	787	874	509	386	671	1840	250	166	224	573	335	160	204.0	144	30	33	2
65	1770	1760	1620	1080	2010	2770	1240	901	753	1240	1090	707	661.0	427	30	33	2
66	2630	3490	2570	1440	1600	2390	1560	983	933	1330	1060	760	559.0	646	30	33	1
67	2500	1430	1380	1600	1330	1180	356	280	463	378	337	737	177.0	154	30	33	2
68	2390	1810	1330	889	1260	1200	238	261	309	529	584	352	248.0	247	30	33	1
69	3930	2890	1960	1390	2780	2530	1110	407	687	1450	809	748	466.0	461	30	33	1
70	1860	2450	2240	3000	3190	2570	1480	722	399	1920	1240	767	683.0	475	30	33	2
71	2380	1410	512	953	3220	3290	1270	410	289	789	689	460	221.0	362	30	33	1

Obs	c21	c22	c23	c24	c25	c26	c27	c28	c29	c30	c31	c32	c33	c34	KE_FIRST	KE_LAST	trt
72	3220	1660	531	1030	2160	4130	1080	500	370	1250	1000	500	233.0	488	30	33	2
73	4400	2090	558	731	763	1260	509	259	298	677	332	487	170.0	340	30	33	2
74	3780	2710	852	574	1970	1040	414	172	237	808	444	508	214.0	383	30	33	1
75	3350	2940	1520	812	1740	1220	302	144	189	245	564	459	123.0	194	30	33	2
76	1990	2420	1140	1730	1460	859	248	211	209	744	356	342	171.0	264	30	33	1
77	1370	1960	1330	1530	1780	2040	683	289	297	329	338	290	156.0	213	30	33	1
78	2060	3100	1600	764	594	695	422	297	292	628	362	226	187.0	144	30	33	2
79	2390	1420	851	1210	835	925	335	158	137	416	315	188	82.5	185	30	33	1
80	2410	1250	452	376	764	993	357	157	197	386	380	230	123.0	145	30	33	2
81	1040	919	1050	3180	4863	5023	620	270	202	505	645	149	168.0	237	30	33	1
82	4080	1660	988	1340	1920	2250	566	317	228	778	803	270	200.0	283	30	33	2
83	4210	2170	980	634	1330	1200	317	170	242	170	436	452	215.0	290	30	33	2
84	4260	1570	888	594	771	1430	306	211	286	289	675	526	268.0	185	30	33	1
85	4890	2780	1360	1090	1210	1380	269	205	233	249	464	570	105.0	165	30	33	1
86	3740	1900	1330	571	853	1100	246	349	436	629	731	368	159.0	288	30	33	2
87	3010	2110	1090	883	1790	1800	275	264	280	240	546	409	264.0	241	30	33	2
88	4160	1790	786	561	1000	1690	276	240	278	417	480	398	143.0	238	30	33	1
89	1740	1930	1000	811	1510	1800	264	165	160	324	503	352	134.0	190	30	33	1
90	3950	1190	591	636	705	759	195	176	293	267	348	210	113.0	166	30	33	2
91	308	142	214	194	317	940	472	404	246	396	607	302	217.0	167	30	33	1
92	740	317	248	431	1850	2270	537	303	382	223	721	302	103.0	201	30	33	2
93	944	1550	814	946	1790	2790	686	266	211	217	317	359	132.0	225	30	33	2
94	3570	2210	1120	766	933	914	370	233	205	338	586	299	235.0	365	30	33	1
95	811	906	1310	1720	2550	3090	551	257	261	498	466	268	147.0	245	30	33	2
96	1070	1280	761	1130	2770	1700	394	342	385	576	550	403	320.0	294	30	33	1
97	2080	2690	2220	1600	1650	1310	621	548	436	269	713	355	287.0	312	30	33	2

Obs	c21	c22	c23	c24	c25	c26	c27	c28	c29	c30	c31	c32	c33	c34	KE_FIRST	KE_LAST	trt
98	3820	2840	2900	1860	1340	1090	629	394	291	317	595	322	270.0	352	30	33	1
99	1080	2970	3700	3450	3250	1980	1130	591	289	157	835	252	226.0	237	30	33	1
100	744	483	679	1100	2120	2280	1770	704	502	355	619	294	276.0	242	30	33	2
101	1570	2220	1140	986	687	673	411	332	337	398	739	678	236.0	338	30	33	2
102	907	531	432	362	477	702	430	178	284	520	655	340	244.0	339	30	33	1
103	620	976	985	828	893	803	640	231	277	371	422	279	200.0	216	30	33	1
104	853	674	527	865	1220	1320	617	230	173	316	469	259	204.0	241	30	33	2
105	1680	1440	601	670	1310	1360	246	466	281	916	554	814	177.0	183	30	33	1
106	1890	903	1220	2730	1310	1590	351	279	569	436	562	284	236.0	216	30	33	2
107	2210	1790	1540	1910	3560	3770	688	737	430	694	1070	478	236.0	270	30	33	1
108	3700	1610	752	1280	2310	2050	581	317	367	577	896	480	302.0	265	30	33	2
109	2680	2870	2170	1670	913	1270	255	210	302	351	406	327	212.0	251	30	33	2
110	2180	1630	847	1430	867	1070	285	244	298	761	405	295	291.0	252	30	33	1
111	1110	2880	1900	1710	3220	3860	1280	496	408	1000	957	320	225.0	464	30	33	2
112	1320	2890	1400	733	771	1370	1580	350	327	1280	879	261	314.0	683	30	33	1
113	2240	1410	1880	2630	4973	3180	994	318	361	723	1200	273	179.0	214	30	33	1
114	1740	2710	2340	2270	868	604	315	232	215	687	1000	204	154.0	313	30	33	2
115	1710	2230	1740	1310	1830	1180	968	456	430	524	364	815	274.0	264	30	33	2
116	1900	2390	2040	2110	2530	1800	1060	609	507	752	483	284	320.0	257	30	33	1
117	1100	723	351	880	1300	4440	573	210	175	615	870	1030	149.0	206	30	33	2
118	250	189	127	177	387	1260	754	338	262	967	735	849	125.0	166	30	33	1
119	3940	3980	3020	2590	1720	1540	607	351	527	666	1030	518	381.0	423	30	33	1
120	4060	4310	1920	1670	1870	1380	760	493	677	526	1030	507	634.0	578	30	33	2
121	431	629	1900	2390	3270	1300	884	585	340	383	549	293	194.0	200	30	33	1
122	1490	2260	3420	4860	3540	1840	364	305	259	589	768	345	270.0	284	30	33	2
123	2010	1470	821	688	804	1470	681	354	505	991	1190	1110	184.0	245	30	33	2

Reference ID: 3227106

Obs	c21	c22	c23	c24	c25	c26	c27	c28	c29	c30	c31	c32	c33	c34	KE_FIRST	KE_LAST	trt
124	4010	2250	909	530	966	2500	1070	379	468	1200	1170	796	247.0	346	30	33	1
125	2310	1350	861	606	1080	2880	1340	367	294	605	616	267	156.0	232	30	33	2
126	460	518	1040	1490	3570	3270	1280	338	303	725	766	424	156.0	168	30	33	1
127	1480	3220	2490	907	847	1660	1320	542	724	510	978	428	339.0	276	30	33	1
128	1240	1890	1060	1130	2720	2640	1740	565	629	515	629	430	307.0	391	30	33	2
129	3020	1950	1130	1110	802	1640	347	243	325	345	640	241	179.0	307	30	33	2
130	1010	1030	481	321	562	2060	837	289	377	459	832	366	143.0	246	30	33	1
131	2570	2580	787	1130	1280	2220	310	522	310	265	847	464	240.0	224	30	33	2
132	978	569	295	646	835	817	154	225	459	473	612	358	179.0	154	30	33	1
133	3520	2660	1330	1320	1040	605	255	217	270	651	1060	292	205.0	157	30	33	1
134	3150	2150	1400	1740	1640	561	257	312	224	366	829	277	146.0	221	30	33	2
135	4090	1600	1510	1060	1300	1570	236	193	296	1080	461	866	212.0	176	30	33	1
136	2720	1390	721	1080	1820	1510	190	318	333	759	417	446	134.0	209	30	33	2
137	1300	795	1680	1160	1100	1800	1100	347	306	274	899	280	277.0	304	30	33	1
138	1220	884	556	412	376	731	550	230	214	384	831	275	255.0	337	30	33	2
139	3850	2690	930	993	1120	1390	391	288	333	292	636	387	124.0	193	30	33	2
140	4700	2980	1680	1330	1590	1210	439	340	506	559	997	531	405.0	338	30	33	1
141	4180	3230	1480	846	524	715	410	155	175	365	603	294	135.0	192	30	33	1
142	3810	1180	582	431	523	784	194	191	183	425	519	438	162.0	132	30	33	2
143	1660	1790	1830	1400	2070	1780	278	327	157	300	393	190	96.1	116	30	33	1
144	862	1140	648	972	1710	805	193	232	216	234	311	194	156.0	116	30	33	2
145	1140	1440	1480	2950	4150	3230	491	298	438	208	819	491	200.0	242	30	33	2
146	1220	1760	1730	1450	1610	2110	396	307	337	359	799	439	279.0	214	30	33	1
147	1760	2260	1320	1230	1380	2100	712	341	341	265	424	410	148.0	182	30	33	1
148	800	1200	1340	987	1350	1470	654	386	277	236	362	530	114.0	213	30	33	2
149	1060	1340	970	1040	3200	2750	366	157	272	214	597	165	117.0	117	30	33	2

Reference ID: 3227106

Obs	c21	c22	c23	c24	c25	c26	c27	c28	c29	c30	c31	c32	c33	c34	KE_FIRST	KE_LAST	trt
150	1390	1570	598	748	1270	995	280	266	237	516	405	252	135.0	213	30	33	1
151	2110	2800	1830	2040	2720	1640	719	272	264	243	627	353	169.0	194	30	33	1
152	1700	2080	1470	1140	1650	1920	495	281	289	298	731	490	278.0	254	30	33	2
153	4813	4850	2260	1270	1540	1600	775	309	344	488	497	614	225.0	355	30	33	2
154	2500	4680	2480	1470	1340	934	968	487	382	712	796	264	348.0	314	30	33	1
155	1390	1770	1870	2320	2820	2680	513	439	1080	792	682	779	446.0	363	30	33	2
156	2400	2380	1390	1080	1530	1240	471	496	561	887	467	503	266.0	400	30	33	1
157	2450	2850	1660	660	1550	1480	579	219	249	957	529	322	195.0	314	30	33	1
158	2590	1410	553	1010	2120	2170	917	266	394	1050	551	451	203.0	328	30	33	2
159	2620	3620	2540	1910	1680	1990	695	447	337	1010	929	451	301.0	308	30	33	1
160	2210	3540	2600	1120	1390	1390	882	462	437	373	802	359	288.0	439	30	33	2

FED CONCENTRATION DATASET (FREE DHA): BASELINE-ADJUSTED

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
1	1	2	1	B	1	0.60	1.90	1.50	0.70	4.40	102.10	123.50	78.70	51.90	51.00	53.10	55.10	44.40	41.50	34.60
2	1	2	2	A	1	0.00	0.00	0.00	0.00	0.00	32.70	73.20	59.50	31.60	27.80	32.80	37.10	31.90	28.00	21.90
3	2	1	1	A	1	0.00	0.00	0.04	0.77	0.38	17.61	46.17	36.19	24.41	23.38	21.63	30.42	24.47	23.07	18.34
4	2	1	2	B	1	0.35	0.36	9.20	65.70	96.30	114.33	93.02	48.34	35.01	32.60	27.50	30.42	25.04	24.89	17.86
5	3	2	1	B	1	0.00	0.00	0.33	2.10	14.20	59.85	79.65	62.12	45.06	40.26	36.45	36.32	27.33	26.24	24.79
6	3	2	2	A	1	0.00	0.00	0.00	6.10	22.80	70.00	101.00	113.40	99.40	79.40	60.00	45.20	36.80	34.00	29.50
7	4	1	1	A	1	0.00	0.00	0.00	0.00	8.30	94.00	128.30	115.60	101.00	85.70	69.20	53.10	40.80	36.80	27.50
8	4	1	2	B	1	0.00	0.00	0.00	0.00	0.00	0.00	23.20	69.70	96.80	119.40	126.70	143.10	122.80	100.30	67.10
9	5	2	1	B	1	0.00	0.00	0.00	0.00	10.40	41.90	103.10	107.30	70.10	45.10	35.20	34.00	30.30	23.60	24.90
10	5	2	2	A	1	0.00	1.60	2.40	5.60	8.00	47.50	99.80	130.20	110.00	81.10	52.00	50.70	35.20	38.90	30.90
11	6	1	1	A	1	0.00	0.74	5.76	16.28	45.08	86.17	54.72	32.96	33.35	32.62	30.95	34.43	29.09	27.18	23.40

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
12	6	1	2	B	1	0.00	0.00	3.75	5.75	63.57	123.36	86.99	34.32	32.25	30.46	30.11	32.54	28.39	24.80	21.08
13	7	2	1	B	1	0.00	0.31	10.82	20.59	42.63	104.76	104.81	76.72	62.22	40.67	39.90	38.25	33.65	32.47	28.49
14	7	2	2	A	1	0.00	0.00	18.00	79.80	90.80	126.10	122.50	104.20	79.40	61.70	47.70	48.80	40.90	34.10	30.50
15	8	1	1	A	1	0.00	0.00	0.00	0.00	1.70	79.90	61.80	35.50	26.20	27.90	28.40	27.20	29.00	24.10	19.20
16	8	1	2	B	1	0.70	1.70	18.30	22.00	43.10	98.40	90.30	52.00	38.30	28.00	24.30	31.10	26.90	25.90	23.44
17	9	2	1	B	1	1.30	1.60	2.95	4.87	19.40	108.20	115.50	86.80	48.20	29.40	29.10	29.00	18.70	18.80	16.90
18	9	2	2	A	1	0.00	1.40	3.30	0.00	2.80	57.90	75.80	55.00	44.20	33.90	33.90	27.50	22.50	23.80	15.80
19	10	1	1	A	1	0.00	0.56	0.11	3.38	17.31	62.13	58.74	61.38	57.07	66.54	45.36	52.19	41.95	39.30	33.78
20	10	1	2	B	1	0.00	0.70	0.10	55.50	65.00	71.80	79.40	75.30	68.80	51.60	54.00	50.90	42.80	25.30	34.80
21	11	1	1	A	1	0.00	0.00	0.00	6.30	34.00	96.20	80.80	51.80	38.40	29.40	32.20	32.80	26.30	24.80	17.40
22	11	1	2	B	1	0.00	0.00	0.00	3.60	27.80	114.70	87.00	65.00	42.70	39.40	32.80	32.50	30.40	35.90	22.70
23	12	2	1	B	1	0.82	1.34	0.67	2.71	0.90	4.24	32.19	33.43	38.27	41.75	37.02	64.10	45.04	47.51	31.83
24	12	2	2	A	1	1.10	1.70	1.00	0.00	0.00	0.00	0.00	27.50	47.70	87.00	62.20	54.60	46.20	34.60	31.10
25	13	2	1	B	1	0.00	0.00	0.00	0.00	0.00	26.10	56.70	50.30	34.90	30.70	26.80	35.00	27.60	26.80	27.10
26	13	2	2	A	1	0.60	0.00	0.00	4.80	10.30	17.90	11.80	14.50	8.50	13.80	32.20	78.50	44.20	32.00	27.40
27	16	1	1	A	1	0.00	1.07	1.44	2.34	14.67	94.70	72.01	50.54	45.60	28.45	30.35	37.61	25.97	23.89	22.79
28	16	1	2	B	1	0.00	0.30	0.00	1.30	8.40	95.70	102.70	71.70	50.10	30.80	24.20	32.70	28.20	18.40	16.30
29	17	2	1	B	1	0.00	0.60	0.50	0.50	10.30	36.80	49.80	42.80	40.10	34.80	31.50	33.50	31.90	29.70	28.40
30	17	2	2	A	1	3.50	4.30	4.90	5.10	21.90	77.20	67.40	47.80	33.70	35.80	33.60	34.40	31.00	27.80	30.10
31	18	1	1	A	1	0.00	0.00	0.00	0.00	0.70	43.00	47.10	24.70	27.30	23.00	27.60	27.10	28.70	23.50	25.60
32	18	1	2	B	1	0.00	0.00	0.00	0.00	0.00	55.16	55.96	28.50	22.80	20.70	22.70	23.05	22.43	18.14	19.13
33	19	1	1	A	1	0.00	0.00	0.00	1.93	12.39	90.85	99.09	73.59	42.03	32.56	28.29	34.68	30.12	25.90	23.24
34	19	1	2	B	1	0.00	0.00	0.00	0.00	0.60	97.30	136.20	103.50	57.10	32.80	29.30	26.50	26.60	23.20	21.30
35	20	2	1	B	1	0.80	0.00	1.47	5.53	38.25	87.89	82.85	57.07	37.75	29.07	26.33	35.02	30.19	29.98	24.46
36	20	2	2	A	1	0.00	0.00	0.00	26.20	58.50	97.90	75.30	53.00	32.90	31.30	27.40	35.80	28.50	26.50	20.10
37	21	1	1	A	1	0.00	2.30	1.30	0.00	0.00	5.90	19.40	11.00	5.00	14.90	22.70	54.80	30.40	29.60	23.70

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
38	21	1	2	B	1	0.00	0.00	0.00	0.00	0.70	82.30	79.50	44.50	25.80	22.50	20.40	27.30	20.90	21.00	16.60
39	22	2	1	B	1	0.00	0.00	0.00	0.00	15.49	52.96	59.14	34.32	26.63	24.66	20.63	27.73	26.31	24.18	18.67
40	22	2	2	A	1	0.00	0.00	0.00	0.00	0.00	30.00	30.70	32.10	22.40	17.90	17.40	20.70	18.40	20.80	14.60
41	23	1	1	A	1	0.00	0.00	0.00	0.00	0.00	22.10	34.10	33.10	44.50	53.30	33.10	34.80	31.80	26.20	24.60
42	23	1	2	B	1	0.00	0.30	3.10	35.90	51.90	67.80	69.00	79.30	67.40	56.90	48.70	41.70	36.00	31.30	26.10
43	24	2	1	B	1	0.00	0.00	0.00	0.00	0.00	14.29	76.43	52.80	31.27	29.60	26.28	30.18	26.37	25.00	22.02
44	24	2	2	A	1	0.00	0.00	0.20	1.30	0.40	33.60	52.90	34.50	22.10	25.00	23.80	44.90	32.00	29.10	24.30
45	25	1	1	A	1	0.00	0.00	0.00	0.00	1.79	0.89	51.66	49.09	23.16	26.83	35.29	35.87	33.37	30.32	26.63
46	25	1	2	B	1	0.00	0.00	0.00	0.00	24.00	99.90	57.90	38.90	32.00	26.90	29.50	29.60	27.60	23.80	23.10
47	26	2	1	B	1	0.00	0.00	0.00	0.00	2.30	39.80	66.60	66.80	48.10	50.60	37.50	42.00	40.70	37.60	38.10
48	26	2	2	A	1	0.00	0.00	0.50	1.30	0.80	57.80	97.60	110.50	76.60	63.70	46.80	45.20	35.10	39.20	34.50
49	27	2	1	B	1	0.00	0.00	1.00	1.80	10.20	42.70	50.30	28.60	27.00	41.60	45.90	53.00	44.20	43.20	33.80
50	27	2	2	A	1	0.50	2.10	3.20	0.00	4.20	56.40	84.30	75.90	59.80	55.80	58.70	58.30	48.40	35.80	36.30
51	28	1	1	A	1	0.87	1.10	1.08	1.85	3.12	9.18	16.16	12.60	13.13	12.40	10.60	34.41	30.90	28.10	25.90
52	28	1	2	B	1	0.00	2.00	0.00	1.10	2.80	2.90	8.30	21.70	47.00	58.90	43.30	61.20	56.90	54.90	45.60
53	29	2	1	B	1	0.00	0.00	0.00	0.00	6.40	94.60	109.70	66.00	45.40	37.10	34.60	32.60	29.80	29.50	29.00
54	29	2	2	A	1	0.00	0.00	0.00	0.00	3.40	117.50	124.60	70.00	37.90	31.90	27.40	24.80	24.90	20.00	21.70
55	30	2	1	B	1	0.00	0.00	0.00	0.30	17.70	75.40	94.30	43.50	35.50	30.00	27.10	35.20	30.70	26.70	23.50
56	30	2	2	A	1	0.00	0.00	0.00	0.00	8.80	90.10	96.90	49.50	37.50	33.30	35.40	38.20	33.30	27.40	30.60
57	31	1	1	A	1	0.00	1.44	1.48	1.76	4.58	26.10	15.03	16.94	21.44	25.43	28.88	36.82	31.34	25.22	21.66
58	31	1	2	B	1	0.00	0.00	0.00	0.00	0.55	19.09	28.44	19.68	19.76	23.32	24.07	32.67	27.23	23.45	22.12
59	32	1	1	A	1	0.00	0.00	0.61	0.81	2.36	3.58	3.51	2.53	2.62	20.00	39.14	30.90	32.80	29.82	29.91
60	32	1	2	B	1	0.00	0.00	0.00	0.06	9.85	24.55	23.43	16.50	15.67	16.96	43.54	57.03	42.12	35.87	29.19
61	33	2	1	B	1	0.00	0.20	0.00	0.00	2.90	41.50	84.20	58.60	32.40	25.40	23.40	25.30	23.60	23.80	16.10
62	33	2	2	A	1	0.30	0.00	1.00	0.20	10.70	98.30	118.20	82.80	61.40	46.60	39.40	33.20	31.30	26.20	24.00
63	34	1	1	A	1	0.00	0.00	0.00	0.00	0.34	16.19	38.49	33.32	50.41	39.86	32.42	39.19	36.74	32.97	32.84

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
64	34	1	2	B	1	0.00	0.00	0.00	0.00	0.00	30.00	51.40	38.00	25.50	29.00	30.50	35.90	32.20	28.30	29.04
65	37	2	1	B	1	4.60	6.90	7.60	9.10	37.30	101.50	192.50	198.50	189.70	190.50	199.00	191.10	161.00	111.10	83.10
66	37	2	2	A	1	0.00	0.00	0.00	3.50	55.50	175.30	225.90	252.90	224.10	214.80	182.60	196.30	182.50	145.90	76.70
67	38	2	1	B	1	0.00	0.00	9.49	66.00	83.42	112.39	106.99	87.32	75.28	64.64	50.76	47.90	36.84	32.13	23.23
68	38	2	2	A	1	0.00	0.00	3.20	49.10	86.60	113.80	114.40	96.70	70.50	56.20	48.30	44.50	37.70	31.70	25.47
69	39	1	1	A	1	0.00	0.00	0.00	0.00	13.30	78.89	89.00	66.73	38.53	37.09	30.51	37.56	27.37	31.35	24.75
70	39	1	2	B	1	0.00	0.00	0.00	0.00	0.00	28.20	39.80	31.20	35.30	28.70	24.30	33.40	26.50	24.00	19.30
71	40	1	1	A	1	0.39	0.88	1.65	2.21	1.11	32.51	24.98	16.86	24.51	59.99	56.04	65.50	49.27	38.99	38.01
72	40	1	2	B	1	0.00	0.00	0.00	0.00	21.40	40.50	29.70	18.80	20.30	25.60	45.00	48.80	41.40	39.40	33.60
73	41	2	1	B	1	0.01	0.00	0.11	3.45	11.05	75.78	40.04	24.17	21.26	21.15	21.65	26.00	20.53	21.34	18.94
74	41	2	2	A	1	0.00	0.00	0.00	5.30	7.00	78.80	73.10	35.00	28.60	24.10	24.30	31.40	24.70	23.70	23.91
75	42	2	1	B	1	0.47	0.44	1.21	4.20	14.54	109.98	106.30	56.81	46.99	36.62	39.91	38.38	36.21	29.55	28.59
76	42	2	2	A	1	0.00	0.40	1.42	10.00	34.00	83.50	111.90	68.30	48.70	43.60	43.50	43.30	39.40	40.60	33.60
77	43	1	1	A	1	0.00	0.00	0.00	0.00	0.44	54.66	52.84	34.10	36.36	35.88	35.59	52.17	35.73	35.50	27.86
78	43	1	2	B	1	0.00	0.20	0.29	2.90	11.70	113.03	95.90	47.02	32.13	26.62	25.50	31.80	27.20	23.50	21.18
79	44	1	1	A	1	0.36	0.38	0.53	0.87	22.96	73.36	63.29	41.35	42.01	38.62	33.03	42.42	38.80	36.72	26.99
80	44	1	2	B	1	0.00	0.00	1.15	1.82	38.02	76.98	58.22	34.91	35.39	37.30	32.32	37.36	33.19	29.00	26.21
81	45	1	1	A	1	0.65	0.26	1.40	0.87	1.04	11.12	17.16	23.52	38.49	36.03	38.11	46.47	42.22	33.25	30.12
82	45	1	2	B	1	0.00	0.00	0.31	1.10	16.20	64.90	59.40	33.90	33.80	34.20	31.00	35.20	25.80	27.63	26.70
83	46	2	1	B	1	0.00	0.00	0.00	0.00	1.70	92.40	66.70	40.80	26.90	25.10	20.20	21.00	25.80	19.80	20.44
84	46	2	2	A	1	0.00	0.00	0.00	0.42	18.50	100.90	84.80	61.60	43.80	45.10	37.10	32.00	31.68	24.98	20.20
85	47	1	1	A	1	0.00	0.00	3.50	17.30	47.70	128.50	85.80	52.20	36.90	32.00	29.00	34.50	28.80	26.20	10.80
86	47	1	2	B	1	0.00	0.00	19.20	61.00	96.30	161.60	103.40	66.60	43.50	37.60	32.00	37.50	34.60	24.40	27.10
87	48	2	1	B	1	0.00	0.16	3.64	3.73	19.87	96.53	78.48	47.39	40.81	33.88	31.96	31.32	28.91	29.44	30.03
88	48	2	2	A	1	0.00	0.00	0.00	0.00	21.08	98.31	62.71	40.55	34.55	32.85	32.49	30.67	30.68	30.34	28.61
89	49	1	1	A	1	0.00	0.20	0.00	0.77	0.60	63.10	44.99	28.23	23.26	23.28	24.04	25.24	23.75	19.03	17.13

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
90	49	1	2	B	1	0.72	1.03	0.87	17.20	41.13	72.91	46.17	36.99	31.79	30.58	26.33	27.37	23.14	19.31	18.65
91	50	1	1	A	1	0.66	1.28	2.20	1.99	1.94	1.20	2.73	5.08	3.93	5.70	19.38	40.93	39.90	32.75	28.24
92	50	1	2	B	1	0.00	0.00	0.30	0.60	0.20	7.00	10.60	9.70	10.20	20.50	29.10	49.00	38.60	37.70	25.30
93	51	2	1	B	1	1.02	1.15	1.72	1.43	1.92	13.70	19.60	20.64	25.08	36.05	43.60	48.34	41.95	37.64	26.92
94	51	2	2	A	1	0.00	0.15	0.42	0.73	34.51	67.93	47.64	40.79	37.58	42.68	41.02	40.65	37.20	34.63	27.41
95	52	2	1	B	1	0.20	0.20	0.20	0.00	0.10	31.10	32.20	26.70	35.60	40.90	42.80	48.10	46.50	44.20	39.90
96	52	2	2	A	1	2.00	2.10	3.00	3.10	18.00	59.60	90.40	78.60	65.30	51.00	53.80	52.40	58.40	46.30	40.00
97	53	2	1	B	1	0.24	0.66	1.03	1.76	2.68	36.84	78.11	86.14	78.80	73.45	49.56	40.73	38.29	34.25	28.17
98	53	2	2	A	1	14.56	3.40	31.80	124.60	26.70	104.60	86.90	65.20	39.00	42.70	46.60	43.90	49.60	46.10	35.80
99	54	1	1	A	1	0.22	0.41	0.45	0.57	0.31	4.45	15.70	31.27	41.82	40.49	32.72	38.44	42.70	37.62	34.31
100	54	1	2	B	1	0.00	0.06	0.00	0.02	0.49	3.76	5.56	7.07	14.68	20.64	20.62	48.60	35.65	36.12	29.24
101	55	2	1	B	1	0.00	0.21	7.01	11.94	11.18	31.45	35.74	28.63	26.67	24.38	23.89	27.82	22.26	21.36	20.07
102	55	2	2	A	1	0.00	0.00	10.10	11.22	14.59	21.23	13.31	11.22	8.79	8.17	8.18	8.77	7.03	7.72	7.72
103	56	1	1	A	1	0.00	1.21	0.40	1.19	0.80	14.50	50.90	55.50	44.10	31.30	30.10	37.90	32.10	25.90	22.50
104	56	1	2	B	1	1.00	2.00	1.90	0.80	1.90	13.90	41.70	47.70	42.10	41.10	35.30	44.50	33.40	29.90	25.90
105	57	1	1	A	1	0.00	0.00	0.00	0.00	0.10	45.70	56.90	44.30	31.80	25.80	19.90	29.60	25.80	24.20	20.80
106	57	1	2	B	1	0.00	0.00	0.00	0.00	2.80	37.60	33.10	41.50	37.20	35.00	31.90	38.00	29.30	32.50	25.10
107	58	1	1	A	1	0.00	0.00	0.00	0.00	5.20	36.30	33.90	25.20	19.60	27.50	27.40	33.00	29.40	26.50	24.40
108	58	1	2	B	1	0.00	0.00	0.00	0.00	11.60	44.90	48.70	31.50	27.00	26.30	23.20	31.40	27.20	27.00	24.90
109	59	2	1	B	1	0.00	0.00	0.00	0.02	7.02	108.71	87.25	46.99	29.79	24.52	23.02	23.82	21.62	17.91	16.21
110	59	2	2	A	1	0.00	0.24	12.85	33.81	35.79	81.84	70.25	37.33	25.97	22.18	20.90	22.62	19.96	17.86	14.41
111	60	2	1	B	1	0.00	0.00	0.00	0.00	0.00	5.50	27.40	28.30	25.90	33.50	36.80	55.10	42.00	38.50	31.80
112	60	2	2	A	1	0.00	0.00	0.00	0.00	0.00	1.30	26.30	28.30	22.70	22.50	25.20	51.90	40.50	39.60	33.10
113	61	1	1	A	1	0.00	0.00	0.00	0.00	0.00	20.18	25.54	41.10	67.00	70.11	56.68	78.88	43.37	36.86	35.36
114	61	1	2	B	1	0.00	0.00	0.00	0.00	0.00	26.20	41.90	48.80	42.70	40.80	33.50	32.70	30.60	25.30	25.78
115	62	2	1	B	1	0.00	0.00	0.00	1.70	37.80	118.87	171.61	166.87	139.68	117.14	83.70	47.33	48.42	43.10	33.10

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
116	62	2	2	A	1	0.00	0.00	0.00	14.90	53.50	170.10	263.90	250.50	210.10	193.90	154.10	102.70	71.00	48.90	40.90
117	63	2	1	B	1	0.69	1.11	0.91	0.71	0.37	11.97	20.09	15.14	15.48	20.47	41.66	39.67	34.70	32.76	27.98
118	63	2	2	A	1	0.99	2.03	1.72	1.65	1.82	1.59	2.05	1.51	2.05	2.77	3.33	37.87	28.85	33.14	30.10
119	64	1	1	A	1	0.10	0.00	0.00	23.30	79.90	128.50	94.70	82.80	65.90	50.60	40.60	35.80	30.10	30.00	22.50
120	64	1	2	B	1	1.50	2.40	0.60	10.20	31.90	112.30	114.10	97.80	88.80	75.40	60.70	51.50	47.00	40.20	32.60
121	65	1	1	A	1	1.05	1.50	1.58	1.70	2.00	3.00	4.50	15.50	62.60	62.60	44.80	51.70	47.80	46.50	34.00
122	65	1	2	B	1	0.00	0.00	0.00	0.00	0.00	15.50	43.30	89.50	97.10	78.50	55.40	38.30	39.90	31.40	27.50
123	66	2	1	B	1	0.00	0.87	2.54	3.35	5.80	28.80	28.90	24.20	20.40	23.74	44.64	44.93	32.66	29.68	44.20
124	66	2	2	A	1	0.00	0.00	0.00	1.10	18.80	50.40	38.30	28.90	21.90	29.50	57.40	65.70	53.30	48.30	39.60
125	67	2	1	B	1	0.20	0.19	0.62	1.06	1.26	23.68	22.67	23.35	18.10	23.91	27.04	42.41	34.17	35.36	25.68
126	67	2	2	A	1	0.44	0.29	0.82	0.64	0.77	0.64	3.09	15.16	26.32	34.38	33.77	38.36	38.49	34.63	30.48
127	68	1	1	A	1	0.00	0.00	0.00	0.40	1.10	24.70	79.40	33.50	23.70	22.70	31.20	53.40	41.00	38.00	26.00
128	68	1	2	B	1	0.00	1.30	0.00	0.00	0.10	15.30	31.70	19.70	17.50	18.90	45.20	52.10	33.70	34.40	29.80
129	69	2	1	B	1	0.00	1.40	2.00	1.50	3.50	57.60	45.40	42.20	36.10	31.20	28.70	31.90	29.00	26.30	23.80
130	69	2	2	A	1	0.50	0.20	1.70	0.10	0.00	9.80	22.70	10.40	12.50	14.60	46.30	49.70	39.10	35.70	35.40
131	70	2	1	B	1	0.80	1.30	1.80	2.30	10.50	71.10	90.60	53.00	48.00	57.50	74.30	74.20	76.70	67.40	54.70
132	70	2	2	A	1	0.00	0.30	32.40	48.30	49.60	47.00	37.00	27.60	27.50	30.70	30.70	30.00	29.70	23.80	29.30
133	71	1	1	A	1	0.00	0.00	0.00	0.00	13.40	90.90	92.20	70.60	49.10	33.70	32.00	28.20	26.00	21.70	23.90
134	71	1	2	B	1	1.70	0.20	0.00	0.00	14.50	97.20	131.40	98.30	64.40	55.80	49.60	48.30	38.60	32.10	28.90
135	72	1	1	A	1	0.00	0.00	0.00	1.90	35.70	92.40	65.60	50.00	38.20	31.40	26.70	28.30	26.10	23.40	17.40
136	72	1	2	B	1	0.00	0.40	0.00	0.00	34.20	91.90	70.30	45.70	33.70	29.20	30.50	28.80	34.60	27.70	17.90
137	73	1	1	A	1	0.00	0.00	0.39	0.00	0.02	11.33	14.02	26.09	29.35	27.65	24.67	37.14	29.32	25.63	21.09
138	73	1	2	B	1	0.00	0.00	0.00	29.00	28.40	39.80	49.90	42.60	32.90	27.30	26.40	30.70	26.96	24.50	22.40
139	74	2	1	B	1	0.00	0.00	0.00	0.00	1.71	76.12	63.66	28.84	20.41	18.24	17.62	22.39	19.76	17.57	15.99
140	74	2	2	A	1	0.00	0.00	0.00	0.00	4.20	55.40	43.00	24.00	20.10	19.90	20.70	24.60	23.20	24.10	19.10
141	75	1	1	A	1	0.00	0.50	1.22	2.18	18.63	66.36	69.40	47.91	40.78	36.19	31.69	38.66	34.72	33.01	28.94

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
142	75	1	2	B	1	0.00	0.00	0.00	16.30	59.80	97.10	59.40	38.20	36.70	34.30	33.20	34.30	32.60	30.00	24.80
143	77	1	1	A	1	0.00	0.00	0.44	0.55	2.36	45.57	60.32	62.70	62.04	49.25	40.92	36.06	34.89	28.86	25.32
144	77	1	2	B	1	0.00	0.00	0.00	0.10	0.80	38.00	49.50	48.70	57.20	48.54	32.70	27.20	27.90	26.40	20.93
145	78	2	1	B	1	0.00	0.00	0.00	0.00	3.40	27.60	46.60	49.10	57.60	62.40	38.10	46.20	35.60	30.40	27.30
146	78	2	2	A	1	0.40	0.00	0.90	0.30	1.70	27.60	91.10	77.20	58.60	42.20	43.30	46.80	40.60	30.70	32.10
147	79	1	1	A	1	2.86	4.24	4.60	3.80	6.27	51.96	68.73	63.36	33.91	53.95	74.64	70.27	58.34	39.89	32.94
148	79	1	2	B	1	0.70	5.30	5.30	4.40	6.60	37.40	77.10	77.40	59.30	58.90	47.90	82.91	60.40	44.70	29.40
149	80	2	1	B	1	0.00	0.00	0.02	0.00	5.59	29.70	35.70	29.06	55.80	36.55	33.14	31.11	28.02	25.83	24.44
150	80	2	2	A	1	0.00	0.00	0.00	0.00	5.69	66.09	49.27	22.57	28.15	30.13	27.77	31.28	28.75	25.28	23.61
151	81	1	1	A	1	0.00	0.00	0.00	0.00	1.85	45.84	62.12	55.08	67.91	54.36	38.49	40.00	35.67	34.26	28.11
152	81	1	2	B	1	0.00	0.00	0.00	0.00	4.30	51.20	78.40	67.00	59.80	46.40	46.80	39.10	38.90	33.70	30.00
153	82	2	1	B	1	0.00	0.00	4.80	2.90	18.80	102.40	70.10	35.00	26.10	23.70	20.70	24.40	20.49	18.00	14.39
154	82	2	2	A	1	4.62	0.78	0.60	0.32	3.60	74.50	85.10	62.20	36.10	29.60	23.60	31.27	24.60	24.41	20.92
155	83	2	1	B	1	0.00	0.00	0.00	0.00	0.00	17.64	38.73	40.81	45.79	36.44	31.14	29.68	28.07	24.17	18.08
156	83	2	2	A	1	0.32	0.00	4.30	16.89	38.26	76.88	69.27	46.56	41.31	32.93	28.84	27.34	25.94	21.84	16.71
157	84	1	1	A	1	0.31	0.25	0.27	0.28	2.52	74.79	66.13	50.56	30.73	31.27	35.09	37.54	30.38	27.70	26.00
158	84	1	2	B	1	0.00	0.22	0.00	18.33	32.22	74.40	64.04	39.94	41.47	47.73	35.93	39.50	38.91	32.43	30.28
159	86	1	1	A	1	1.12	2.99	6.95	12.86	11.38	58.61	111.11	113.79	90.22	73.08	54.86	50.64	44.08	31.70	20.92
160	86	1	2	B	1	0.70	0.40	1.40	4.50	12.00	57.80	123.00	98.50	66.00	55.50	44.50	53.00	39.10	35.00	28.90

Obs	c16	c17	c18	c19	KE_FIRST	KE_LAST	trt
1	33.10	33.60	29.60	27.40	16	19	2
2	9.70	10.90	8.10	7.20	16	19	1
3	14.66	14.06	12.41	10.62	16	19	1
4	16.67	17.60	14.71	10.62	16	19	2
5	19.64	19.20	17.06	14.42	16	19	2

Obs	c16	c17	c18	c19	KE_FIRST	KE_LAST	trt
6	23.70	21.40	17.80	14.40	16	19	1
7	24.20	25.30	20.20	16.20	16	19	1
8	30.40	30.00	27.40	22.30	16	19	2
9	18.40	19.50	12.40	11.90	16	19	2
10	23.00	21.90	18.60	17.40	16	19	1
11	21.12	19.68	18.55	16.63	16	19	1
12	16.79	17.47	15.45	14.84	16	19	2
13	26.86	26.33	23.62	18.75	16	19	2
14	31.20	26.50	22.70	18.50	16	19	1
15	17.60	16.80	13.90	13.70	16	19	1
16	22.70	16.90	14.70	13.60	16	19	2
17	14.20	17.80	11.20	9.00	16	19	2
18	17.00	16.10	15.70	15.50	16	19	1
19	31.73	25.51	25.67	23.59	16	19	1
20	27.30	23.00	18.10	16.20	16	19	2
21	18.50	17.60	15.50	15.90	16	19	1
22	19.00	18.90	15.90	16.40	16	19	2
23	32.82	31.39	24.07	27.20	16	19	2
24	33.70	27.90	23.00	24.90	16	19	1
25	19.20	18.40	15.30	14.40	16	19	2
26	18.80	20.30	23.00	21.40	16	19	1
27	17.40	16.57	15.40	14.31	16	19	1
28	10.60	12.40	7.90	3.30	16	19	2
29	24.60	26.60	19.90	19.40	16	19	2
30	23.20	22.10	19.10	16.80	16	19	1
31	16.20	18.10	14.30	12.30	16	19	1

Obs	c16	c17	c18	c19	KE_FIRST	KE_LAST	trt
32	14.98	17.60	14.40	12.65	16	19	2
33	23.56	23.09	20.63	18.48	16	19	1
34	18.80	19.90	16.10	15.50	16	19	2
35	22.42	23.05	17.35	17.72	16	19	2
36	17.30	16.30	14.60	12.60	16	19	1
37	23.40	20.60	19.50	20.70	16	19	1
38	14.50	18.80	13.60	13.60	16	19	2
39	16.41	13.69	12.13	14.43	16	19	2
40	5.60	9.70	4.30	3.70	16	19	1
41	19.10	21.90	12.80	10.80	16	19	1
42	24.40	23.10	19.60	16.20	16	19	2
43	17.17	19.03	15.37	13.78	16	19	2
44	17.80	18.10	16.20	13.60	16	19	1
45	22.72	21.49	17.36	15.67	16	19	1
46	20.50	20.20	18.50	16.40	16	19	2
47	33.00	35.20	31.70	27.80	16	19	2
48	31.50	35.90	28.10	22.30	16	19	1
49	28.20	31.40	22.90	24.10	16	19	2
50	28.10	34.00	23.70	26.30	16	19	1
51	27.02	32.92	29.93	31.51	16	19	1
52	44.30	52.50	37.40	34.40	16	19	2
53	20.90	22.50	22.40	18.50	16	19	2
54	16.00	16.20	16.00	14.10	16	19	1
55	22.10	20.90	19.80	19.40	16	19	2
56	24.80	22.50	19.30	19.40	16	19	1
57	21.16	22.65	18.34	19.12	16	19	1

Obs	c16	c17	c18	c19	KE_FIRST	KE_LAST	trt
58	17.70	19.49	15.26	13.67	16	19	2
59	25.88	28.32	23.43	19.90	16	19	1
60	24.10	28.25	23.47	19.93	16	19	2
61	16.50	14.50	11.30	11.20	16	19	2
62	19.00	15.00	13.00	9.20	16	19	1
63	27.96	29.74	26.11	24.49	16	19	1
64	23.20	19.40	18.80	20.00	16	19	2
65	74.70	60.40	50.60	36.50	16	19	2
66	34.70	22.90	19.70	20.30	16	19	1
67	19.03	19.32	17.08	16.50	16	19	2
68	19.60	19.30	15.50	13.00	16	19	1
69	24.41	21.00	18.73	16.56	16	19	1
70	4.70	3.90	6.70	6.20	16	19	2
71	35.60	34.55	30.61	26.50	16	19	1
72	29.50	28.80	21.60	21.70	16	19	2
73	18.12	15.85	14.46	13.70	16	19	2
74	16.60	14.80	12.50	11.60	16	19	1
75	26.67	25.44	22.99	21.88	16	19	2
76	29.30	29.10	24.20	23.10	16	19	1
77	22.76	19.53	17.76	15.87	16	19	1
78	17.31	14.50	13.13	11.40	16	19	2
79	26.73	26.96	21.91	20.42	16	19	1
80	19.70	20.12	16.69	13.06	16	19	2
81	27.65	25.64	21.09	18.87	16	19	1
82	16.90	21.70	15.10	13.40	16	19	2
83	15.70	14.40	11.50	12.30	16	19	2

Obs	c16	c17	c18	c19	KE_FIRST	KE_LAST	trt
84	18.90	17.20	18.70	13.50	16	19	1
85	18.20	18.80	14.60	14.90	16	19	1
86	18.30	15.30	12.90	12.10	16	19	2
87	24.00	22.47	20.51	17.72	16	19	2
88	19.57	20.78	19.25	18.47	16	19	1
89	16.42	15.22	12.76	10.84	16	19	1
90	17.84	14.63	11.79	10.97	16	19	2
91	23.05	26.54	25.63	25.93	16	19	1
92	26.00	25.90	23.80	18.00	16	19	2
93	27.44	25.36	21.88	19.84	16	19	2
94	24.20	21.71	19.38	15.85	16	19	1
95	36.10	32.50	27.10	26.50	16	19	2
96	38.50	37.90	29.20	28.60	16	19	1
97	29.46	29.79	27.10	23.93	16	19	2
98	46.86	33.40	20.20	23.90	16	19	1
99	32.21	32.83	27.12	24.04	16	19	1
100	15.10	29.08	26.68	23.50	16	19	2
101	17.56	16.08	13.77	13.62	16	19	2
102	5.18	3.69	2.99	3.09	16	19	1
103	18.48	18.80	18.10	13.80	16	19	1
104	26.50	27.00	21.30	17.20	16	19	2
105	16.40	16.40	14.60	14.50	16	19	1
106	21.00	17.90	18.70	16.20	16	19	2
107	16.20	15.20	9.70	12.10	16	19	1
108	15.10	11.40	10.40	8.10	16	19	2
109	14.69	13.12	11.49	10.32	16	19	2

Obs	c16	c17	c18	c19	KE_FIRST	KE_LAST	trt
110	13.41	12.59	10.07	9.12	16	19	1
111	27.80	26.70	25.50	24.90	16	19	2
112	23.60	23.60	22.70	20.80	16	19	1
113	30.50	30.90	25.30	21.48	16	19	1
114	20.40	21.40	17.50	14.90	16	19	2
115	29.11	30.70	25.78	21.83	16	19	2
116	32.80	34.40	29.70	26.70	16	19	1
117	27.61	26.34	23.98	19.87	16	19	2
118	26.69	27.42	23.15	20.57	16	19	1
119	22.20	22.50	16.30	13.60	16	19	1
120	28.70	34.60	26.00	20.40	16	19	2
121	36.65	34.40	31.80	25.70	16	19	1
122	23.60	25.90	22.10	15.60	16	19	2
123	31.84	33.20	28.60	26.63	16	19	2
124	34.30	34.20	31.20	25.70	16	19	1
125	22.57	23.45	21.30	17.41	16	19	2
126	30.06	25.14	24.32	19.46	16	19	1
127	33.30	32.30	27.00	23.90	16	19	1
128	26.90	25.80	24.50	20.40	16	19	2
129	21.60	20.40	16.80	15.20	16	19	2
130	28.90	26.70	20.40	20.30	16	19	1
131	57.20	57.90	42.60	34.60	16	19	2
132	23.80	26.30	19.90	20.10	16	19	1
133	14.40	16.30	13.60	12.90	16	19	1
134	28.90	26.10	18.80	19.30	16	19	2
135	17.20	15.10	14.60	12.60	16	19	1

Obs	c16	c17	c18	c19	KE_FIRST	KE_LAST	trt
136	19.20	18.00	11.20	12.30	16	19	2
137	20.25	20.23	17.45	14.44	16	19	1
138	18.40	15.80	12.80	10.70	16	19	2
139	13.45	12.65	11.81	11.09	16	19	2
140	10.50	10.80	10.20	9.90	16	19	1
141	25.84	26.63	18.88	18.46	16	19	1
142	22.50	22.00	17.80	17.20	16	19	2
143	22.24	24.46	20.54	18.86	16	19	1
144	18.50	20.30	17.50	17.50	16	19	2
145	24.40	24.30	19.50	19.30	16	19	2
146	33.90	27.50	21.60	21.70	16	19	1
147	31.79	39.57	32.51	26.97	16	19	1
148	28.40	34.70	28.00	36.81	16	19	2
149	19.19	20.90	17.40	15.61	16	19	2
150	19.67	18.69	15.85	13.18	16	19	1
151	27.79	31.96	24.11	24.50	16	19	1
152	24.50	25.90	20.90	20.10	16	19	2
153	12.30	12.40	11.10	10.20	16	19	2
154	23.92	17.80	14.90	14.27	16	19	1
155	15.24	16.27	13.89	12.38	16	19	2
156	15.08	15.96	11.61	10.64	16	19	1
157	22.12	22.61	17.83	17.04	16	19	1
158	23.74	24.22	18.57	12.40	16	19	2
159	26.10	28.28	23.52	20.14	16	19	1
160	27.80	27.80	20.70	18.80	16	19	2

FED CONCENTRATION DATASET (TOTAL DHA): BASELINE-NON-ADJUSTED

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	c20
1	1	2	1	B	1	68.0	68.2	70.8	71.6	74.7	71.7	69.6	69.2	71.6	72.0	72.1	70.8	70.0	66.5	61.3	68.5	75.0	75.2	73.4	78.0
2	1	2	2	A	1	102.0	103.0	101.0	102.0	101.0	99.0	98.7	96.6	105.0	101.0	101.0	95.5	99.1	93.4	91.9	107.0	114.0	116.0	110.0	113.0
3	2	1	1	A	1	37.7	37.1	37.6	38.3	39.8	40.7	39.3	38.3	39.0	38.7	40.8	38.5	38.7	37.6	36.4	37.6	41.2	41.9	42.3	43.1
4	2	1	2	B	1	38.1	38.1	38.3	35.6	38.6	37.4	38.4	37.7	37.7	40.3	38.0	37.9	38.9	39.1	38.7	39.8	40.2	48.7	85.1	103.0
5	3	2	1	B	1	39.3	37.2	36.7	39.5	38.9	42.5	41.7	41.6	42.5	44.1	42.9	41.6	41.2	40.6	40.2	38.0	38.6	41.1	44.6	54.6
6	3	2	2	A	1	43.7	42.1	41.5	44.3	46.5	45.1	44.8	42.0	47.1	46.6	47.6	47.0	48.5	46.1	45.7	44.1	46.3	48.9	55.9	69.3
7	4	1	1	A	1	71.0	70.0	68.3	72.3	74.8	73.6	73.5	74.0	69.0	66.9	67.0	66.9	65.7	66.6	65.2	60.9	68.8	68.4	72.5	84.3
8	4	1	2	B	1	73.9	74.4	76.0	73.7	78.3	75.4	73.0	71.2	69.1	71.8	77.2	72.8	71.5	71.2	74.1	72.7	76.7	80.0	78.9	81.7
9	5	2	1	B	1	47.9	47.2	47.5	46.4	46.9	50.5	50.7	52.2	53.9	50.5	53.0	50.9	52.0	52.4	48.6	48.4	49.9	48.4	54.5	65.9
10	5	2	2	A	1	58.6	56.7	55.4	58.3	59.0	54.6	57.3	56.2	54.8	57.2	55.4	53.9	54.1	50.2	51.5	53.2	56.0	61.8	67.1	68.8
11	6	1	1	A	1	35.5	34.0	32.4	34.1	33.4	36.3	33.7	31.0	33.8	33.9	33.7	31.6	34.7	33.5	34.1	31.9	37.8	40.8	52.2	75.8
12	6	1	2	B	1	39.0	34.2	36.9	36.9	38.4	38.1	37.8	37.5	35.1	35.8	40.7	40.1	37.1	34.1	34.4	35.2	39.7	43.5	39.2	88.6
13	7	2	1	B	1	54.7	54.0	55.7	57.0	51.3	55.9	58.4	56.4	51.0	52.1	53.1	50.7	52.3	49.3	43.7	47.6	55.4	67.3	73.6	84.3
14	7	2	2	A	1	68.6	72.9	79.5	77.9	76.1	78.2	76.1	76.4	74.1	56.8	63.1	68.2	71.5	73.0	65.2	68.6	78.5	91.2	141.0	138.0
15	8	1	1	A	1	75.2	74.0	72.6	74.6	76.8	77.3	80.0	86.4	77.5	70.9	72.3	79.5	77.0	72.1	78.3	73.4	76.6	80.3	76.0	80.6
16	8	1	2	B	1	63.3	63.8	66.6	70.4	73.5	73.5	79.0	72.5	70.1	71.7	51.5	66.1	66.6	65.9	64.4	73.2	80.0	86.3	94.5	109.0
17	9	2	1	B	1	35.9	38.6	39.0	38.6	41.0	47.2	42.4	43.9	49.2	49.0	44.6	38.6	41.6	47.0	39.9	41.8	43.8	46.5	48.4	52.9
18	9	2	2	A	1	41.7	41.3	43.0	44.0	43.3	45.4	46.4	49.2	47.5	47.1	58.5	44.0	44.4	40.5	40.4	40.5	48.1	57.3	50.4	54.7
19	10	1	1	A	1	47.9	46.8	51.1	50.2	44.9	44.4	46.8	44.7	47.2	50.6	47.6	49.0	47.7	42.2	50.4	45.1	49.2	48.4	49.1	62.0
20	10	1	2	B	1	51.0	52.7	49.8	52.1	45.4	61.2	45.3	46.9	59.5	51.3	55.1	51.7	50.0	62.0	64.0	50.4	52.4	52.0	102.0	97.3
21	11	1	1	A	1	34.3	40.2	37.7	38.4	36.9	36.3	38.3	35.2	37.0	36.0	35.5	33.7	40.7	34.5	33.4	37.9	41.0	34.1	49.7	64.7
22	11	1	2	B	1	40.2	41.5	40.4	41.4	40.7	41.8	44.9	37.4	42.2	38.0	44.6	42.2	41.5	39.9	38.1	44.7	44.6	46.9	53.3	65.8
23	12	2	1	B	1	45.0	42.7	46.1	37.4	43.8	49.4	45.5	41.6	49.0	48.3	44.0	41.1	49.4	41.3	39.6	41.9	43.8	42.2	49.5	44.7
24	12	2	2	A	1	47.5	45.2	47.0	51.9	50.8	53.7	58.1	56.4	51.2	65.8	54.4	52.8	50.3	51.6	51.7	52.4	50.6	52.3	51.9	54.4
25	13	2	1	B	1	77.2	76.4	82.6	70.4	75.5	79.8	71.7	73.6	79.5	73.3	84.6	73.7	87.6	76.0	66.4	84.8	81.3	78.5	76.2	76.4

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	c20
26	13	2	2	A	1	76.5	66.7	64.3	70.2	62.8	66.5	71.4	67.0	66.3	71.2	76.6	69.8	70.2	66.3	73.8	77.5	74.1	69.5	91.3	79.0
27	16	1	1	A	1	36.3	41.3	42.8	38.4	40.5	43.7	40.7	42.1	37.1	47.8	37.2	42.9	36.5	40.9	37.3	37.3	39.1	40.4	41.0	48.6
28	16	1	2	B	1	58.7	57.7	51.9	52.9	57.9	62.3	56.0	57.4	61.4	57.8	61.8	57.3	60.3	52.1	57.9	64.1	61.4	51.3	62.2	78.8
29	17	2	1	B	1	63.6	63.4	64.7	66.5	68.9	68.3	65.1	66.1	69.1	65.2	68.0	64.6	63.1	59.2	60.5	64.5	69.4	70.6	72.4	79.5
30	17	2	2	A	1	65.8	65.1	64.4	70.5	68.6	70.0	67.0	67.2	68.3	71.3	67.3	66.2	67.9	68.3	67.8	72.4	74.1	73.3	76.2	89.6
31	18	1	1	A	1	55.8	54.8	56.9	56.7	56.8	59.2	55.7	56.7	55.8	59.1	59.4	55.9	54.1	53.0	52.6	54.4	56.3	56.6	56.5	62.0
32	18	1	2	B	1	56.1	56.5	57.2	56.1	56.6	56.6	54.5	54.6	55.0	56.2	55.3	54.1	52.2	55.3	50.0	52.6	57.2	55.4	56.8	59.6
33	19	1	1	A	1	61.1	56.0	58.1	53.4	51.0	55.3	53.5	53.6	51.2	53.0	52.3	52.6	54.6	52.2	53.3	52.0	53.4	56.1	58.5	65.6
34	19	1	2	B	1	63.5	61.8	62.8	65.7	61.6	61.0	57.7	61.6	58.6	61.3	59.2	58.5	61.9	59.7	62.2	65.5	65.9	66.8	69.7	62.1
35	20	2	1	B	1	44.0	49.7	46.9	49.1	54.2	50.2	48.2	48.2	50.6	51.6	48.9	47.1	45.0	46.3	43.1	47.0	48.2	48.4	54.1	80.8
36	20	2	2	A	1	53.7	53.5	52.4	55.7	59.8	56.3	53.8	54.4	57.9	56.3	55.3	57.5	60.4	57.0	50.8	51.0	57.4	60.2	83.3	99.2
37	21	1	1	A	1	62.2	63.8	58.8	59.2	62.3	59.1	58.3	56.2	60.8	63.3	60.6	62.0	60.0	58.0	54.3	56.6	57.8	56.8	53.5	56.6
38	21	1	2	B	1	60.0	57.1	62.2	57.9	60.7	59.9	64.3	53.7	57.1	62.7	63.3	59.7	55.6	57.4	59.5	58.4	55.7	55.5	58.8	56.5
39	22	2	1	B	1	33.8	40.4	33.9	33.2	35.1	33.0	32.5	35.5	31.3	35.9	35.6	34.6	33.4	33.2	31.2	34.0	32.7	32.3	32.8	37.9
40	22	2	2	A	1	49.2	47.8	50.2	49.3	52.1	50.4	54.0	47.9	49.2	50.2	50.1	50.0	47.7	45.9	45.9	41.9	45.3	45.1	45.8	47.8
41	23	1	1	A	1	105.0	111.0	117.0	114.0	113.0	118.0	115.0	116.0	112.0	112.0	111.0	111.0	108.0	112.0	103.0	109.0	113.0	115.0	111.0	96.5
42	23	1	2	B	1	97.6	95.9	98.7	100.0	105.0	94.9	101.0	91.6	96.9	95.0	94.2	94.7	90.0	95.3	96.9	92.9	98.6	103.0	131.0	145.0
43	24	2	1	B	1	56.8	57.8	53.7	54.9	51.9	57.5	54.7	56.9	56.5	55.7	61.0	56.6	54.2	54.9	51.4	49.4	55.2	56.2	54.8	53.6
44	24	2	2	A	1	60.6	57.6	58.6	57.3	58.8	58.0	55.7	58.0	59.9	59.9	59.8	58.9	56.1	57.2	59.4	56.4	58.4	63.6	61.1	61.2
45	25	1	1	A	1	68.4	63.4	60.1	58.2	61.2	60.2	61.3	59.6	58.8	62.8	59.9	55.4	57.3	50.1	49.1	50.1	59.2	57.6	58.4	61.8
46	25	1	2	B	1	68.7	64.5	68.7	65.8	69.8	69.1	68.4	69.5	66.3	68.4	71.4	66.9	65.8	66.3	61.4	64.7	73.9	72.9	68.9	87.9
47	26	2	1	B	1	71.7	68.4	67.0	68.0	71.8	73.3	69.4	69.6	67.6	68.7	72.4	65.1	46.3	64.5	63.2	62.1	62.0	60.5	64.0	70.8
48	26	2	2	A	1	72.3	68.7	66.2	64.2	70.6	71.2	71.3	69.1	68.8	71.9	69.7	71.7	66.9	71.0	68.9	74.6	71.9	73.2	73.3	71.8
49	27	2	1	B	1	49.9	47.4	49.7	50.3	50.7	51.5	50.3	53.0	49.1	50.5	46.6	48.3	63.2	45.9	39.9	41.6	49.3	50.9	51.8	60.9
50	27	2	2	A	1	57.3	54.0	51.5	56.9	51.9	56.1	59.0	54.4	57.6	64.3	56.7	52.5	58.5	57.6	53.0	58.6	59.3	58.5	58.6	63.4
51	28	1	1	A	1	65.9	66.7	65.6	66.5	69.5	67.6	64.6	72.5	66.4	69.0	78.1	66.0	77.5	69.8	70.7	66.5	65.4	63.7	70.8	77.2

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	c20
52	28	1	2	B	1	72.5	68.4	79.6	74.5	63.6	76.5	69.2	63.7	73.6	78.1	79.9	70.1	75.7	66.6	76.8	75.0	84.1	73.1	79.4	76.2
53	29	2	1	B	1	59.7	54.1	51.8	51.3	50.7	50.1	50.6	49.6	49.5	51.3	51.3	52.0	51.0	50.3	53.2	53.7	55.5	53.2	54.6	60.1
54	29	2	2	A	1	54.9	54.2	50.3	48.0	50.9	50.2	50.3	48.3	48.4	50.3	51.4	49.3	48.7	48.3	52.5	49.7	52.6	50.3	49.3	54.4
55	30	2	1	B	1	61.9	55.4	58.2	55.6	57.9	56.2	57.0	56.7	54.6	54.2	57.1	54.8	51.0	49.3	52.0	56.4	58.2	54.3	56.7	72.3
56	30	2	2	A	1	57.4	58.1	55.6	58.3	58.2	54.8	57.0	56.5	56.3	54.4	54.7	54.6	54.4	53.0	56.0	55.3	59.9	57.2	55.6	63.9
57	31	1	1	A	1	23.9	21.1	22.1	23.8	21.2	23.3	22.5	20.9	24.0	23.9	26.1	24.9	22.5	23.4	25.0	22.3	26.0	24.0	25.8	26.6
58	31	1	2	B	1	27.8	27.5	28.1	29.3	29.8	28.8	27.3	29.3	30.7	34.5	30.6	29.1	28.9	30.9	31.6	29.4	29.7	30.5	29.8	30.3
59	32	1	1	A	1	31.6	28.9	28.1	28.3	30.0	29.0	28.3	28.1	28.7	29.7	32.3	27.6	30.8	27.8	25.8	28.7	25.6	30.6	28.8	34.5
60	32	1	2	B	1	63.4	42.3	39.6	36.9	37.8	35.7	40.3	42.4	35.6	36.4	39.5	37.4	38.2	37.3	35.5	38.0	39.5	41.2	41.9	44.7
61	33	2	1	B	1	53.1	53.4	54.0	55.5	53.8	56.5	50.8	51.6	52.3	52.6	53.9	51.4	56.5	51.7	51.5	52.7	56.0	55.9	56.1	61.4
62	33	2	2	A	1	65.3	69.2	65.4	65.7	68.9	70.0	67.7	73.4	69.2	69.5	72.3	72.5	69.3	68.2	65.9	70.8	73.1	74.9	76.3	86.7
63	34	1	1	A	1	39.9	38.9	37.0	41.7	39.6	38.0	39.1	38.0	39.9	41.3	39.1	37.6	37.4	38.1	33.0	37.9	38.7	39.2	38.4	40.2
64	34	1	2	B	1	43.0	42.4	40.1	43.1	41.9	42.6	44.6	41.5	45.7	42.4	44.3	40.7	41.7	42.7	37.6	40.4	42.4	43.1	46.5	50.6
65	37	2	1	B	1	89.2	86.6	89.4	95.6	92.4	97.6	91.7	93.2	91.2	93.5	95.8	95.2	90.8	85.4	94.2	90.9	96.9	98.9	104.0	130.0
66	37	2	2	A	1	148.0	144.0	148.0	141.0	158.0	142.0	139.0	136.0	135.0	134.0	135.0	132.0	130.0	135.0	125.0	127.0	136.0	135.0	141.0	231.0
67	38	2	1	B	1	34.2	35.1	32.8	35.4	36.9	34.6	35.8	34.9	35.1	34.6	34.5	34.6	34.0	32.4	31.6	31.6	35.8	43.4	81.7	86.7
68	38	2	2	A	1	50.6	50.1	49.5	51.8	49.9	51.3	48.8	48.0	47.8	47.0	49.4	48.6	49.1	45.1	43.1	46.5	48.0	54.1	84.8	107.0
69	39	1	1	A	1	70.9	69.9	75.1	71.9	77.6	73.8	71.7	71.0	72.6	73.2	70.5	69.7	68.6	66.5	61.7	64.6	66.2	70.0	66.1	84.2
70	39	1	2	B	1	103.0	103.0	105.0	105.0	107.0	98.4	98.5	99.8	101.0	101.0	102.0	96.0	97.6	98.5	89.3	95.5	97.6	103.0	95.7	95.4
71	40	1	1	A	1	50.8	51.1	50.7	48.5	50.5	47.9	47.1	45.2	47.1	50.3	46.4	48.9	48.4	49.5	46.3	46.4	51.1	51.4	47.6	45.4
72	40	1	2	B	1	63.6	57.3	53.1	56.1	56.1	57.0	57.1	58.2	60.1	58.2	58.8	57.3	56.4	57.5	56.6	51.9	57.9	56.9	55.3	68.8
73	41	2	1	B	1	50.3	50.1	52.7	53.3	54.2	57.1	51.8	52.9	56.0	54.5	55.3	53.6	50.3	50.9	51.7	53.3	51.7	55.0	54.5	60.9
74	41	2	2	A	1	58.8	57.8	59.7	58.5	62.5	60.7	59.3	55.8	59.6	60.5	59.6	64.6	57.7	56.4	50.7	55.5	60.1	59.4	64.0	60.0
75	42	2	1	B	1	41.8	44.4	42.0	43.7	44.6	44.2	40.6	43.8	41.5	46.7	43.4	44.0	39.7	42.9	40.6	40.5	43.0	41.1	47.5	55.9
76	42	2	2	A	1	47.5	46.8	44.4	49.0	49.7	44.2	54.7	50.2	51.3	53.3	57.0	51.9	52.2	47.0	50.9	49.0	53.3	53.0	59.7	77.8
77	43	1	1	A	1	32.4	33.2	31.2	30.9	32.5	32.3	31.9	32.1	29.9	33.0	32.3	30.8	31.2	31.4	30.2	30.7	30.2	27.1	29.1	31.0

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	c20
78	43	1	2	B	1	40.7	33.8	34.5	35.2	34.8	34.6	34.7	33.2	34.7	35.1	34.4	35.1	34.3	36.5	33.2	26.8	36.6	36.8	38.8	44.9
79	44	1	1	A	1	20.5	20.7	21.3	19.9	21.1	23.0	21.1	23.6	22.3	22.4	22.5	22.2	22.1	20.8	19.7	22.5	23.3	24.3	24.1	39.1
80	44	1	2	B	1	32.6	28.4	26.5	26.8	27.5	28.5	28.1	27.7	27.9	28.8	29.1	29.4	29.3	29.1	28.0	30.3	30.7	32.4	31.8	60.7
81	45	1	1	A	1	30.4	33.4	29.0	31.1	30.9	31.7	30.5	30.5	32.0	31.4	31.5	32.9	32.7	28.6	32.0	32.8	30.0	31.2	34.0	32.0
82	45	1	2	B	1	38.9	39.0	36.0	35.6	35.4	38.0	36.5	38.0	34.7	37.2	40.4	35.7	35.2	35.3	33.4	36.6	42.2	42.4	43.9	55.8
83	46	2	1	B	1	36.6	37.0	38.6	36.6	41.6	39.9	38.4	39.5	39.6	40.9	42.3	39.6	39.9	39.3	35.4	41.4	44.9	43.4	43.0	46.5
84	46	2	2	A	1	45.3	46.2	47.6	42.2	45.0	45.6	45.9	50.6	43.9	44.4	42.2	48.4	43.1	43.3	46.6	46.2	46.7	47.0	45.8	66.4
85	47	1	1	A	1	42.3	42.3	42.2	42.2	43.6	45.4	41.7	41.6	42.1	39.9	46.0	39.0	41.3	38.0	37.6	38.2	43.7	50.2	60.6	82.3
86	47	1	2	B	1	53.6	56.7	51.6	52.5	54.6	53.0	49.8	51.3	53.1	52.7	53.3	47.8	48.6	51.1	44.6	51.3	54.6	79.1	104.0	134.0
87	48	2	1	B	1	49.2	47.6	50.0	55.3	55.5	52.2	56.6	49.8	51.2	51.9	51.1	51.6	49.1	50.9	47.1	49.7	50.0	54.4	54.3	65.7
88	48	2	2	A	1	52.4	54.9	50.4	50.2	51.0	57.5	57.7	52.4	53.7	53.8	53.9	52.7	51.7	53.4	47.6	50.4	52.6	54.6	53.1	72.0
89	49	1	1	A	1	30.2	28.1	28.9	27.6	28.9	29.5	26.3	28.1	29.4	27.9	31.7	29.2	28.0	28.4	28.1	29.5	33.1	29.3	29.5	32.1
90	49	1	2	B	1	29.3	30.9	28.6	28.5	29.1	36.0	34.3	32.9	33.8	34.5	33.6	35.8	34.1	34.4	33.0	35.0	34.2	33.9	44.5	60.1
91	50	1	1	A	1	39.1	39.2	40.2	41.8	39.4	41.9	40.9	39.4	43.8	43.5	43.1	43.4	39.9	41.9	40.6	39.9	39.2	49.9	44.3	40.6
92	50	1	2	B	1	48.6	54.0	51.3	43.7	45.0	55.7	47.4	47.3	48.1	50.1	50.0	50.1	51.3	48.3	49.1	54.1	50.5	48.7	47.3	49.5
93	51	2	1	B	1	32.2	32.7	32.7	33.0	34.3	33.3	32.8	31.7	32.5	32.4	34.6	33.9	33.8	31.4	32.2	33.8	34.6	35.8	36.5	37.5
94	51	2	2	A	1	46.3	44.6	42.8	44.2	43.3	43.0	44.6	43.6	44.3	45.0	45.4	42.5	45.1	43.0	43.0	43.8	45.4	45.2	45.5	71.3
95	52	2	1	B	1	37.5	37.4	36.1	37.5	36.7	37.6	38.2	39.4	38.9	38.4	36.3	37.7	37.6	37.3	36.5	38.4	40.3	39.6	37.3	39.0
96	52	2	2	A	1	47.4	47.7	49.1	48.4	51.8	54.6	50.9	49.6	51.8	55.2	53.6	51.7	51.1	52.5	47.8	49.7	51.7	56.1	55.5	71.2
97	53	2	1	B	1	48.8	50.4	49.5	48.7	49.7	49.3	49.3	51.8	50.2	50.1	49.3	49.1	48.0	49.2	46.7	48.7	52.9	51.3	56.4	57.5
98	53	2	2	A	1	33.3	54.3	57.5	55.0	58.7	61.3	56.0	55.8	54.0	100.0	58.1	59.3	50.4	53.2	55.1	59.5	60.7	84.9	61.5	149.0
99	54	1	1	A	1	25.0	23.7	24.5	23.9	25.2	25.9	25.1	24.6	25.2	25.5	27.3	25.9	25.3	24.8	25.4	26.8	28.0	27.3	28.6	28.4
100	54	1	2	B	1	50.2	28.3	31.5	30.6	31.6	32.5	30.3	29.8	30.9	30.9	31.0	28.9	30.2	30.0	33.2	33.1	32.1	34.2	34.0	34.8
101	55	2	1	B	1	49.9	46.5	47.4	49.2	49.3	47.6	47.2	49.1	49.9	48.6	48.4	49.4	49.8	51.5	47.1	52.0	50.2	55.6	62.8	59.4
102	55	2	2	A	1	51.9	51.5	52.6	51.9	55.0	51.7	53.3	51.1	52.3	54.3	52.1	47.2	48.1	44.8	46.2	45.6	45.6	54.6	53.4	56.7
103	56	1	1	A	1	46.3	45.2	46.9	45.3	47.2	46.3	46.7	45.5	46.3	47.7	49.7	47.9	46.8	47.0	45.8	44.7	49.0	48.0	48.9	48.8

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	c20
104	56	1	2	B	1	49.5	45.8	47.0	49.3	49.5	49.7	50.4	50.3	48.6	51.5	54.3	50.4	52.2	52.4	53.1	52.4	55.3	56.6	55.1	57.3
105	57	1	1	A	1	85.9	85.8	86.8	85.5	87.7	84.8	81.8	79.7	85.5	84.2	87.1	86.3	83.1	83.4	83.2	81.5	82.1	85.7	83.3	88.6
106	57	1	2	B	1	82.3	83.9	86.1	80.9	88.3	88.0	89.9	83.4	80.8	88.6	88.8	82.1	81.3	83.6	89.2	80.3	84.4	84.1	80.3	89.5
107	58	1	1	A	1	60.3	62.6	58.3	56.0	58.7	57.3	60.7	57.6	58.7	57.5	57.5	57.6	56.7	53.5	48.5	52.1	56.1	56.2	52.0	68.1
108	58	1	2	B	1	66.3	66.8	66.1	65.0	69.9	68.1	67.2	67.8	68.0	66.0	71.9	64.5	65.6	65.4	62.7	61.6	67.2	66.2	65.7	82.3
109	59	2	1	B	1	25.9	26.2	26.5	26.6	26.1	26.4	27.0	27.9	27.4	25.8	27.2	27.7	27.1	25.9	26.6	27.0	29.0	29.7	29.3	34.1
110	59	2	2	A	1	36.1	36.6	36.5	36.2	38.0	38.0	37.1	35.7	34.4	35.8	34.8	34.5	32.2	30.4	31.7	32.3	37.2	46.5	59.5	58.2
111	60	2	1	B	1	71.0	71.9	67.4	69.3	71.9	70.2	72.3	72.0	71.7	74.8	77.6	73.2	70.3	72.0	67.3	67.5	70.5	70.7	68.0	72.4
112	60	2	2	A	1	75.3	73.7	74.4	76.6	74.8	78.8	78.6	79.6	80.3	80.5	84.3	83.6	82.2	78.2	70.1	73.2	76.6	77.2	78.7	77.7
113	61	1	1	A	1	32.8	33.0	32.2	32.5	33.3	32.0	32.9	33.5	33.0	32.9	32.7	31.5	32.7	31.7	30.2	31.3	33.3	34.6	34.2	34.0
114	61	1	2	B	1	33.0	31.8	31.8	31.0	30.9	31.0	33.0	32.4	31.5	33.9	33.2	32.3	32.6	34.1	34.6	33.5	36.2	37.1	36.2	35.3
115	62	2	1	B	1	47.6	46.5	48.6	46.7	53.0	52.1	51.9	51.3	51.7	49.2	49.9	50.7	49.2	45.7	45.7	43.9	45.9	47.1	51.8	84.3
116	62	2	2	A	1	65.2	63.6	59.7	63.8	68.1	65.2	67.2	63.7	64.6	67.1	62.4	64.9	64.2	60.6	56.7	58.5	65.7	67.0	80.7	121.0
117	63	2	1	B	1	53.6	55.4	54.1	56.7	57.3	54.9	56.8	57.8	56.7	55.6	56.0	56.3	53.2	51.8	52.2	55.1	59.1	55.0	58.1	54.8
118	63	2	2	A	1	66.8	63.9	64.9	62.9	62.2	65.7	63.9	68.3	66.5	65.6	69.0	62.1	61.5	59.5	60.1	66.9	67.9	67.5	65.5	65.6
119	64	1	1	A	1	62.9	66.9	67.2	69.8	69.3	70.0	71.7	70.0	69.8	67.6	72.9	69.2	70.8	67.3	66.5	67.1	71.9	72.2	94.0	134.0
120	64	1	2	B	1	62.5	66.0	68.4	69.9	68.8	69.8	72.8	70.5	69.5	69.3	66.3	68.6	66.1	66.4	63.3	61.3	67.4	67.7	79.0	95.5
121	65	1	1	A	1	57.2	58.6	52.7	57.8	59.5	57.5	59.5	58.1	58.4	59.8	59.1	59.5	55.1	53.8	53.7	55.4	57.3	55.1	56.6	59.9
122	65	1	2	B	1	90.5	83.3	86.7	85.7	88.3	90.1	85.4	92.0	85.9	83.2	85.4	89.4	81.2	91.3	83.2	82.1	85.0	86.5	84.3	83.6
123	66	2	1	B	1	59.4	58.3	56.8	55.9	59.9	57.8	59.5	60.1	57.1	57.7	56.0	53.9	54.9	53.4	50.4	50.9	59.2	62.0	61.8	68.8
124	66	2	2	A	1	71.4	64.6	66.9	63.0	65.9	69.6	69.5	67.3	68.6	69.9	70.6	68.9	61.5	63.1	66.4	66.7	64.8	66.3	68.2	86.4
125	67	2	1	B	1	36.7	40.1	37.4	37.3	40.0	38.7	38.4	36.2	38.1	37.7	39.9	40.7	39.5	37.0	37.6	37.8	36.2	37.5	39.0	38.7
126	67	2	2	A	1	40.4	38.9	41.2	39.6	40.7	39.0	42.6	41.3	41.0	45.3	45.7	42.3	39.8	41.0	40.4	43.5	43.6	49.3	46.8	46.9
127	68	1	1	A	1	68.3	72.1	71.9	64.6	73.7	73.9	75.3	79.0	81.2	85.3	73.3	73.9	68.3	74.9	66.8	65.4	72.6	74.3	76.9	78.1
128	68	1	2	B	1	70.3	58.5	67.7	67.9	66.1	68.6	63.9	75.9	67.5	73.5	77.7	72.6	68.7	64.8	62.8	62.9	74.3	66.7	64.1	69.7
129	69	2	1	B	1	51.0	51.0	54.1	54.9	55.3	54.9	57.3	58.7	58.2	57.8	58.7	54.9	54.7	52.9	49.8	52.0	59.4	62.8	59.5	59.7

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	c20
130	69	2	2	A	1	50.5	52.0	50.3	54.3	60.0	57.9	55.7	57.0	59.3	61.7	61.3	56.5	59.5	56.0	54.3	54.2	56.2	58.7	59.1	53.6
131	70	2	1	B	1	57.0	57.5	57.5	56.9	64.3	64.1	60.2	61.0	65.1	59.3	61.1	59.2	60.4	56.2	53.7	54.7	60.8	61.1	60.4	66.5
132	70	2	2	A	1	58.9	58.7	55.5	56.2	58.5	65.8	62.2	58.2	66.0	64.3	61.3	61.3	58.6	58.8	58.2	58.4	64.9	80.6	86.7	88.2
133	71	1	1	A	1	56.4	61.5	55.3	63.1	60.0	62.8	63.5	60.4	58.1	61.7	57.3	58.7	59.0	56.0	53.6	54.5	59.3	61.2	66.5	82.5
134	71	1	2	B	1	41.4	62.4	64.4	62.5	64.7	64.0	62.3	63.6	65.2	64.7	59.0	58.8	62.7	61.3	52.0	64.7	73.8	68.0	71.2	83.6
135	72	1	1	A	1	46.7	44.9	46.5	47.9	45.6	45.7	44.1	45.1	42.5	43.4	46.4	41.0	44.0	43.3	41.5	41.2	42.0	44.1	49.0	73.8
136	72	1	2	B	1	41.5	41.8	42.5	44.8	42.2	41.6	42.5	42.5	45.0	41.7	44.0	43.0	39.2	41.7	42.5	44.0	45.5	46.7	46.9	78.0
137	73	1	1	A	1	33.8	33.0	31.6	32.1	35.0	36.4	34.5	33.6	33.6	33.4	33.0	32.8	30.8	31.7	29.5	32.2	33.3	33.3	33.9	34.5
138	73	1	2	B	1	43.8	43.0	43.0	41.3	43.3	42.6	41.9	41.7	40.6	42.6	41.0	41.9	37.5	40.3	41.2	42.0	46.6	44.9	65.0	59.8
139	74	2	1	B	1	42.9	42.3	43.8	44.8	46.9	44.3	44.8	43.9	45.6	45.4	48.3	42.5	41.9	43.9	42.5	41.2	41.9	44.0	42.6	43.6
140	74	2	2	A	1	96.6	93.1	90.7	92.2	94.7	98.5	91.3	90.6	91.0	94.8	98.7	94.9	91.1	88.7	89.1	83.6	82.0	82.4	86.0	89.1
141	75	1	1	A	1	33.9	34.3	32.1	34.5	34.8	35.0	36.2	33.3	34.8	33.4	34.3	33.2	35.3	33.3	32.0	32.1	37.0	38.6	40.0	53.7
142	75	1	2	B	1	45.7	46.3	46.6	45.9	46.3	50.0	49.9	46.0	45.4	46.7	43.1	43.6	45.2	41.7	39.4	43.7	44.4	46.8	60.7	84.6
143	77	1	1	A	1	22.3	23.3	22.6	24.1	24.1	24.0	24.6	25.0	24.3	24.1	23.6	24.4	24.5	22.9	22.3	23.6	25.9	29.9	30.7	32.3
144	77	1	2	B	1	32.5	31.9	32.9	32.1	32.4	32.9	34.4	32.2	32.3	30.9	32.7	32.9	33.3	31.6	31.1	32.8	34.7	34.9	34.2	35.8
145	78	2	1	B	1	70.7	67.6	63.5	65.7	69.9	71.1	63.9	70.5	65.7	62.9	61.3	58.6	64.4	59.9	55.6	60.2	63.3	62.7	65.1	73.2
146	78	2	2	A	1	62.5	61.6	62.6	66.0	67.6	65.1	57.4	65.9	61.2	70.9	68.1	64.6	69.3	71.4	59.5	67.0	66.6	69.6	69.8	68.2
147	79	1	1	A	1	37.6	37.0	38.5	43.9	43.1	45.8	50.0	51.2	45.9	45.7	42.5	42.3	41.7	41.4	36.3	40.1	47.2	50.8	53.1	57.9
148	79	1	2	B	1	49.1	44.7	48.3	50.8	49.2	50.5	49.7	49.8	51.7	56.7	49.3	45.2	50.1	54.1	40.8	46.6	50.1	52.6	57.6	61.3
149	80	2	1	B	1	21.5	22.0	21.4	22.4	22.5	23.5	23.1	22.0	22.1	21.9	22.7	21.0	22.1	19.9	18.5	19.6	20.2	21.4	21.3	27.4
150	80	2	2	A	1	25.4	25.6	23.6	23.5	24.1	22.8	21.7	23.4	22.9	26.3	23.6	24.7	24.8	24.0	25.2	24.5	25.9	24.8	25.8	29.7
151	81	1	1	A	1	52.2	49.3	48.4	52.3	50.8	55.7	56.9	53.6	57.8	53.8	53.3	51.7	54.0	54.4	47.8	45.7	52.2	48.4	52.9	52.6
152	81	1	2	B	1	58.4	58.4	62.0	63.8	64.6	69.3	66.5	67.1	65.9	66.7	61.7	65.0	66.3	61.7	58.7	62.1	68.5	69.7	67.6	76.7
153	82	2	1	B	1	46.7	49.5	49.8	48.0	48.1	50.2	47.6	50.1	50.4	49.3	50.3	49.8	49.4	51.2	50.1	47.3	50.1	51.7	48.8	61.8
154	82	2	2	A	1	48.4	46.8	49.2	49.7	50.0	53.9	53.9	51.6	55.3	54.2	54.9	51.7	51.0	50.8	51.2	50.9	54.1	55.6	53.3	58.8
155	83	2	1	B	1	68.8	69.4	69.8	71.4	71.5	69.6	68.1	70.0	69.5	70.5	66.6	69.5	63.8	62.6	66.3	62.4	64.6	68.9	65.2	65.1

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	c20
156	83	2	2	A	1	54.8	55.4	58.7	54.8	54.5	56.8	57.6	59.4	60.3	58.3	56.7	57.4	58.1	55.4	57.6	59.7	58.1	63.9	75.9	95.8
157	84	1	1	A	1	33.7	33.7	34.9	35.5	36.4	38.0	38.1	36.4	37.7	37.6	38.8	38.1	37.5	36.1	36.0	37.6	38.5	38.8	39.6	42.0
158	84	1	2	B	1	46.4	44.2	46.6	46.3	47.1	47.0	45.8	47.2	47.7	46.5	49.3	46.9	48.4	46.6	48.8	49.4	50.9	49.3	63.4	68.4
159	86	1	1	A	1	42.2	43.6	44.6	44.8	45.7	46.8	47.3	48.3	46.0	47.4	47.1	47.0	45.6	44.1	44.3	85.3	51.7	54.8	63.4	57.9
160	86	1	2	B	1	55.6	57.9	59.1	57.9	63.1	62.3	60.5	60.5	64.0	63.9	62.8	63.4	65.2	63.8	60.9	63.4	65.2	68.8	71.6	76.5

Obs	c21	c22	c23	c24	c25	c26	c27	c28	c29	c30	c31	c32	c33	c34	KE_FIRST	KE_LAST	trt
1	142.0	137.0	110.0	93.5	98.6	102.0	94.5	77.7	72.9	70.9	81.4	83.2	81.8	82.0	30	33	2
2	133.0	147.0	140.0	123.0	116.0	123.0	115.0	104.0	92.7	88.5	101.0	104.0	104.0	92.6	30	33	1
3	56.7	72.4	58.6	50.3	50.0	47.6	50.1	45.5	43.9	38.6	41.1	43.4	42.5	40.6	30	33	1
4	113.0	93.5	66.9	58.0	56.7	49.8	51.7	46.8	46.6	41.4	45.7	48.3	45.2	41.3	30	33	2
5	90.1	96.1	79.6	69.7	66.7	63.5	58.7	49.8	52.2	49.5	48.9	51.1	53.3	51.3	30	33	2
6	106.0	123.0	128.0	115.0	99.4	87.5	73.3	66.7	65.0	60.4	60.9	61.2	58.0	55.2	30	33	1
7	143.0	170.0	157.0	144.0	134.0	122.0	106.0	92.2	87.5	70.8	76.0	82.2	75.3	65.5	30	33	1
8	82.2	98.0	133.0	148.0	164.0	176.0	179.0	143.0	133.0	105.0	88.2	99.6	93.2	83.9	30	33	2
9	97.2	146.0	130.0	107.0	90.0	78.2	72.6	69.4	59.0	60.3	60.1	61.7	54.7	54.7	30	33	2
10	110.0	134.0	149.0	146.0	121.0	98.9	94.4	71.3	76.4	65.6	62.4	62.9	67.4	62.4	30	33	1
11	96.9	59.9	45.6	44.2	45.1	45.8	43.1	39.3	39.2	39.4	41.2	42.1	42.0	40.9	30	33	1
12	116.0	72.2	46.2	47.3	44.0	44.1	44.4	38.2	37.4	34.7	36.8	39.2	39.8	39.8	30	33	2
13	119.0	108.0	91.7	87.4	70.8	73.5	67.6	60.2	61.7	57.2	64.7	66.2	57.7	59.3	30	33	2
14	163.0	130.0	136.0	119.0	114.0	99.4	87.3	80.8	73.7	72.7	88.6	85.1	79.5	70.5	30	33	1
15	143.0	117.0	95.3	88.0	85.1	99.3	78.7	76.3	67.8	66.2	80.8	75.3	75.8	66.3	30	33	1
16	142.0	129.0	100.0	104.0	74.2	81.1	79.5	65.6	67.7	69.3	78.3	76.0	76.6	71.4	30	33	2
17	111.0	100.0	79.6	66.2	53.3	55.9	55.4	45.3	50.2	47.0	46.3	57.6	51.9	45.9	30	33	2
18	91.9	94.2	80.4	65.3	58.0	63.2	53.7	49.7	52.9	49.3	50.6	52.9	56.5	53.7	30	33	1

Obs	c21	c22	c23	c24	c25	c26	c27	c28	c29	c30	c31	c32	c33	c34	KE_FIRST	KE_LAST	trt
19	96.4	78.5	77.3	76.6	80.6	67.9	63.1	63.5	59.0	52.5	52.8	48.3	49.8	53.5	30	33	1
20	102.0	103.0	91.5	100.0	75.2	85.9	76.8	61.9	47.3	67.6	61.1	56.3	59.0	57.7	30	33	2
21	106.0	82.8	54.8	51.0	40.1	43.2	47.8	43.4	37.9	38.1	41.7	41.9	41.5	49.4	30	33	1
22	131.0	91.9	71.6	59.7	62.0	56.3	49.3	39.5	63.0	42.8	49.5	53.4	46.5	50.8	30	33	2
23	56.6	67.7	56.4	62.1	65.8	59.4	64.8	49.4	53.2	43.7	51.3	52.9	54.2	48.0	30	33	2
24	62.0	54.2	59.9	71.5	98.6	85.4	66.3	62.2	50.6	49.1	57.2	53.4	58.0	53.3	30	33	1
25	99.0	109.0	91.5	79.3	81.3	79.9	72.8	81.8	73.7	70.1	76.9	71.7	77.4	81.8	30	33	2
26	87.6	80.1	75.5	68.7	77.2	97.5	99.3	86.3	73.8	74.7	69.5	75.6	75.2	81.3	30	33	1
27	125.0	81.5	69.5	62.8	53.7	49.4	58.7	48.5	48.3	45.2	49.2	44.1	44.6	50.7	30	33	1
28	150.0	128.0	100.0	78.2	71.7	59.6	70.8	64.0	51.9	51.8	60.4	68.1	61.8	54.4	30	33	2
29	95.9	98.1	89.8	86.4	80.9	80.2	74.7	67.8	63.8	65.6	70.1	76.1	69.5	67.7	30	33	2
30	125.0	103.0	91.7	80.0	80.5	78.9	73.9	69.7	66.7	71.8	67.1	72.2	70.1	68.3	30	33	1
31	88.5	79.5	64.7	69.0	66.4	69.5	59.7	57.1	53.2	57.8	57.0	59.9	56.0	51.9	30	33	1
32	98.2	81.2	63.5	62.7	61.2	63.7	56.5	53.5	49.3	52.9	54.0	61.4	55.1	52.4	30	33	2
33	127.0	119.0	97.3	77.7	68.3	59.3	63.0	56.5	52.5	50.9	53.5	53.0	51.9	50.8	30	33	1
34	143.0	146.0	127.0	101.0	84.7	74.0	62.4	61.5	57.2	56.0	59.8	64.9	57.8	56.4	30	33	2
35	108.0	88.1	72.7	57.1	55.9	53.3	56.7	52.4	52.5	49.7	52.4	55.6	50.5	54.6	30	33	2
36	114.0	84.5	75.9	63.9	63.6	59.7	66.4	57.3	53.5	50.1	56.7	57.4	56.0	53.6	30	33	1
37	54.8	61.1	59.6	55.6	62.7	62.5	65.8	54.1	55.8	51.9	57.3	50.7	56.7	59.6	30	33	1
38	70.1	66.7	62.0	58.6	59.1	59.3	54.5	53.4	52.5	50.5	53.0	57.1	57.7	54.9	30	33	2
39	43.0	43.1	37.4	33.5	36.6	33.3	31.8	31.6	32.2	29.6	35.8	36.8	35.8	36.4	30	33	2
40	54.5	55.5	49.9	50.2	47.4	49.4	43.2	42.2	39.1	39.1	44.2	46.2	44.5	43.9	30	33	1
41	135.0	144.0	135.0	142.0	154.0	134.0	129.0	121.0	111.0	106.0	111.0	123.0	103.0	94.7	30	33	1
42	156.0	156.0	168.0	148.0	139.0	129.0	121.0	109.0	103.0	95.6	103.0	110.0	106.0	92.9	30	33	2
43	64.2	102.0	80.2	65.8	69.7	67.8	62.8	57.1	56.1	54.8	53.7	57.1	53.9	50.6	30	33	2
44	84.7	91.9	74.9	66.6	73.6	68.8	83.0	65.4	62.4	61.1	57.6	60.5	59.9	56.8	30	33	1

Reference ID: 3227106

Obs	c21	c22	c23	c24	c25	c26	c27	c28	c29	c30	c31	c32	c33	c34	KE_FIRST	KE_LAST	trt
45	58.6	106.0	82.8	62.4	71.3	80.8	65.8	63.1	60.1	59.6	66.8	63.9	58.8	58.4	30	33	1
46	131.0	95.8	78.9	72.2	67.3	68.2	62.4	59.0	57.7	59.7	71.6	71.7	68.5	67.8	30	33	2
47	93.3	105.0	101.0	86.7	90.2	77.7	71.0	64.4	61.3	67.1	68.2	77.0	74.2	70.1	30	33	2
48	114.0	135.0	134.0	105.0	96.5	85.9	78.0	64.8	70.9	69.5	81.8	83.8	75.9	72.6	30	33	1
49	74.3	73.4	51.8	59.8	65.4	63.6	64.7	56.2	56.9	48.6	50.9	55.9	50.3	50.7	30	33	2
50	104.0	106.0	87.3	80.8	80.8	82.7	70.3	63.3	55.4	55.4	58.4	63.8	56.8	60.1	30	33	1
51	76.0	78.0	71.9	70.1	72.6	66.0	70.1	63.3	64.4	62.0	67.1	78.4	68.8	78.5	30	33	1
52	83.0	79.4	83.1	101.0	92.2	89.3	93.7	84.6	79.9	74.1	83.7	81.9	76.1	73.6	30	33	2
53	139.0	134.0	91.0	76.8	74.9	71.4	61.2	57.9	56.9	58.2	55.9	56.7	56.3	53.9	30	33	2
54	152.0	137.0	87.9	67.3	65.1	62.0	54.5	54.0	49.4	55.5	53.1	51.4	51.5	50.5	30	33	1
55	109.0	104.0	67.9	65.5	62.3	60.7	65.6	57.7	50.1	51.5	60.8	57.0	57.7	58.1	30	33	2
56	123.0	98.7	70.7	67.6	62.9	68.2	66.7	58.8	52.2	59.7	60.3	59.1	55.9	57.4	30	33	1
57	44.7	28.5	29.9	32.9	38.7	38.8	31.3	33.0	26.9	24.0	29.1	32.8	30.2	34.4	30	33	1
58	41.6	40.9	34.0	38.1	38.0	38.5	35.2	33.4	30.7	31.5	32.9	37.4	31.0	35.8	30	33	2
59	32.5	30.6	28.7	29.1	42.9	56.0	40.2	43.2	39.6	34.1	34.5	38.8	33.4	34.4	30	33	1
60	56.9	48.2	45.7	42.5	40.7	62.7	61.7	52.8	42.0	37.2	47.1	52.8	48.1	45.8	30	33	2
61	85.3	108.0	87.2	77.1	67.1	62.7	62.2	56.5	57.4	53.4	59.7	60.9	55.8	58.0	30	33	2
62	145.0	149.0	124.0	110.0	99.2	96.8	82.0	73.5	66.6	71.2	72.5	71.4	68.0	64.9	30	33	1
63	52.1	55.3	48.1	63.9	55.3	49.7	48.6	43.8	41.5	43.8	44.8	48.3	46.5	46.2	30	33	1
64	67.0	66.3	52.8	47.4	52.6	55.3	47.6	44.3	41.4	42.1	43.1	38.1	39.0	43.8	30	33	2
65	219.0	245.0	240.0	233.0	214.0	222.0	220.0	190.0	143.0	119.0	119.0	121.0	116.0	102.0	30	33	2
66	316.0	355.0	359.0	325.0	305.0	251.0	277.0	267.0	228.0	166.0	141.0	142.0	135.0	131.0	30	33	1
67	103.0	92.7	74.4	67.7	61.5	52.5	53.5	46.1	44.0	38.3	42.2	46.6	45.7	47.6	30	33	2
68	120.0	108.0	93.2	74.8	66.8	62.8	63.3	59.1	53.3	50.2	59.2	63.1	56.6	55.2	30	33	1
69	129.0	128.0	109.0	91.9	93.2	82.1	79.5	70.2	73.3	68.6	79.0	79.0	74.7	72.3	30	33	1
70	124.0	125.0	120.0	120.0	113.0	110.0	103.0	97.6	94.1	86.3	87.9	91.8	96.6	87.3	30	33	2

Reference ID: 3227106

Obs	c21	c22	c23	c24	c25	c26	c27	c28	c29	c30	c31	c32	c33	c34	KE_FIRST	KE_LAST	trt
71	69.5	56.7	53.1	56.9	79.6	70.1	61.1	49.4	44.5	42.2	49.0	48.3	46.7	44.0	30	33	1
72	83.2	62.7	55.4	54.6	58.2	72.3	59.5	53.8	52.0	50.3	55.8	56.3	50.1	52.6	30	33	2
73	103.0	64.6	56.8	54.2	56.3	58.3	58.2	49.8	53.3	51.5	58.5	55.9	55.0	55.8	30	33	2
74	112.0	94.4	67.8	63.5	59.6	59.2	64.8	55.8	56.3	57.6	62.4	62.4	57.5	57.8	30	33	1
75	124.0	90.4	62.2	60.0	54.8	58.7	53.9	48.4	46.5	47.0	51.7	53.7	50.4	53.0	30	33	2
76	109.0	115.0	75.7	66.2	64.4	65.7	58.6	58.0	59.7	56.1	57.2	61.0	57.0	57.9	30	33	1
77	70.5	61.1	44.8	47.0	46.6	43.5	48.1	38.0	38.4	36.3	38.2	36.9	36.3	37.9	30	33	1
78	117.0	85.5	49.5	44.3	40.8	40.2	42.7	39.0	36.6	38.5	39.0	37.6	37.4	37.8	30	33	2
79	70.0	50.7	40.6	41.5	38.7	35.0	34.5	30.9	30.5	44.4	29.3	29.3	27.2	27.8	30	33	1
80	75.7	54.3	40.6	43.6	44.9	40.7	38.4	34.1	31.4	31.8	33.2	34.0	30.3	29.0	30	33	2
81	42.4	39.5	43.5	52.8	52.4	54.1	48.1	46.0	36.6	36.5	36.5	42.5	36.6	33.3	30	33	1
82	84.9	67.7	53.3	51.0	53.8	47.4	42.0	37.1	40.4	41.5	40.4	46.4	37.9	36.7	30	33	2
83	102.0	65.5	55.2	56.2	57.2	54.7	50.5	54.6	46.2	25.0	44.9	48.2	45.4	47.9	30	33	2
84	112.0	88.1	79.7	69.1	73.7	64.0	57.5	53.9	49.9	47.9	53.0	47.8	49.5	43.8	30	33	1
85	139.0	91.4	69.1	56.7	54.6	55.3	53.2	47.9	45.8	41.0	49.9	50.0	49.7	48.4	30	33	1
86	156.0	103.0	84.6	67.7	67.3	62.7	59.3	53.9	48.1	54.4	61.5	59.6	55.2	52.7	30	33	2
87	114.0	80.7	61.8	62.2	56.0	54.1	48.3	45.7	48.2	44.8	52.2	55.9	53.4	53.3	30	33	2
88	119.0	76.3	66.0	63.2	60.7	59.5	50.3	51.0	52.4	50.9	52.1	53.2	55.1	54.8	30	33	1
89	76.4	49.1	38.7	37.8	39.9	36.5	31.8	30.6	30.7	29.5	34.1	35.5	32.1	30.4	30	33	1
90	75.3	52.9	46.1	42.6	42.6	41.6	37.2	36.0	33.6	34.9	36.4	35.3	32.4	32.6	30	33	2
91	43.5	40.1	44.2	41.9	48.1	54.1	52.6	56.2	49.6	45.7	47.8	50.4	56.9	57.5	30	33	1
92	60.1	51.3	50.7	53.5	60.5	66.9	56.8	55.4	53.3	44.8	54.1	54.9	62.0	53.4	30	33	2
93	46.0	44.3	41.1	43.3	50.4	55.5	44.6	39.5	36.5	32.7	38.2	37.7	36.8	38.3	30	33	2
94	90.5	64.1	55.7	52.6	58.3	57.2	49.9	48.0	47.6	45.0	49.9	49.2	49.6	46.1	30	33	1
95	64.1	52.9	51.0	55.1	56.5	56.0	50.7	47.7	46.8	46.8	50.9	50.6	48.1	51.2	30	33	2
96	97.3	104.0	86.6	81.8	70.1	73.7	61.5	65.1	57.3	56.4	62.4	68.5	60.1	62.9	30	33	1

Reference ID: 3227106

Obs	c21	c22	c23	c24	c25	c26	c27	c28	c29	c30	c31	c32	c33	c34	KE_FIRST	KE_LAST	trt
97	79.9	103.0	105.0	95.6	94.2	71.3	58.1	51.6	47.1	43.1	51.8	56.2	51.8	51.9	30	33	2
98	116.0	102.0	85.9	73.0	71.4	63.4	60.6	63.5	61.2	54.8	62.4	66.4	63.7	61.0	30	33	1
99	31.6	38.9	54.4	65.6	66.6	54.7	53.5	48.4	38.4	35.0	38.2	40.6	36.7	36.1	30	33	1
100	37.3	38.3	37.6	43.1	47.3	49.3	70.7	54.3	49.4	39.5	43.0	42.9	39.8	38.4	30	33	2
101	78.4	75.3	68.1	66.5	62.2	58.5	58.6	50.9	50.0	50.2	49.6	48.5	48.0	48.7	30	33	2
102	56.9	49.3	47.0	44.1	44.8	45.3	42.7	39.5	42.0	43.1	46.4	44.0	43.0	40.7	30	33	1
103	64.8	89.1	83.0	69.3	60.1	63.7	67.4	59.3	54.5	50.6	50.5	54.0	54.4	50.5	30	33	1
104	68.4	83.7	83.0	74.6	76.4	71.2	73.1	60.8	58.4	56.6	64.0	65.3	60.1	54.8	30	33	2
105	117.0	102.0	92.6	86.3	86.6	83.1	89.5	82.0	80.2	79.3	81.6	84.1	79.8	81.4	30	33	1
106	108.0	88.9	96.8	91.9	96.1	92.3	89.0	77.7	86.7	80.4	85.1	79.2	80.4	79.1	30	33	2
107	84.3	72.7	65.2	63.4	69.3	68.3	63.2	56.6	53.5	51.2	59.5	58.4	55.2	58.7	30	33	1
108	100.0	90.0	77.5	73.0	71.5	72.7	67.9	61.8	59.7	58.0	63.0	62.2	60.4	58.2	30	33	2
109	105.0	72.0	50.3	43.7	40.0	38.2	35.0	32.7	28.7	30.0	32.8	33.4	31.6	31.1	30	33	2
110	97.0	76.9	52.0	44.6	41.6	39.7	38.6	35.6	34.3	34.1	39.0	39.5	35.9	36.7	30	33	1
111	77.5	87.2	84.1	79.5	84.2	86.2	88.8	76.1	71.9	65.9	68.7	68.4	70.0	73.2	30	33	2
112	86.3	98.1	92.7	86.3	86.7	88.8	96.6	84.2	82.4	73.9	78.0	75.0	79.2	78.3	30	33	1
113	49.1	49.6	62.5	77.6	77.0	66.0	83.9	47.7	41.7	43.1	45.9	48.6	42.3	39.1	30	33	1
114	55.6	59.9	64.9	61.6	60.9	54.5	50.1	45.7	40.9	44.8	44.4	47.8	41.7	39.4	30	33	2
115	148.0	174.0	156.0	140.0	111.0	89.5	56.2	62.2	58.6	53.0	56.5	65.3	62.6	59.2	30	33	2
116	228.0	286.0	270.0	212.0	207.0	170.0	130.0	106.0	85.4	79.1	84.1	87.6	84.1	81.4	30	33	1
117	62.1	60.5	57.1	55.3	60.4	77.8	59.4	55.7	52.1	52.6	59.1	62.4	60.0	57.1	30	33	2
118	66.0	63.9	62.6	62.0	60.7	62.8	72.2	66.0	67.1	66.2	66.7	70.3	64.6	63.4	30	33	1
119	160.0	132.0	118.0	106.0	93.4	85.5	79.1	73.2	73.2	68.6	76.4	79.1	72.7	66.8	30	33	1
120	160.0	135.0	131.0	122.0	108.0	93.7	86.8	80.4	74.2	69.8	73.2	88.1	81.9	71.7	30	33	2
121	59.1	57.2	70.6	98.9	84.1	74.0	74.4	66.6	63.2	53.3	63.0	63.2	62.3	59.1	30	33	1
122	96.5	114.0	139.0	134.0	115.0	104.0	82.3	80.9	72.0	70.1	75.8	82.4	77.5	76.5	30	33	2

Reference ID: 3227106

Obs	c21	c22	c23	c24	c25	c26	c27	c28	c29	c30	c31	c32	c33	c34	KE_FIRST	KE_LAST	trt
123	83.1	74.7	67.9	62.0	64.5	79.4	74.5	59.4	57.6	71.5	65.7	69.2	69.4	61.9	30	33	2
124	104.0	87.3	74.3	68.4	78.2	103.0	95.2	75.0	70.6	66.8	75.7	77.5	76.0	66.8	30	33	1
125	53.8	50.6	51.8	49.6	54.1	55.3	55.2	45.4	49.7	40.3	42.8	49.1	42.0	40.5	30	33	2
126	45.3	40.7	49.5	59.3	66.0	66.9	59.5	61.1	52.7	51.0	52.8	54.2	50.5	45.7	30	33	1
127	88.6	145.0	92.4	86.5	80.4	87.3	102.0	81.8	79.8	60.7	80.6	83.6	83.3	78.9	30	33	1
128	78.2	90.0	77.2	72.1	75.8	91.9	82.8	70.6	67.7	63.4	69.4	69.6	71.5	70.0	30	33	2
129	103.0	80.0	80.0	77.0	69.1	67.1	64.0	55.9	53.4	51.6	60.0	64.3	60.8	59.1	30	33	2
130	61.4	66.8	55.5	59.7	61.5	87.1	79.7	65.5	58.7	59.2	60.0	61.9	56.2	59.8	30	33	1
131	113.0	92.3	81.2	79.8	85.0	94.3	83.4	78.9	67.9	60.3	73.5	79.4	65.5	59.7	30	33	2
132	82.3	77.9	69.2	68.4	73.3	69.2	64.8	62.2	55.6	63.5	63.4	69.1	60.0	63.9	30	33	1
133	135.0	118.0	102.0	86.2	71.5	73.4	65.7	61.6	58.2	62.1	67.4	72.3	67.2	65.2	30	33	1
134	138.0	140.0	108.0	91.9	88.8	79.7	77.7	68.0	61.0	62.9	72.7	77.1	69.1	67.5	30	33	2
135	110.0	95.0	72.2	64.6	58.8	55.2	49.6	46.8	46.2	39.3	47.8	50.2	48.0	43.8	30	33	1
136	107.0	75.9	63.3	60.8	56.0	56.8	51.8	55.4	48.7	44.3	50.4	52.6	47.7	49.1	30	33	2
137	42.3	41.4	48.6	51.6	49.0	47.0	50.5	41.1	37.1	35.3	43.3	44.8	40.8	40.5	30	33	1
138	65.5	69.3	64.2	56.3	53.4	53.5	53.8	47.4	45.6	47.3	50.6	50.6	46.3	46.2	30	33	2
139	93.4	70.0	51.7	48.1	46.3	46.2	48.2	44.6	42.3	42.2	43.5	45.4	44.0	44.1	30	33	2
140	126.0	104.0	86.4	83.9	83.7	86.2	81.5	77.4	77.2	72.9	75.4	74.5	74.1	76.3	30	33	1
141	82.8	75.5	59.1	57.0	52.9	47.6	48.4	42.8	42.1	40.2	45.8	49.6	40.5	41.0	30	33	1
142	103.0	71.5	55.7	56.7	55.8	54.0	50.3	49.7	47.4	45.6	52.7	56.5	50.4	51.1	30	33	2
143	66.3	61.6	59.8	57.4	49.8	44.8	38.3	34.5	29.7	29.4	30.3	34.6	32.2	33.6	30	33	1
144	60.9	56.0	55.3	60.4	52.9	43.4	37.7	36.9	34.8	33.6	36.2	38.6	36.3	38.0	30	33	2
145	89.6	106.0	97.1	109.0	101.0	78.2	84.0	64.0	65.0	56.2	67.1	73.7	69.7	62.7	30	33	2
146	88.2	134.0	113.0	105.0	90.5	94.5	92.6	73.8	66.2	67.2	78.9	79.9	73.4	69.4	30	33	1
147	96.5	89.5	77.7	45.7	74.0	93.5	82.4	63.3	47.4	46.6	49.1	65.8	58.0	52.2	30	33	1
148	91.5	109.0	90.8	74.1	84.8	74.2	89.7	70.7	57.2	45.1	55.0	68.0	59.7	63.6	30	33	2

Obs	c21	c22	c23	c24	c25	c26	c27	c28	c29	c30	c31	c32	c33	c34	KE_FIRST	KE_LAST	trt
149	43.0	39.9	37.2	69.1	42.3	38.6	32.2	28.8	26.3	26.4	24.8	28.8	26.3	27.1	30	33	2
150	73.7	48.7	33.7	40.5	42.3	37.6	35.7	33.8	31.1	31.5	32.8	32.6	30.2	30.3	30	33	1
151	81.9	89.3	84.2	97.4	83.3	68.8	64.3	57.1	53.2	47.2	56.7	62.5	58.8	57.7	30	33	1
152	109.0	118.0	112.0	105.0	95.9	95.8	80.1	73.0	65.6	61.4	68.1	70.5	66.7	62.4	30	33	2
153	127.0	88.4	62.7	56.9	52.4	51.2	53.1	49.2	45.0	45.1	47.8	52.9	53.1	54.4	30	33	2
154	116.0	111.0	91.9	78.8	73.4	64.9	69.5	60.2	61.9	58.9	61.3	63.1	61.6	59.9	30	33	1
155	82.7	93.0	88.7	92.3	84.1	78.2	73.9	71.0	65.8	59.5	65.4	73.4	67.0	64.5	30	33	2
156	123.0	109.0	88.7	85.9	77.9	71.0	68.1	68.1	62.2	56.5	59.7	68.2	63.9	61.1	30	33	1
157	99.8	75.7	66.8	57.7	60.0	59.0	57.0	49.0	46.7	48.1	46.3	51.0	47.4	48.5	30	33	1
158	98.7	85.0	67.8	71.7	75.3	64.2	68.1	61.9	55.7	55.4	54.2	59.3	53.4	57.7	30	33	2
159	101.0	126.0	121.0	104.0	93.8	81.8	76.4	68.3	54.0	86.8	54.8	63.6	59.6	57.1	30	33	1
160	112.0	150.0	118.0	98.2	97.1	88.4	93.9	76.1	69.6	66.7	75.3	80.8	70.5	65.7	30	33	2

FED CONCENTRATION DATASET (TOTAL DHA): BASELINE- ADJUSTED

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	KE_FIRST	KE_LAST	trt
1	1	2	1	B	1	0.5	6.8	4.4	1.8	3.3	70.3	67.4	40.8	21.9	26.6	29.9	23.7	7.7	6.4	9.6	13.4	8.5	10.2	11.2	10	13	2
2	1	2	2	A	1	5.0	11.0	15.0	8.0	12.0	34.0	48.3	43.4	18.0	15.0	22.0	19.5	4.9	0.0	0.0	0.0	3.0	0.0	0.0	10	13	1
3	2	1	1	A	1	0.0	4.1	4.3	4.0	3.3	16.0	33.1	20.3	11.3	11.3	6.8	11.6	6.8	6.3	2.2	3.4	3.6	3.5	2.1	10	13	1
4	2	1	2	B	1	1.7	2.1	10.4	49.5	64.4	75.6	55.1	29.2	20.3	16.4	11.8	13.8	7.9	7.5	2.7	7.6	9.7	7.5	3.4	10	13	2
5	3	2	1	B	1	0.0	1.4	4.4	5.1	15.7	47.6	54.4	38.0	27.2	22.6	20.6	17.1	8.6	11.6	9.3	9.6	12.2	10.8	9.7	10	13	2
6	3	2	2	A	1	0.4	4.2	7.4	11.6	22.8	60.9	78.2	86.0	67.9	52.8	39.9	26.3	18.2	18.9	14.7	17.2	14.7	10.9	8.2	10	13	1
7	4	1	1	A	1	0.0	0.0	0.1	0.2	9.5	69.4	96.5	83.0	75.0	67.1	55.0	39.1	26.5	20.9	5.6	5.0	7.4	6.3	0.0	10	13	1
8	4	1	2	B	1	0.0	2.3	4.0	5.2	3.4	6.8	25.0	61.8	78.9	92.2	98.8	106.2	71.5	61.8	30.9	14.3	21.3	24.1	11.1	10	13	2
9	5	2	1	B	1	0.5	2.7	0.9	8.1	19.0	46.7	95.3	77.8	53.1	39.5	25.2	21.7	17.4	6.6	11.7	12.2	14.8	0.8	3.8	10	13	2
10	5	2	2	A	1	0.0	0.0	6.4	8.8	9.8	55.4	76.7	92.8	91.2	63.8	43.5	40.5	17.2	26.2	14.1	3.8	3.9	12.6	8.5	10	13	1
11	6	1	1	A	1	0.0	3.8	8.4	18.1	42.4	60.6	26.2	14.6	10.4	11.2	12.1	11.5	4.6	5.7	5.3	5.7	8.7	8.2	9.3	10	13	1

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	KE_FIRST	KE_LAST	trt
12	6	1	2	B	1	0.0	5.5	6.6	2.3	50.2	77.9	34.4	8.7	12.2	8.2	3.4	4.3	1.1	3.3	0.3	0.0	0.8	4.7	0.0	10	13	2
13	7	2	1	B	1	0.0	1.4	11.6	16.6	33.0	63.1	49.6	35.3	36.4	18.7	20.4	16.9	7.9	12.4	13.5	10.0	14.9	6.7	8.6	10	13	2
14	7	2	2	A	1	0.0	5.6	11.7	63.1	61.9	84.8	53.9	59.6	44.9	57.2	36.3	19.1	9.3	0.7	7.5	20.0	9.0	5.4	2.3	10	13	1
15	8	1	1	A	1	0.0	2.6	7.7	1.4	3.8	65.7	37.0	8.9	10.5	14.2	27.0	0.0	0.0	0.0	0.0	5.6	0.0	0.0	0.0	10	13	1
16	8	1	2	B	1	9.9	16.2	19.7	24.1	35.5	68.5	50.0	27.5	33.9	2.5	29.6	13.4	0.0	1.8	4.9	15.0	2.5	6.5	5.3	10	13	2
17	9	2	1	B	1	5.9	5.2	7.5	9.8	11.9	63.8	57.6	35.7	17.0	4.3	11.3	16.8	3.7	3.2	7.1	10.4	16.6	2.7	7.3	10	13	2
18	9	2	2	A	1	0.0	6.8	14.3	6.4	11.4	46.5	47.8	31.2	17.8	10.9	4.7	9.7	5.3	12.4	8.9	8.9	9.6	9.0	9.7	10	13	1
19	10	1	1	A	1	0.0	2.4	0.0	0.0	17.1	52.0	31.7	32.6	29.4	30.0	20.3	14.1	15.8	16.8	2.1	4.9	3.4	2.6	4.5	10	13	1
20	10	1	2	B	1	0.0	0.0	2.2	49.9	51.9	40.8	57.7	44.6	40.5	23.9	30.8	25.1	11.9	0.0	3.6	10.1	10.9	0.0	6.0	10	13	2
21	11	1	1	A	1	3.6	0.8	0.0	11.3	27.8	69.7	44.5	19.6	14.0	4.1	7.7	14.1	2.7	3.4	4.7	7.4	5.0	4.5	15.7	10	13	1
22	11	1	2	B	1	4.5	3.1	6.5	11.9	25.1	89.2	47.0	34.2	17.5	24.0	11.7	7.1	0.0	23.1	4.7	9.3	12.7	4.3	8.6	10	13	2
23	12	2	1	B	1	0.0	1.1	0.0	12.1	0.9	7.2	22.2	14.8	13.1	17.5	15.4	23.7	0.0	11.9	4.1	6.3	9.1	5.2	6.9	10	13	2
24	12	2	2	A	1	4.9	5.4	5.3	0.0	3.6	8.3	0.0	3.5	20.3	32.8	31.0	13.5	11.9	0.0	0.0	9.7	2.6	6.8	0.5	10	13	1
25	13	2	1	B	1	7.6	4.9	0.0	5.8	0.9	19.2	37.3	17.9	0.0	8.0	0.0	0.0	0.0	0.0	3.7	0.0	0.0	0.0	8.1	10	13	2
26	13	2	2	A	1	1.0	7.4	5.2	21.1	16.2	21.1	8.7	8.5	2.4	6.0	20.9	29.5	16.1	7.5	0.9	0.0	12.8	8.9	11.5	10	13	1
27	16	1	1	A	1	1.0	0.0	0.0	2.6	8.1	81.3	40.8	27.4	25.7	5.9	12.2	15.8	12.0	7.4	7.9	12.9	3.6	7.5	7.8	10	13	1
28	16	1	2	B	1	5.4	3.7	0.0	9.3	20.9	87.7	72.0	42.6	16.8	13.9	0.0	13.5	3.7	0.0	0.0	1.7	10.2	0.4	0.0	10	13	2
29	17	2	1	B	1	0.9	6.0	5.9	5.9	10.6	27.6	33.0	23.7	17.3	15.7	12.2	10.1	4.7	4.6	5.1	6.5	7.2	0.4	3.1	10	13	2
30	17	2	2	A	1	6.6	9.0	8.9	5.7	21.0	55.0	36.0	24.5	11.7	9.2	11.6	7.7	1.8	0.0	4.0	1.3	3.6	1.8	2.1	10	13	1
31	18	1	1	A	1	0.0	1.5	0.0	0.0	5.2	29.3	23.8	8.0	13.2	7.3	10.1	3.8	3.0	0.2	5.2	1.2	3.1	0.2	0.0	10	13	1
32	18	1	2	B	1	0.0	0.7	0.0	0.7	3.0	41.6	26.7	8.9	7.7	5.0	8.4	2.4	1.3	0.0	2.9	0.0	4.8	0.1	0.0	10	13	2
33	19	1	1	A	1	0.0	0.0	0.0	5.1	14.6	71.7	65.5	43.7	26.5	15.3	7.0	10.4	1.9	0.3	0.0	0.0	2.0	0.7	0.0	10	13	1
34	19	1	2	B	1	2.0	4.1	4.0	4.0	0.5	82.0	88.3	65.4	42.4	23.4	14.8	3.9	0.0	0.0	0.0	0.0	3.3	0.0	0.0	10	13	2
35	20	2	1	B	1	3.0	0.0	1.5	5.0	26.6	57.8	39.9	24.5	6.5	4.3	4.4	9.6	7.4	6.2	6.6	8.4	1.4	0.0	7.5	10	13	2
36	20	2	2	A	1	0.0	3.9	7.8	27.6	39.4	57.7	30.7	21.5	6.0	7.3	4.4	8.9	0.0	0.0	0.0	3.0	0.0	0.0	0.0	10	13	1
37	21	1	1	A	1	0.0	0.0	0.0	0.0	0.0	0.0	2.8	3.4	0.0	0.0	1.9	3.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10	13	1

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	KE_FIRST	KE_LAST	trt
38	21	1	2	B	1	0.0	0.0	0.0	0.9	0.0	10.2	2.4	8.3	1.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.6	0.0	10	13	2
39	22	2	1	B	1	0.2	0.0	0.0	0.0	2.8	10.0	10.6	1.9	2.2	0.7	0.0	0.0	0.0	0.0	0.0	2.0	1.7	4.5	1.8	10	13	2
40	22	2	2	A	1	0.0	0.0	0.0	0.0	0.0	4.1	1.5	2.0	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10	13	1
41	23	1	1	A	1	4.0	2.0	0.0	0.0	0.0	17.0	29.0	19.0	30.0	42.0	23.0	18.0	13.0	0.0	3.0	6.0	10.0	0.0	0.0	10	13	1
42	23	1	2	B	1	0.0	2.7	4.3	31.0	40.0	61.1	55.0	76.4	51.1	44.0	34.8	26.3	19.0	7.7	0.0	5.4	5.0	9.1	0.0	10	13	2
43	24	2	1	B	1	0.0	0.0	2.5	0.0	1.7	6.7	47.3	23.3	9.3	14.0	6.8	6.2	2.9	1.2	3.4	0.0	5.2	0.0	0.0	10	13	2
44	24	2	2	A	1	0.0	0.8	5.0	3.8	2.4	26.7	36.2	16.9	6.7	13.7	9.0	24.1	9.3	5.2	1.7	0.0	1.7	0.0	0.0	10	13	1
45	25	1	1	A	1	0.0	0.0	0.0	0.2	0.6	0.0	44.7	23.2	3.6	8.5	20.9	10.4	5.8	10.0	10.5	0.0	2.7	0.0	3.0	10	13	1
46	25	1	2	B	1	0.0	9.4	4.2	3.1	18.1	61.9	27.4	9.4	5.9	0.0	0.0	0.0	0.0	0.0	0.0	2.9	1.9	2.2	0.9	10	13	2
47	26	2	1	B	1	0.0	0.0	0.0	0.0	0.0	20.0	35.6	31.4	19.1	21.5	5.3	5.9	18.1	0.0	3.9	0.0	5.2	6.6	5.0	10	13	2
48	26	2	2	A	1	2.3	3.2	7.0	9.1	1.2	42.8	63.7	64.9	36.2	24.6	16.2	6.3	0.0	0.0	0.6	9.5	13.2	7.1	0.9	10	13	1
49	27	2	1	B	1	0.0	1.9	1.2	1.5	10.2	22.8	23.1	0.0	10.7	14.9	17.0	16.4	0.0	11.0	8.7	1.0	5.2	1.2	2.4	10	13	2
50	27	2	2	A	1	1.3	5.3	7.0	1.7	11.5	47.9	47.0	32.9	23.2	16.5	26.0	17.8	4.8	0.0	2.4	1.1	11.9	0.0	7.6	10	13	1
51	28	1	1	A	1	0.6	0.0	0.0	4.3	7.7	8.4	13.4	0.0	3.7	3.6	0.0	4.1	0.0	0.0	0.0	1.2	8.9	2.4	12.5	10	13	1
52	28	1	2	B	1	2.5	15.7	0.0	4.9	12.6	6.5	10.2	19.4	27.4	14.1	9.4	23.6	8.9	13.3	0.0	11.2	18.3	2.5	3.5	10	13	2
53	29	2	1	B	1	0.0	1.4	1.4	3.3	9.4	88.9	83.4	41.4	27.3	23.6	20.1	9.2	6.9	6.6	5.0	0.0	6.0	6.8	1.9	10	13	2
54	29	2	2	A	1	0.0	0.0	0.0	1.3	3.5	101.8	86.7	39.6	18.9	14.8	10.6	5.2	5.3	1.1	3.0	0.0	0.5	3.1	1.2	10	13	1
55	30	2	1	B	1	0.0	2.8	0.0	1.1	14.4	52.8	47.0	11.2	10.9	8.1	3.6	10.8	6.7	0.8	0.0	0.0	0.0	3.1	3.3	10	13	2
56	30	2	2	A	1	0.0	1.8	1.6	0.0	5.7	68.2	41.7	14.2	11.3	8.5	13.5	12.1	4.4	0.0	3.7	2.9	0.9	0.0	2.8	10	13	1
57	31	1	1	A	1	0.0	4.9	1.9	2.0	5.4	21.4	6.0	9.0	8.9	14.8	12.7	6.4	10.5	3.5	0.0	5.2	11.6	6.2	9.5	10	13	1
58	31	1	2	B	1	1.6	2.2	2.4	0.5	0.5	12.8	13.6	4.7	7.4	3.5	7.9	6.1	4.5	0.0	0.0	5.1	7.6	0.3	6.7	10	13	2
59	32	1	1	A	1	0.0	0.0	2.5	0.5	4.5	3.5	2.3	0.6	0.4	13.2	23.7	12.6	12.4	11.8	8.3	2.9	8.8	4.7	6.8	10	13	1
60	32	1	2	B	1	0.0	0.0	1.6	5.0	6.9	21.2	7.9	3.3	6.9	4.3	23.2	24.3	14.6	4.7	1.7	0.0	15.0	12.5	8.4	10	13	2
61	33	2	1	B	1	0.0	2.6	1.9	0.6	7.6	28.8	57.2	35.6	24.8	14.5	8.8	10.8	0.0	5.7	1.9	6.6	7.1	3.5	6.6	10	13	2
62	33	2	2	A	1	5.5	3.9	9.5	10.6	17.8	75.0	81.3	50.6	40.8	29.7	24.5	9.5	4.2	0.0	5.3	7.2	2.5	0.0	0.0	10	13	1
63	34	1	1	A	1	0.0	0.0	2.2	0.0	0.6	14.1	16.2	10.1	24.0	14.0	10.6	11.0	6.4	3.4	10.8	4.9	8.7	6.6	8.6	10	13	1

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	KE_FIRST	KE_LAST	trt
64	34	1	2	B	1	0.0	0.0	3.0	3.4	8.7	24.4	21.7	11.3	1.7	10.2	11.0	6.9	2.6	0.0	4.5	0.1	0.0	0.0	3.1	10	13	2
65	37	2	1	B	1	1.7	10.3	9.5	8.4	37.6	121.4	153.3	146.8	141.8	120.5	126.2	124.8	99.2	57.6	24.8	29.8	28.6	24.8	6.8	10	13	2
66	37	2	2	A	1	0.0	0.0	0.0	0.0	73.0	174.0	216.0	223.0	190.0	171.0	116.0	145.0	137.0	93.0	41.0	0.0	0.0	0.0	0.0	10	13	1
67	38	2	1	B	1	0.0	0.7	10.6	46.3	49.8	68.4	56.9	39.5	32.6	26.9	18.0	18.9	12.1	11.6	6.7	8.0	9.7	10.6	13.0	10	13	2
68	38	2	2	A	1	0.0	0.0	4.6	33.0	57.1	68.7	59.2	45.2	27.0	19.8	13.4	14.7	10.0	8.2	7.1	8.6	13.2	8.8	6.6	10	13	1
69	39	1	1	A	1	0.0	0.0	0.0	0.0	6.6	55.2	56.3	38.0	19.3	20.0	11.6	9.8	1.6	6.8	6.9	8.1	1.4	2.1	2.6	10	13	1
70	39	1	2	B	1	0.0	0.0	0.0	0.0	0.0	25.6	26.5	20.2	19.0	12.0	8.0	7.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10	13	2
71	40	1	1	A	1	0.0	0.0	0.7	0.0	0.0	21.6	9.6	7.9	9.8	29.3	23.7	12.2	1.0	0.0	0.0	0.0	0.0	0.0	0.0	10	13	1
72	40	1	2	B	1	0.0	0.6	3.8	0.0	12.7	26.2	5.6	0.0	0.0	0.0	13.5	2.2	0.0	0.0	0.0	0.0	0.2	0.0	0.0	10	13	2
73	41	2	1	B	1	3.0	1.6	2.3	1.2	6.7	45.9	12.8	3.9	0.0	1.8	3.0	4.6	0.0	2.4	0.0	8.2	1.7	0.0	2.2	10	13	2
74	41	2	2	A	1	0.0	2.3	0.0	5.5	0.0	51.3	35.1	12.0	3.9	0.0	0.0	0.2	0.0	0.0	6.9	3.6	0.0	0.0	0.0	10	13	1
75	42	2	1	B	1	0.0	0.0	0.0	3.8	11.3	79.8	49.8	18.4	18.5	8.1	15.3	9.9	8.7	3.6	6.4	9.9	9.1	8.9	9.0	10	13	2
76	42	2	2	A	1	1.5	6.5	8.6	10.7	28.1	64.8	60.3	25.5	14.9	11.1	8.7	6.7	5.8	12.7	5.2	9.7	11.3	5.7	6.0	10	13	1
77	43	1	1	A	1	0.0	0.0	0.0	0.0	0.0	38.2	29.2	12.7	17.1	13.6	11.2	17.3	6.8	7.0	6.1	5.8	4.4	6.4	7.1	10	13	1
78	43	1	2	B	1	0.0	2.8	2.3	3.6	10.1	82.4	50.8	16.3	9.6	5.7	5.8	7.6	4.7	0.1	5.3	0.0	2.8	2.7	2.7	10	13	2
79	44	1	1	A	1	2.0	2.6	3.0	4.2	18.0	47.0	29.6	17.0	19.2	16.3	12.5	12.3	8.8	9.7	24.7	8.8	8.2	4.9	5.6	10	13	1
80	44	1	2	B	1	0.0	2.3	5.9	5.0	33.2	47.2	26.2	12.9	15.7	16.1	11.6	9.0	4.8	2.3	3.8	0.6	6.5	2.4	0.0	10	13	2
81	45	1	1	A	1	2.4	0.0	2.2	2.9	1.1	10.7	9.0	13.0	20.8	21.0	22.6	15.2	13.3	8.0	4.5	6.1	11.6	4.6	0.4	10	13	1
82	45	1	2	B	1	0.0	3.2	6.4	8.3	20.4	46.9	31.2	15.3	16.3	16.6	7.0	6.3	1.9	5.1	8.1	1.5	11.0	3.2	1.0	10	13	2
83	46	2	1	B	1	4.8	7.9	4.8	6.4	4.9	62.1	27.1	15.7	16.6	16.3	12.4	10.9	14.7	6.9	0.0	8.3	6.6	5.8	8.3	10	13	2
84	46	2	2	A	1	0.9	0.5	0.0	3.6	21.4	66.4	42.2	29.1	25.2	29.3	21.8	9.1	10.8	6.6	1.3	7.7	2.8	5.6	0.0	10	13	1
85	47	1	1	A	1	0.0	1.4	8.0	18.4	38.7	93.6	49.7	27.5	14.6	14.7	9.3	14.2	6.6	7.8	3.4	7.6	6.4	7.6	9.4	10	13	1
86	47	1	2	B	1	0.0	0.0	27.5	51.5	79.4	103.0	53.2	33.3	14.6	14.6	9.4	11.5	5.3	0.0	9.8	7.9	5.0	2.1	4.9	10	13	2
87	48	2	1	B	1	0.5	2.4	4.4	0.0	10.2	61.8	24.1	12.0	11.0	4.1	3.0	0.0	0.0	0.0	0.0	3.0	0.4	2.2	1.7	10	13	2
88	48	2	2	A	1	0.0	0.0	4.2	2.9	21.0	61.5	18.6	13.6	9.5	6.9	5.6	0.0	0.0	0.0	3.3	0.0	2.2	1.4	2.1	10	13	1
89	49	1	1	A	1	0.0	5.0	0.4	1.9	3.2	46.9	22.8	10.6	8.4	12.0	4.8	2.6	2.6	2.3	1.4	3.9	6.6	2.7	1.2	10	13	1

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	KE_FIRST	KE_LAST	trt
90	49	1	2	B	1	5.7	3.3	5.3	16.0	31.0	39.3	18.6	13.2	8.8	8.1	8.0	1.4	1.9	0.0	1.9	7.1	6.2	0.0	0.0	10	13	2
91	50	1	1	A	1	0.8	0.0	9.7	2.5	1.2	1.6	0.0	4.8	0.0	4.6	11.0	9.2	16.3	7.7	5.1	8.7	11.0	13.1	14.1	10	13	1
92	50	1	2	B	1	5.5	0.0	0.0	3.6	4.5	4.4	3.9	3.4	5.4	10.4	16.9	6.7	4.1	5.0	0.0	5.5	9.9	13.9	3.3	10	13	2
93	51	2	1	B	1	1.6	1.9	3.1	3.5	3.2	12.7	11.5	9.4	10.8	18.0	20.9	10.7	5.7	5.1	0.5	6.0	3.4	4.3	4.4	10	13	2
94	51	2	2	A	1	0.0	0.8	2.4	1.3	28.0	47.5	19.5	12.1	8.3	13.3	11.8	7.4	2.9	4.6	2.0	3.6	5.9	5.3	3.6	10	13	1
95	52	2	1	B	1	0.9	2.9	3.5	0.0	2.3	26.5	14.7	11.6	16.2	18.1	19.7	13.0	10.1	9.5	10.3	13.4	13.9	9.2	13.5	10	13	2
96	52	2	2	A	1	2.3	4.0	7.0	7.1	19.4	42.7	53.1	37.0	30.0	14.9	20.1	9.8	14.0	4.8	8.6	15.0	16.7	8.3	11.2	10	13	1
97	53	2	1	B	1	0.0	2.5	1.8	7.7	7.8	30.6	53.7	53.2	45.4	44.1	22.0	9.0	3.6	0.0	0.0	3.0	6.5	1.6	2.8	10	13	2
98	53	2	2	A	1	26.2	6.4	27.4	6.5	90.3	54.7	46.0	30.1	19.0	0.0	5.3	1.3	13.1	8.0	0.0	29.1	7.7	9.7	1.7	10	13	1
99	54	1	1	A	1	1.8	4.3	2.8	4.7	3.2	5.7	13.8	29.8	40.4	41.1	27.4	27.6	23.1	13.6	9.6	13.2	15.4	11.5	10.2	10	13	1
100	54	1	2	B	1	0.0	3.8	2.7	3.4	3.2	4.8	8.0	7.8	12.2	16.4	18.3	41.8	24.1	19.4	6.3	0.0	11.3	8.9	9.5	10	13	2
101	55	2	1	B	1	2.1	3.7	8.2	13.6	10.1	30.8	28.1	19.0	16.6	13.6	10.1	9.2	1.1	0.0	3.1	0.0	0.0	0.0	0.0	10	13	2
102	55	2	2	A	1	0.0	0.0	2.0	1.5	1.7	5.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10	13	1
103	56	1	1	A	1	0.0	3.8	1.1	3.6	1.6	18.5	42.4	37.5	23.0	12.4	14.0	19.5	12.5	7.5	4.8	4.2	6.8	8.1	2.6	10	13	1
104	56	1	2	B	1	2.9	9.5	9.6	5.8	7.8	18.7	33.3	32.7	26.0	24.9	16.9	22.7	8.6	6.0	3.5	14.5	15.8	11.5	4.4	10	13	2
105	57	1	1	A	1	0.0	0.0	0.0	0.0	0.9	32.2	20.2	12.9	0.8	2.4	0.0	3.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10	13	1
106	57	1	2	B	1	0.0	0.5	0.0	0.0	1.2	20.0	0.0	13.4	11.1	7.5	3.5	6.9	0.0	3.1	0.0	2.8	0.0	0.0	0.0	10	13	2
107	58	1	1	A	1	0.0	0.0	0.0	0.0	9.4	27.0	12.0	7.6	4.7	11.8	10.8	5.6	0.0	0.0	2.7	0.0	0.0	0.0	1.1	10	13	1
108	58	1	2	B	1	0.0	0.4	0.1	0.7	12.4	31.9	22.8	9.7	5.0	5.5	0.8	3.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10	13	2
109	59	2	1	B	1	1.1	2.8	3.2	2.7	8.0	78.6	45.0	22.4	16.3	14.2	11.0	7.3	5.6	2.8	3.4	6.9	7.3	4.2	3.4	10	13	2
110	59	2	2	A	1	0.0	0.6	10.0	23.3	20.2	59.0	39.8	16.3	10.2	5.8	4.9	4.1	3.4	3.9	2.4	2.9	1.5	1.5	2.2	10	13	1
111	60	2	1	B	1	0.0	0.0	3.3	0.0	0.5	7.3	14.9	12.1	7.8	9.4	8.6	15.6	5.8	0.0	0.0	0.0	0.0	0.0	0.0	10	13	2
112	60	2	2	A	1	0.0	2.9	2.8	2.1	2.9	7.5	19.5	13.1	6.0	6.2	4.5	13.0	2.0	4.2	3.8	2.7	0.2	0.0	0.0	10	13	1
113	61	1	1	A	1	0.0	0.3	2.4	1.7	0.7	17.1	16.7	29.0	44.6	44.1	33.3	52.4	15.0	10.0	12.9	13.1	15.3	9.3	7.6	10	13	1
114	61	1	2	B	1	0.5	4.4	5.3	5.2	4.4	24.6	26.9	32.5	30.1	27.0	21.3	17.8	13.1	6.8	10.2	11.4	16.9	10.2	7.1	10	13	2
115	62	2	1	B	1	0.0	0.0	0.0	5.1	31.3	95.9	122.1	104.7	88.3	61.8	39.6	5.5	13.0	12.9	7.3	8.9	12.3	10.9	8.5	10	13	2

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	KE_FIRST	KE_LAST	trt
116	62	2	2	A	1	0.0	2.1	7.3	16.9	52.9	162.8	218.8	206.3	147.4	139.9	107.6	65.1	41.8	24.8	22.4	18.9	19.5	19.5	16.5	10	13	1
117	63	2	1	B	1	1.5	3.7	0.9	1.4	0.0	7.2	3.7	0.0	0.0	4.8	21.8	3.1	2.5	0.3	0.4	5.5	5.1	3.3	0.8	10	13	2
118	63	2	2	A	1	0.1	4.0	2.6	2.6	3.4	0.3	0.0	0.0	0.0	0.0	0.0	10.1	4.5	7.6	6.1	0.0	8.1	0.0	1.3	10	13	1
119	64	1	1	A	1	4.2	5.0	5.0	24.2	64.7	90.0	60.3	48.0	36.2	25.8	12.6	9.9	2.4	5.9	2.1	13.5	9.8	2.9	0.0	10	13	1
120	64	1	2	B	1	0.0	1.4	0.0	9.1	26.7	90.2	62.2	60.5	52.5	38.7	27.4	18.2	14.3	7.8	6.5	10.7	19.3	12.4	3.1	10	13	2
121	65	1	1	A	1	0.0	0.0	2.4	0.0	0.4	1.6	0.0	12.5	40.5	24.3	14.9	14.9	11.5	9.4	0.0	5.8	3.7	3.9	0.0	10	13	1
122	65	1	2	B	1	0.0	1.7	0.0	0.0	0.0	6.4	28.6	47.0	48.1	31.8	18.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10	13	2
123	66	2	1	B	1	0.0	0.9	5.2	5.9	8.9	25.3	15.2	7.8	4.9	6.8	23.4	20.6	4.5	4.2	21.1	6.3	9.3	12.3	8.0	10	13	2
124	66	2	2	A	1	0.0	0.2	0.0	5.2	20.5	34.4	17.8	7.0	0.0	8.3	32.4	26.3	13.5	7.5	0.4	4.3	11.6	7.4	0.0	10	13	1
125	67	2	1	B	1	1.1	0.0	0.1	1.7	0.0	15.1	12.2	15.6	11.5	16.4	15.4	14.5	5.9	12.7	2.7	6.1	9.1	3.9	0.0	10	13	2
126	67	2	2	A	1	3.1	4.7	8.1	7.2	6.2	6.3	0.0	8.2	18.3	20.7	21.2	17.2	21.3	11.7	10.6	12.4	13.5	9.5	3.4	10	13	1
127	68	1	1	A	1	0.0	0.5	2.4	12.3	4.4	14.7	69.7	13.4	5.3	0.0	14.0	28.1	13.5	4.9	0.0	12.3	9.9	2.1	5.0	10	13	1
128	68	1	2	B	1	0.0	15.8	0.0	0.0	3.6	9.6	26.1	1.3	4.6	2.3	14.2	10.2	1.9	2.9	0.6	0.0	3.5	4.0	0.0	10	13	2
129	69	2	1	B	1	1.0	8.4	8.7	4.6	4.4	48.1	22.7	21.3	18.8	11.3	8.4	9.1	1.2	0.5	1.8	9.0	9.0	2.6	4.2	10	13	2
130	69	2	2	A	1	3.7	4.2	8.4	4.8	0.0	3.5	11.1	0.0	0.4	0.0	25.8	23.2	6.0	2.7	4.9	9.5	1.9	0.0	3.3	10	13	1
131	70	2	1	B	1	0.0	3.3	3.6	3.5	2.2	48.9	32.1	20.2	14.7	25.7	33.2	24.2	18.5	11.7	6.6	16.5	15.1	0.4	0.5	10	13	2
132	70	2	2	A	1	0.0	6.2	25.1	30.5	29.7	16.5	15.7	11.0	2.4	9.0	7.9	3.5	3.6	0.0	5.3	4.5	10.6	0.0	2.6	10	13	1
133	71	1	1	A	1	0.0	0.0	5.9	3.4	22.5	72.2	54.5	41.6	28.1	9.8	16.1	7.0	2.6	2.2	8.5	11.0	12.3	9.1	6.5	10	13	1
134	71	1	2	B	1	23.3	11.4	3.6	8.7	18.9	74.0	77.7	44.4	26.7	24.1	20.7	18.9	5.3	0.0	10.9	31.3	12.4	3.9	8.7	10	13	2
135	72	1	1	A	1	0.0	0.0	0.0	1.1	28.2	64.3	50.9	27.1	22.1	15.4	8.8	8.6	2.8	2.9	0.0	1.1	4.6	5.5	2.8	10	13	1
136	72	1	2	B	1	2.5	3.7	4.2	2.1	35.8	65.4	33.4	20.8	15.8	14.3	12.8	8.8	16.2	7.0	1.8	8.9	10.4	2.7	6.1	10	13	2
137	73	1	1	A	1	0.0	0.3	1.7	1.8	0.0	5.9	6.9	15.0	18.0	15.6	14.0	17.7	10.3	5.4	5.8	9.5	9.8	7.2	7.7	10	13	1
138	73	1	2	B	1	0.0	3.6	1.9	23.7	16.5	22.9	27.4	22.5	15.7	10.8	12.5	11.9	9.9	5.3	6.1	6.8	7.3	5.7	4.3	10	13	2
139	74	2	1	B	1	0.0	0.0	0.2	0.0	0.0	49.1	25.2	7.8	2.5	0.9	0.0	5.7	2.7	0.0	0.0	0.6	0.0	0.0	1.6	10	13	2
140	74	2	2	A	1	0.0	0.0	0.0	0.0	0.0	27.5	12.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10	13	1
141	75	1	1	A	1	0.0	2.7	6.5	5.5	18.9	47.8	39.3	25.8	22.2	19.5	13.3	15.2	7.5	8.8	8.2	11.9	14.8	5.7	7.8	10	13	1

Reference ID: 3227106

Obs	sub	seq	per	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	KE_FIRST	KE_LAST	trt
142	75	1	2	B	1	0.0	0.0	0.2	14.8	38.3	53.0	21.6	9.7	11.3	9.1	10.9	6.7	4.5	5.7	6.2	7.0	10.2	5.0	7.5	10	13	2
143	77	1	1	A	1	1.3	2.6	7.3	6.6	8.2	42.3	37.0	34.8	33.1	25.7	21.2	13.9	10.0	6.8	7.1	8.0	10.5	7.9	9.2	10	13	1
144	77	1	2	B	1	0.3	2.8	2.0	2.1	3.4	28.0	21.6	23.1	28.1	22.0	10.7	4.8	3.6	3.2	2.5	3.7	6.2	4.0	5.1	10	13	2
145	78	2	1	B	1	0.0	0.0	0.0	0.0	3.3	18.5	42.1	26.6	43.3	38.1	16.9	25.4	0.0	5.1	0.6	0.0	3.8	4.0	4.1	10	13	2
146	78	2	2	A	1	4.5	5.0	7.0	3.8	0.6	23.1	76.6	47.1	43.8	19.6	26.4	28.0	4.5	0.0	7.7	16.4	12.3	12.2	4.8	10	13	1
147	79	1	1	A	1	2.5	10.2	12.3	9.2	14.8	50.7	39.5	26.5	0.0	28.3	51.0	40.1	21.6	6.0	10.3	11.5	22.7	12.1	9.9	10	13	1
148	79	1	2	B	1	0.0	5.4	4.3	6.8	12.1	41.0	59.3	41.0	22.4	28.1	24.9	44.5	20.6	3.1	4.3	5.9	18.8	8.0	18.4	10	13	2
149	80	2	1	B	1	0.0	0.0	0.0	0.0	4.9	19.5	16.8	15.2	47.0	20.4	15.9	11.2	6.7	6.4	7.9	3.3	6.3	4.2	6.1	10	13	2
150	80	2	2	A	1	0.0	0.3	1.2	2.3	5.6	50.9	27.0	10.3	17.6	16.0	14.0	11.0	9.0	7.1	6.3	7.4	8.5	7.3	5.6	10	13	1
151	81	1	1	A	1	0.0	2.9	0.0	0.6	1.8	26.2	32.4	30.6	39.6	29.5	15.5	12.6	3.1	0.0	0.0	4.5	11.7	1.0	6.0	10	13	1
152	81	1	2	B	1	3.7	10.1	7.7	3.8	12.1	39.7	51.5	44.9	39.1	29.2	34.1	15.1	6.7	3.9	2.7	9.7	5.9	0.8	0.0	10	13	2
153	82	2	1	B	1	0.6	0.6	1.9	0.8	13.7	76.8	40.8	12.6	6.5	3.1	0.9	3.3	0.0	0.0	0.0	1.1	4.8	2.7	4.6	10	13	2
154	82	2	2	A	1	2.5	7.3	6.4	3.6	8.8	62.1	57.1	40.3	23.5	19.2	10.0	17.8	9.2	11.1	7.7	12.9	13.1	6.3	8.2	10	13	1
155	83	2	1	B	1	0.0	0.0	0.0	0.0	0.0	13.1	24.9	18.7	22.8	13.6	11.6	4.4	7.2	3.2	0.0	0.0	1.9	0.0	0.0	10	13	2
156	83	2	2	A	1	4.9	2.7	5.2	21.1	41.3	66.2	51.4	29.3	25.6	19.6	14.3	10.7	10.0	6.8	0.0	4.9	13.7	3.6	3.7	10	13	1
157	84	1	1	A	1	3.9	4.8	3.9	4.1	5.6	61.8	37.6	30.4	20.0	22.4	20.2	18.9	11.5	10.6	12.1	12.6	14.6	9.7	10.4	10	13	1
158	84	1	2	B	1	3.0	6.7	2.7	17.1	21.3	51.7	39.2	20.6	24.0	28.8	14.9	21.2	13.5	9.1	6.6	7.8	12.2	5.7	10.8	10	13	2
159	86	1	1	A	1	43.1	8.1	10.2	18.6	12.2	54.2	78.7	72.7	58.0	46.4	34.7	29.4	22.7	9.9	42.5	12.6	17.9	13.6	10.1	10	13	1
160	86	1	2	B	1	7.8	7.3	9.7	13.7	13.4	49.7	89.5	57.5	34.2	33.2	25.6	30.5	10.9	5.8	5.8	19.7	17.7	6.5	2.3	10	13	2

Reference ID: 3227106

091028 FED FIRM TO REVIEWER RATIO- Free EPA Baseline-Adjusted)

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
1	1	2	1	1	2	6.1103	6.2088	1.3607	B	6.1103	.	1.3607	1.00000	.	1
2	1	2	2	1	1	3.8506	3.9580	0.6781	A	3.8506	.	0.6781	1.00000	.	1
3	2	1	1	1	1	4.8037	4.8653	0.6264	A	4.8079	.	0.6264	1.00087	.	1
4	2	1	2	1	2	6.5539	6.8409	1.1033	B	6.5539	6.76334	1.1033	1.00000	0.98866	1
5	3	2	1	1	2	5.5510	5.6279	0.6991	B	5.5510	6.09904	0.6991	1.00000	1.08372	1
6	3	2	2	1	1	4.8645	5.1090	0.4723	A	4.8645	.	0.4723	1.00000	.	1
7	4	1	1	1	1	7.9358	8.0600	0.9980	A	7.9358	8.45302	0.9980	1.00000	1.04876	1
8	4	1	2	1	2	8.3637	8.6449	0.6106	B	8.3637	.	0.6106	1.00000	.	1
9	5	2	1	1	2	6.9725	7.0858	1.1078	B	6.9725	7.62847	1.1078	1.00000	1.07658	1
10	5	2	2	1	1	8.0220	8.2325	0.8342	A	8.0220	8.96141	0.8342	1.00000	1.08853	1
11	6	1	1	1	1	5.5215	5.7699	0.9068	A	5.5215	.	0.9068	1.00000	.	1
12	6	1	2	1	2	6.7741	7.1799	1.5780	B	6.7750	.	1.5780	1.00014	.	1
13	7	2	1	1	2	9.9884	10.4190	1.4425	B	9.9884	.	1.4425	1.00000	.	1
14	7	2	2	1	1	10.0010	10.6935	1.3650	A	10.0010	.	1.3650	1.00000	.	1
15	8	1	1	1	1	6.1230	6.3790	1.3609	A	6.1230	.	1.3609	1.00000	.	1
16	8	1	2	1	2	5.8895	6.8003	0.7978	B	5.8895	.	0.7978	1.00000	.	1
17	9	2	1	1	2	5.4021	5.6263	0.8234	B	5.4021	.	0.8234	1.00000	.	1
18	9	2	2	1	1	3.9735	4.1876	0.5238	A	3.9735	.	0.5238	1.00000	.	1
19	10	1	1	1	1	6.4794	6.6249	0.6389	A	6.4794	.	0.6389	1.00000	.	1
20	10	1	2	1	2	7.0459	7.2791	0.8977	B	7.0459	.	0.8977	1.00000	.	1
21	11	1	1	1	1	6.8603	7.1301	1.3872	A	6.8603	.	1.3872	1.00000	.	1
22	11	1	2	1	2	6.6772	7.1349	1.5917	B	6.6772	.	1.5917	1.00000	.	1
23	12	2	1	1	2	6.3096	6.4642	0.6192	B	6.3103	7.40779	0.6192	1.00011	1.14597	1
24	12	2	2	1	1	7.0335	7.2157	0.8638	A	7.0432	.	0.8638	1.00138	.	1
25	13	2	1	1	2	3.9008	3.9281	0.9559	B	3.9008	.	0.9559	1.00000	.	1
26	13	2	2	1	1	6.0329	6.2298	1.0835	A	6.0569	.	1.0835	1.00398	.	1
27	16	1	1	1	1	7.6560	7.8237	1.5075	A	7.6560	.	1.5075	1.00000	.	1
28	16	1	2	1	2	7.7406	7.7994	1.0742	B	7.7406	.	1.0742	1.00000	.	1
29	17	2	1	1	2	6.1200	6.2392	0.7190	B	6.1200	.	0.7190	1.00000	.	1
30	17	2	2	1	1	6.6696	7.1925	1.0202	A	6.6696	.	1.0202	1.00000	.	1
31	18	1	1	1	1	6.8830	6.9959	1.5650	A	6.8830	.	1.5650	1.00000	.	1
32	18	1	2	1	2	4.8719	4.9973	0.7472	B	4.8719	.	0.7472	1.00000	.	1
33	19	1	1	1	1	5.3620	5.4562	1.0309	A	5.3620	.	1.0309	1.00000	.	1
34	19	1	2	1	2	6.8593	6.9386	1.1257	B	6.8593	.	1.1257	1.00000	.	1
35	20	2	1	1	2	5.8259	5.9826	0.7092	B	5.8259	.	0.7092	1.00000	.	1
36	20	2	2	1	1	7.1017	7.3976	0.9292	A	7.1017	.	0.9292	1.00000	.	1

Reference ID: 3227106

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
37	21	1	1	1	1	4.7748	4.9622	0.7230	A	4.7748	.	0.7230	1.00000	.	1
38	21	1	2	1	2	4.3272	4.7165	1.0786	B	4.3272	.	1.0786	1.00000	.	1
39	22	2	1	1	2	5.2724	5.4178	1.1713	B	5.2724	.	1.1713	1.00000	.	1
40	22	2	2	1	1	5.2853	5.3019	1.1506	A	5.2853	.	1.1506	1.00000	.	1
41	23	1	1	1	1	6.4107	6.4904	1.2810	A	6.4107	.	1.2810	1.00000	.	1
42	23	1	2	1	2	5.4351	6.1842	0.5158	B	5.4351	.	0.5158	1.00000	.	1
43	24	2	1	1	2	5.5622	5.6885	1.0341	B	5.5622	.	1.0341	1.00000	.	1
44	24	2	2	1	1	4.1465	4.3654	0.4979	A	4.1500	.	0.4979	1.00085	.	1
45	25	1	1	1	1	4.3756	4.4395	0.7910	A	4.3756	.	0.7910	1.00000	.	1
46	25	1	2	1	2	3.3904	3.5227	0.8307	B	3.3904	.	0.8307	1.00000	.	1
47	26	2	1	1	2	3.4568	3.5375	0.5002	B	3.4568	.	0.5002	1.00000	.	1
48	26	2	2	1	1	3.6872	3.8101	0.4169	A	3.6872	.	0.4169	1.00000	.	1
49	27	2	1	1	2	5.4491	5.5456	0.9030	B	5.4492	.	0.9030	1.00000	.	1
50	27	2	2	1	1	4.7992	4.8837	0.5354	A	4.7992	.	0.5354	1.00000	.	1
51	28	1	1	1	1	1.2106	1.2866	0.1221	A	1.2106	.	0.1221	1.00000	.	1
52	28	1	2	1	2	3.9792	4.1268	0.4052	B	3.9792	.	0.4052	1.00000	.	1
53	29	2	1	1	2	4.3810	4.4674	0.6242	B	4.3810	4.52952	0.6242	1.00000	1.01391	1
54	29	2	2	1	1	3.5468	3.6276	0.6357	A	3.5468	.	0.6357	1.00000	.	1
55	30	2	1	1	2	6.3214	6.5002	1.1948	B	6.3214	.	1.1948	1.00000	.	1
56	30	2	2	1	1	6.5645	6.8082	1.2358	A	6.5645	.	1.2358	1.00000	.	1
57	31	1	1	1	1	6.1741	6.2538	1.5106	A	6.1741	.	1.5106	1.00000	.	1
58	31	1	2	1	2	7.0135	7.1143	1.0843	B	7.0135	.	1.0843	1.00000	.	1
59	32	1	1	1	1	5.3537	5.4808	1.0301	A	5.3537	.	1.0301	1.00000	.	1
60	32	1	2	1	2	7.2677	7.4089	0.8450	B	7.2677	7.69915	0.8450	1.00000	1.03918	1
61	33	2	1	1	2	5.0457	5.1906	1.2239	B	5.0457	.	1.2239	1.00000	.	1
62	33	2	2	1	1	5.6854	5.7606	0.8353	A	5.6854	5.84550	0.8353	1.00000	1.01474	1
63	34	1	1	1	1	2.9501	3.0061	0.4926	A	2.9501	.	0.4926	1.00000	.	1
64	34	1	2	1	2	2.7349	2.7706	0.3865	B	2.7349	.	0.3865	1.00000	.	1
65	37	2	1	1	2	6.3461	6.4443	0.5610	B	6.3461	.	0.5610	1.00000	.	1
66	37	2	2	1	1	6.9242	7.0470	0.7670	A	6.9242	.	0.7670	1.00000	.	1
67	38	2	1	1	2	6.6118	6.7287	0.9706	B	6.6118	.	0.9706	1.00000	.	1
68	38	2	2	1	1	5.7617	5.9703	1.2707	A	5.7617	.	1.2707	1.00000	.	1
69	39	1	1	1	1	6.3363	6.4556	0.9011	A	6.3363	.	0.9011	1.00000	.	1
70	39	1	2	1	2	6.2486	6.2997	0.8700	B	6.2486	.	0.8700	1.00000	.	1
71	40	1	1	1	1	7.0083	7.1897	1.0451	A	7.0083	.	1.0451	1.00000	.	1
72	40	1	2	1	2	9.8955	10.2154	1.7785	B	9.8955	.	1.7785	1.00000	.	1
73	41	2	1	1	2	4.3925	4.5813	1.3396	B	4.3925	.	1.3396	1.00000	.	1
74	41	2	2	1	1	4.6223	4.8396	1.0552	A	4.6223	.	1.0552	1.00000	.	1

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
75	42	2	1	1	2	5.8058	5.9223	1.0987	B	5.8058	.	1.0987	1.00000	.	1
76	42	2	2	1	1	5.2812	5.5854	0.6853	A	5.2812	.	0.6853	1.00000	.	1
77	43	1	1	1	1	5.2315	5.3271	0.6344	A	5.2349	.	0.6344	1.00066	.	1
78	43	1	2	1	2	5.5035	5.6171	0.9877	B	5.4922	.	0.9877	0.99795	.	1
79	44	1	1	1	1	4.4615	4.6738	0.6271	A	4.4615	.	0.6271	1.00000	.	1
80	44	1	2	1	2	4.4735	4.5780	0.7941	B	4.4736	4.62046	0.7941	1.00003	1.00927	1
81	45	1	1	1	1	7.7311	7.8411	1.6866	A	7.7311	.	1.6866	1.00000	.	1
82	45	1	2	1	2	6.5100	6.6751	1.3295	B	6.5072	.	1.3295	0.99957	.	1
83	46	2	1	1	2	4.4423	4.6256	1.2747	B	4.4423	.	1.2747	1.00000	.	1
84	46	2	2	1	1	4.8214	4.9060	1.2307	A	4.8214	4.97566	1.2307	1.00000	1.01421	1
85	47	1	1	1	1	6.2328	6.4521	1.6423	A	6.2328	.	1.6423	1.00000	.	1
86	47	1	2	1	2	6.3358	7.4664	1.2215	B	6.3372	.	1.2215	1.00022	.	1
87	48	2	1	1	2	4.9452	5.2149	0.9122	B	4.9452	.	0.9122	1.00000	.	1
88	48	2	2	1	1	4.8938	5.0557	1.1902	A	4.8938	.	1.1902	1.00000	.	1
89	49	1	1	1	1	4.7477	4.8074	0.8534	A	4.7479	.	0.8534	1.00004	.	1
90	49	1	2	1	2	7.2348	7.4591	2.4270	B	7.2348	.	2.4270	1.00000	.	1
91	50	1	1	1	1	1.9861	2.1538	0.1732	A	1.9861	.	0.1732	1.00000	.	1
92	50	1	2	1	2	3.3070	3.4040	0.6328	B	3.3073	.	0.6328	1.00009	.	1
93	51	2	1	1	2	5.2249	5.3339	0.9698	B	5.2220	.	0.9698	0.99945	.	1
94	51	2	2	1	1	5.8752	6.2409	1.1482	A	5.8647	.	1.1482	0.99822	.	1
95	52	2	1	1	2	5.2981	5.3957	0.8117	B	5.2981	.	0.8117	1.00000	.	1
96	52	2	2	1	1	5.6729	5.8601	0.8647	A	5.6634	7.41835	0.8647	0.99832	1.26591	1
97	53	2	1	1	2	5.7958	5.9413	0.7812	B	5.7950	.	0.7812	0.99986	.	1
98	53	2	2	1	1	6.3926	6.5866	1.0448	A	6.3926	7.77554	1.0448	1.00000	1.18052	1
99	54	1	1	1	1	8.0423	8.1620	1.2395	A	8.0423	8.70341	1.2395	1.00000	1.06633	1
100	54	1	2	1	2	5.6342	5.7394	0.7147	B	5.6342	7.32582	0.7147	1.00000	1.27641	1
101	55	2	1	1	2	2.9096	3.2045	0.4685	B	2.9096	.	0.4685	1.00001	.	1
102	55	2	2	1	1	1.3861	1.5203	0.2680	A	1.3880	.	0.2680	1.00134	.	1
103	56	1	1	1	1	2.5908	2.6445	0.2547	A	2.5908	.	0.2547	1.00000	.	1
104	56	1	2	1	2	2.7874	2.8697	0.3079	B	2.7874	.	0.3079	1.00000	.	1
105	57	1	1	1	1	3.5974	3.6625	0.5343	A	3.5974	.	0.5343	1.00000	.	1
106	57	1	2	1	2	3.8535	4.4894	0.7218	B	3.8512	.	0.7218	0.99941	.	1
107	58	1	1	1	1	6.2597	6.4037	0.9330	A	6.2662	.	0.9330	1.00103	.	1
108	58	1	2	1	2	5.3317	5.4306	1.0750	B	5.3317	.	1.0750	1.00000	.	1
109	59	2	1	1	2	4.8317	4.9330	1.0839	B	4.8317	.	1.0839	1.00000	.	1
110	59	2	2	1	1	4.3892	4.7393	0.7414	A	4.3892	.	0.7414	1.00000	.	1
111	60	2	1	1	2	7.5319	7.6731	1.0361	B	7.5319	.	1.0361	1.00000	.	1
112	60	2	2	1	1	5.7330	6.1323	0.7054	A	5.7295	.	0.7054	0.99939	.	1

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
113	61	1	1	1	1	8.1571	8.2205	1.6670	A	8.1571	.	1.6670	1.00000	.	1
114	61	1	2	1	2	4.6993	4.8992	0.8375	B	4.6993	.	0.8375	1.00000	.	1
115	62	2	1	1	2	5.9000	5.9899	0.5634	B	5.9000	6.14829	0.5634	1.00000	1.02644	1
116	62	2	2	1	1	7.2050	7.4989	0.6825	A	7.2050	.	0.6825	1.00000	.	1
117	63	2	1	1	2	4.7035	4.7559	1.2247	B	4.7035	.	1.2247	1.00000	.	1
118	63	2	2	1	1	2.5903	2.6878	0.3216	A	2.5903	.	0.3216	1.00000	.	1
119	64	1	1	1	1	6.8782	7.0789	1.0811	A	6.8782	.	1.0811	1.00000	.	1
120	64	1	2	1	2	7.0755	7.5427	1.0258	B	7.0755	.	1.0258	1.00000	.	1
121	65	1	1	1	1	4.3768	4.4157	0.8764	A	4.3768	5.18264	0.8764	1.00000	1.17369	1
122	65	1	2	1	2	6.5050	6.5787	1.4630	B	6.4859	.	1.4630	0.99706	.	1
123	66	2	1	1	2	4.4255	4.5941	0.4196	B	4.4255	4.62497	0.4196	1.00000	1.00671	1
124	66	2	2	1	1	6.3360	6.5053	0.9431	A	6.3360	6.57264	0.9431	1.00000	1.01035	1
125	67	2	1	1	2	5.3777	5.4802	0.8051	B	5.3777	.	0.8051	1.00000	.	1
126	67	2	2	1	1	6.2656	6.3340	1.0894	A	6.2656	.	1.0894	1.00000	.	1
127	68	1	1	1	1	5.2713	5.3374	0.8742	A	5.2713	5.54822	0.8742	1.00000	1.03951	1
128	68	1	2	1	2	6.0980	6.2023	0.7002	B	6.0980	.	0.7002	1.00000	.	1
129	69	2	1	1	2	4.4053	4.5453	0.9198	B	4.4053	.	0.9198	1.00000	.	1
130	69	2	2	1	1	4.4775	4.5908	0.6820	A	4.4776	.	0.6820	1.00000	.	1
131	70	2	1	1	2	5.9432	6.1214	0.8376	B	5.9432	6.70157	0.8376	1.00000	1.09477	1
132	70	2	2	1	1	3.0110	3.3478	0.2771	A	3.0110	3.19302	0.2771	1.00000	0.95375	1
133	71	1	1	1	1	3.9455	4.0064	0.9637	A	3.9455	.	0.9637	1.00000	.	1
134	71	1	2	1	2	4.4706	4.6047	0.8498	B	4.4706	.	0.8498	1.00000	.	1
135	72	1	1	1	1	5.6687	5.7768	1.2090	A	5.6687	.	1.2090	1.00000	.	1
136	72	1	2	1	2	4.8338	4.9642	0.8206	B	4.8338	.	0.8206	1.00000	.	1
137	73	1	1	1	1	4.1346	4.2102	0.5532	A	4.1341	.	0.5532	0.99988	.	1
138	73	1	2	1	2	3.5574	3.8184	0.3751	B	3.5574	.	0.3751	1.00000	.	1
139	74	2	1	1	2	5.9214	5.9812	1.3939	B	5.9214	.	1.3939	1.00000	.	1
140	74	2	2	1	1	5.8585	6.1305	1.3350	A	5.8585	.	1.3350	1.00000	.	1
141	75	1	1	1	1	5.9654	6.1381	1.2150	A	5.9654	.	1.2150	1.00000	.	1
142	75	1	2	1	2	5.9597	6.2152	1.1050	B	5.9585	6.58900	1.1050	0.99980	1.06014	1
143	77	1	1	1	1	5.8826	5.9894	0.7170	A	5.8826	.	0.7170	1.00000	.	1
144	77	1	2	1	2	4.5031	4.6025	0.6684	B	4.4926	.	0.6684	0.99768	.	1
145	78	2	1	1	2	5.5950	5.6974	1.1086	B	5.5950	.	1.1086	1.00000	.	1
146	78	2	2	1	1	4.6485	4.7376	0.5681	A	4.6485	.	0.5681	1.00000	.	1
147	79	1	1	1	1	5.3293	5.4204	0.6483	A	5.3306	.	0.6483	1.00025	.	1
148	79	1	2	1	2	4.6902	4.7898	0.4220	B	4.6902	.	0.4220	1.00000	.	1
149	80	2	1	1	2	4.3025	4.3499	0.7545	B	4.3025	.	0.7545	1.00000	.	1
150	80	2	2	1	1	3.2917	3.4697	0.4809	A	3.2917	.	0.4809	1.00000	.	1

Reference ID: 3227106

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
151	81	1	1	1	1	5.4005	5.4887	0.8065	A	5.4005	.	0.8065	1.00000	.	1
152	81	1	2	1	2	4.6639	4.7812	0.6362	B	4.6640	.	0.6362	1.00000	.	1
153	82	2	1	1	2	7.7011	7.8161	1.9005	B	7.7011	.	1.9005	1.00000	.	1
154	82	2	2	1	1	6.2486	6.3285	1.4780	A	6.2486	.	1.4780	1.00000	.	1
155	83	2	1	1	2	5.4893	5.5668	0.7029	B	5.4893	.	0.7029	1.00000	.	1
156	83	2	2	1	1	5.0444	5.2161	0.6965	A	5.0444	.	0.6965	1.00000	.	1
157	84	1	1	1	1	4.7597	4.8868	0.7958	A	4.7597	.	0.7958	1.00000	.	1
158	84	1	2	1	2	5.7519	5.8595	0.5974	B	5.7512	.	0.5974	0.99989	.	1
159	86	1	1	1	1	8.1302	8.3380	1.1342	A	8.1302	.	1.1342	1.00000	.	1
160	86	1	2	1	2	6.7805	7.0318	1.1256	B	6.7780	.	1.1256	0.99963	.	1

091028 FED FIRM TO REVIEWER RATIO- Total EPA Baseline-Adjusted)

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
1	1	2	1	1	2	1397.55	1494.57	123.50	B	1397.55	2977.43	123.50	1.00000	1.99216	1
2	1	2	2	1	1	712.80	865.69	73.20	A	712.80	954.61	73.20	1.00000	1.10271	1
3	2	1	1	1	1	619.50	650.83	46.17	A	619.79	1008.81	46.17	1.00046	1.55005	1
4	2	1	2	1	2	1010.48	1076.14	114.33	B	1010.48	1287.76	114.33	1.00000	1.19665	1
5	3	2	1	1	2	915.87	995.45	79.65	B	915.87	1467.81	79.65	1.00000	1.47452	1
6	3	2	2	1	1	1246.50	1648.17	113.40	A	1246.50	1589.58	113.40	1.00000	0.96445	1
7	4	1	1	1	1	1356.10	2777.68	128.30	A	1356.10	1809.52	128.30	1.00000	0.65145	1
8	4	1	2	1	2	1996.05	2218.03	143.10	B	1996.05	2870.37	143.10	1.00000	1.29411	1
9	5	2	1	1	2	954.70	1318.41	107.30	B	954.70	1225.13	107.30	1.00000	0.92925	1
10	5	2	2	1	1	1265.10	1353.72	130.20	A	1265.10	1960.82	130.20	1.00000	1.44847	1
11	6	1	1	1	1	926.95	1066.83	86.17	A	926.95	1783.97	86.17	1.00000	1.67221	1
12	6	1	2	1	2	934.72	1258.34	123.36	B	935.02	2140.09	123.36	1.00032	1.70072	1
13	7	2	1	1	2	1223.29	1363.69	104.81	B	1223.29	1855.16	104.81	1.00000	1.36039	1
14	7	2	2	1	1	1516.35	1997.93	126.10	A	1516.35	1945.90	126.10	1.00000	0.97396	1
15	8	1	1	1	1	757.70	1065.85	79.90	A	757.70	1340.06	79.90	1.00000	1.25727	1
16	8	1	2	1	2	960.76	1066.00	98.40	B	960.76	1285.27	98.40	1.00000	1.20570	1
17	9	2	1	1	2	871.42	929.41	115.50	B	871.42	1068.00	115.50	1.00000	1.14911	1
18	9	2	2	1	1	785.95	889.47	75.80	A	785.95	2837.04	75.80	1.00000	3.18958	1
19	10	1	1	1	1	1215.38	1296.80	66.54	A	1215.38	2283.93	66.54	1.00000	1.76120	1
20	10	1	2	1	2	1257.70	1337.75	79.40	B	1257.70	1616.66	79.40	1.00000	1.20849	1
21	11	1	1	1	1	885.60	3028.82	96.20	A	885.60	1979.49	96.20	1.00000	0.65355	1
22	11	1	2	1	2	1001.70	1547.26	114.70	B	1001.70	2069.55	114.70	1.00000	1.33756	1
23	12	2	1	1	2	1107.09	1192.81	64.10	B	1107.16	.	64.10	1.00007	.	1
24	12	2	2	1	1	1076.75	1166.61	87.00	A	1077.50	1982.11	87.00	1.00069	1.69903	1

Reference ID: 3227106

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
25	13	2	1	1	2	793.30	1181.20	56.70	B	793.30	1343.16	56.70	1.00000	1.13711	1
26	13	2	2	1	1	872.40	968.55	78.50	A	871.68	.	78.50	0.99918	.	1
27	16	1	1	1	1	872.44	952.55	94.70	A	872.44	1740.02	94.70	1.00000	1.82669	1
28	16	1	2	1	2	769.70	787.64	102.70	B	769.70	803.10	102.70	1.00000	1.01964	1
29	17	2	1	1	2	920.15	991.93	49.80	B	920.15	1694.13	49.80	1.00000	1.70792	1
30	17	2	2	1	1	976.05	1100.37	77.20	A	976.05	1579.17	77.20	1.00000	1.43513	1
31	18	1	1	1	1	710.70	828.06	47.10	A	710.70	1174.03	47.10	1.00000	1.41780	1
32	18	1	2	1	2	652.29	799.68	55.96	B	652.29	958.73	55.96	1.00000	1.19889	1
33	19	1	1	1	1	1001.22	1318.10	99.09	A	1001.22	1879.92	99.09	1.00000	1.42623	1
34	19	1	2	1	2	982.65	1474.68	136.20	B	982.65	1766.52	136.20	1.00000	1.19790	1
35	20	2	1	1	2	984.70	1089.40	87.89	B	984.70	1700.76	87.89	1.00000	1.56120	1
36	20	2	2	1	1	922.70	1130.83	97.90	A	922.70	1397.65	97.90	1.00000	1.23595	1
37	21	1	1	1	1	743.25	840.65	54.80	A	743.25	.	54.80	1.00000	.	1
38	21	1	2	1	2	726.50	1016.22	82.30	B	726.50	1062.52	82.30	1.00000	1.04557	1
39	22	2	1	1	2	697.23	1212.30	59.14	B	697.23	.	59.14	1.00000	.	1
40	22	2	2	1	1	444.00	526.74	32.10	A	444.00	474.71	32.10	1.00000	0.90123	1
41	23	1	1	1	1	783.75	2859.95	53.30	A	783.75	975.97	53.30	1.00000	0.34125	1
42	23	1	2	1	2	1159.15	1259.61	79.30	B	1159.15	1624.33	79.30	1.00000	1.28955	1
43	24	2	1	1	2	753.83	1216.05	76.43	B	753.83	1384.90	76.43	1.00000	1.13886	1
44	24	2	2	1	1	779.60	825.71	52.90	A	779.75	1373.72	52.90	1.00019	1.66368	1
45	25	1	1	1	1	819.93	898.69	51.66	A	819.94	1291.95	51.66	1.00000	1.43759	1
46	25	1	2	1	2	871.65	1139.70	99.90	B	871.65	1737.84	99.90	1.00000	1.52482	1
47	26	2	1	1	2	1216.25	1553.68	66.80	B	1216.25	3012.28	66.80	1.00000	1.93881	1
48	26	2	2	1	1	1321.80	1407.00	110.50	A	1321.80	2018.04	110.50	1.00000	1.43429	1
49	27	2	1	1	2	1109.45	1221.89	53.00	B	1109.45	.	53.00	1.00000	.	1
50	27	2	2	1	1	1291.80	1397.42	84.30	A	1291.80	.	84.30	1.00000	.	1
51	28	1	1	1	1	827.98	957.28	34.41	A	827.98	.	34.41	1.00000	.	1
52	28	1	2	1	2	1398.55	1513.91	61.20	B	1398.55	2049.52	61.20	1.00000	1.35379	1
53	29	2	1	1	2	1040.60	1971.27	109.70	B	1040.60	1796.69	109.70	1.00000	0.91144	1
54	29	2	2	1	1	893.60	1263.57	124.60	A	893.60	1706.07	124.60	1.00000	1.35020	1
55	30	2	1	1	2	933.25	1094.75	94.30	B	933.25	2677.15	94.30	1.00000	2.44544	1
56	30	2	2	1	1	1022.00	2117.10	96.90	A	1022.00	1893.79	96.90	1.00000	0.89452	1
57	31	1	1	1	1	742.98	830.76	36.82	A	742.98	.	36.82	1.00000	.	1
58	31	1	2	1	2	662.72	750.38	32.67	B	662.72	1198.93	32.67	1.00000	1.59775	1
59	32	1	1	1	1	781.55	845.98	39.14	A	781.55	1595.62	39.14	1.00000	1.88611	1
60	32	1	2	1	2	938.14	1010.12	57.03	B	938.14	.	57.03	1.00000	.	1
61	33	2	1	1	2	705.50	763.46	84.20	B	705.50	1022.85	84.20	1.00000	1.33976	1
62	33	2	2	1	1	988.45	1022.10	118.20	A	988.45	1147.15	118.20	1.00000	1.12235	1

Reference ID: 3227106

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
63	34	1	1	1	1	993.59	1123.06	50.41	A	993.59	2849.93	50.41	1.00000	2.53765	1
64	34	1	2	1	2	842.51	1970.98	51.40	B	842.51	.	51.40	1.00000	.	1
65	37	2	1	1	2	3420.10	3573.84	199.00	B	3420.10	4047.91	199.00	1.00000	1.13265	1
66	37	2	2	1	1	3277.80	3418.17	252.90	A	3277.80	3739.46	252.90	1.00000	1.09399	1
67	38	2	1	1	2	1295.18	2378.52	112.39	B	1295.18	2492.56	112.39	1.00000	1.04795	1
68	38	2	2	1	1	1267.93	1984.43	114.40	A	1267.93	1626.30	114.40	1.00000	0.81953	1
69	39	1	1	1	1	981.90	1477.52	89.00	A	981.90	1500.04	89.00	1.00000	1.01524	1
70	39	1	2	1	2	542.25	780.34	39.80	B	542.25	.	39.80	1.00000	.	1
71	40	1	1	1	1	1203.55	1286.94	65.50	A	1203.55	2256.51	65.50	1.00000	1.75339	1
72	40	1	2	1	2	1019.80	1439.29	48.80	B	1019.80	1737.80	48.80	1.00000	1.20740	1
73	41	2	1	1	2	683.45	723.85	75.78	B	683.45	1272.29	75.78	1.00000	1.75767	1
74	41	2	2	1	1	766.09	1042.12	78.80	A	766.09	1139.05	78.80	1.00000	1.09302	1
75	42	2	1	1	2	1133.54	1217.95	109.98	B	1133.54	2392.53	109.98	1.00000	1.96438	1
76	42	2	2	1	1	1265.27	1379.51	111.90	A	1265.27	2294.62	111.90	1.00000	1.66336	1
77	43	1	1	1	1	933.35	1040.37	54.66	A	933.63	1473.09	54.66	1.00030	1.41593	1
78	43	1	2	1	2	843.82	890.22	113.03	B	844.01	1183.23	113.03	1.00023	1.32915	1
79	44	1	1	1	1	1056.90	1123.07	73.36	A	1056.90	1861.44	73.36	1.00000	1.65746	1
80	44	1	2	1	2	917.37	1009.95	76.98	B	917.80	1285.66	76.98	1.00047	1.27300	1
81	45	1	1	1	1	920.25	976.89	46.47	A	920.25	1482.90	46.47	1.00000	1.51798	1
82	45	1	2	1	2	843.60	911.40	64.90	B	843.73	1066.11	64.90	1.00015	1.16974	1
83	46	2	1	1	2	709.66	1544.51	92.40	B	709.66	1223.73	92.40	1.00000	0.79231	1
84	46	2	2	1	1	940.07	1075.21	100.90	A	940.07	.	100.90	1.00000	.	1
85	47	1	1	1	1	932.00	1458.84	128.50	A	932.00	1630.70	128.50	1.00000	1.11780	1
86	47	1	2	1	2	1173.20	1364.50	161.60	B	1173.77	1516.61	161.60	1.00048	1.11148	1
87	48	2	1	1	2	1004.69	1092.55	96.53	B	1004.69	1712.54	96.53	1.00000	1.56746	1
88	48	2	2	1	1	942.29	1382.61	98.31	A	942.29	2196.15	98.31	1.00000	1.58841	1
89	49	1	1	1	1	643.36	685.01	63.10	A	643.38	947.79	63.10	1.00003	1.38360	1
90	49	1	2	1	2	751.06	811.74	72.91	B	751.06	1013.08	72.91	1.00000	1.24804	1
91	50	1	1	1	1	781.06	878.23	40.93	A	781.06	.	40.93	1.00000	.	1
92	50	1	2	1	2	831.05	878.95	49.00	B	831.03	1437.23	49.00	0.99998	1.63517	1
93	51	2	1	1	2	926.78	997.29	48.34	B	926.77	1635.02	48.34	0.99999	1.63947	1
94	51	2	2	1	1	996.05	1049.50	67.93	A	994.65	1453.05	67.93	0.99860	1.38452	1
95	52	2	1	1	2	1148.50	1211.87	48.10	B	1148.50	2104.19	48.10	1.00000	1.73631	1
96	52	2	2	1	1	1452.90	1580.56	90.40	A	1453.58	2446.18	90.40	1.00047	1.54767	1
97	53	2	1	1	2	1200.66	1275.63	86.14	B	1200.79	2533.31	86.14	1.00011	1.98593	1
98	53	2	2	1	1	1520.22	1875.44	124.60	A	1520.22	1899.17	124.60	1.00000	1.01266	1
99	54	1	1	1	1	1013.76	1075.39	42.70	A	1013.76	1913.51	42.70	1.00000	1.77936	1
100	54	1	2	1	2	807.47	855.99	48.60	B	807.47	1689.89	48.60	1.00000	1.97420	1

Reference ID: 3227106

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
101	55	2	1	1	2	674.45	759.85	35.74	B	674.54	1267.62	35.74	1.00014	1.66826	1
102	55	2	2	1	1	250.16	313.12	21.23	A	250.39	320.34	21.23	1.00092	1.02305	1
103	56	1	1	1	1	801.87	850.81	55.50	A	801.87	1405.80	55.50	1.00000	1.65231	1
104	56	1	2	1	2	929.25	994.85	47.70	B	929.25	1377.80	47.70	1.00000	1.38492	1
105	57	1	1	1	1	719.65	811.69	56.90	A	719.65	1913.91	56.90	1.00000	2.35792	1
106	57	1	2	1	2	830.35	1032.92	41.50	B	829.09	1710.95	41.50	0.99848	1.65642	1
107	58	1	1	1	1	679.30	893.12	36.30	A	679.58	.	36.30	1.00042	.	1
108	58	1	2	1	2	686.40	3422.25	48.70	B	686.40	851.68	48.70	1.00000	0.24887	1
109	59	2	1	1	2	726.12	781.34	108.71	B	726.12	1072.45	108.71	1.00000	1.37258	1
110	59	2	2	1	1	710.51	822.03	81.84	A	710.51	974.87	81.84	1.00000	1.18593	1
111	60	2	1	1	2	982.50	1191.57	55.10	B	982.50	3627.99	55.10	1.00000	3.04471	1
112	60	2	2	1	1	896.10	1009.24	51.90	A	896.21	2895.77	51.90	1.00012	2.86925	1
113	61	1	1	1	1	1195.23	1661.72	78.88	A	1195.23	1881.62	78.88	1.00000	1.13233	1
114	61	1	2	1	2	823.27	1299.84	48.80	B	823.27	1344.38	48.80	1.00000	1.03427	1
115	62	2	1	1	2	1718.44	2059.52	171.61	B	1718.44	2559.63	171.61	1.00000	1.24283	1
116	62	2	2	1	1	2486.75	6904.48	263.90	A	2486.75	3884.28	263.90	1.00000	0.56257	1
117	63	2	1	1	2	859.49	923.87	41.66	B	859.49	1594.89	41.66	1.00000	1.72631	1
118	63	2	2	1	1	726.12	818.91	37.87	A	726.12	1591.64	37.87	1.00000	1.94360	1
119	64	1	1	1	1	1169.65	1257.21	128.50	A	1169.65	1473.15	128.50	1.00000	1.17176	1
120	64	1	2	1	2	1471.30	1562.41	114.10	B	1471.30	1780.20	114.10	1.00000	1.13940	1
121	65	1	1	1	1	1160.01	1244.08	62.60	A	1160.01	2059.11	62.60	1.00000	1.65513	1
122	65	1	2	1	2	1085.20	2245.89	97.10	B	1084.44	1530.25	97.10	0.99930	0.68135	1
123	66	2	1	1	2	1054.40	1179.35	44.93	B	1054.40	2608.99	44.93	1.00000	2.21223	1
124	66	2	2	1	1	1266.50	1421.96	65.70	A	1266.50	2339.83	65.70	1.00000	1.64549	1
125	67	2	1	1	2	821.56	870.55	42.41	B	821.56	1617.54	42.41	1.00000	1.85808	1
126	67	2	2	1	1	869.50	921.94	38.49	A	869.50	1451.40	38.49	1.00000	1.57430	1
127	68	1	1	1	1	1057.30	1154.37	79.40	A	1057.30	1871.42	79.40	1.00000	1.62116	1
128	68	1	2	1	2	915.90	989.55	52.10	B	915.90	1841.62	52.10	1.00000	1.86106	1
129	69	2	1	1	2	825.45	900.63	57.60	B	825.45	1312.49	57.60	1.00000	1.45731	1
130	69	2	2	1	1	912.60	969.74	49.70	A	912.60	1523.68	49.70	1.00000	1.57123	1
131	70	2	1	1	2	1870.75	1987.81	90.60	B	1870.75	2633.30	90.60	1.00000	1.32472	1
132	70	2	2	1	1	974.65	1208.57	49.60	A	974.65	1572.75	49.60	1.00000	1.30133	1
133	71	1	1	1	1	870.00	1062.18	92.20	A	870.00	1311.14	92.20	1.00000	1.23439	1
134	71	1	2	1	2	1256.55	1343.70	131.40	B	1256.55	1758.08	131.40	1.00000	1.30839	1
135	72	1	1	1	1	816.65	1284.90	92.40	A	816.65	1337.68	92.40	1.00000	1.04108	1
136	72	1	2	1	2	850.85	949.00	91.90	B	850.85	1122.61	91.90	1.00000	1.18295	1
137	73	1	1	1	1	700.63	741.57	37.14	A	700.36	1197.31	37.14	0.99962	1.61457	1
138	73	1	2	1	2	777.32	1171.04	49.90	B	777.32	1010.32	49.90	1.00000	0.86276	1

Reference ID: 3227106

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
139	74	2	1	1	2	610.20	1399.55	76.12	B	610.20	1295.28	76.12	1.00000	0.92549	1
140	74	2	2	1	1	587.75	962.80	55.40	A	587.75	2282.38	55.40	1.00000	2.37056	1
141	75	1	1	1	1	1014.58	1097.28	69.40	A	1014.58	1560.37	69.40	1.00000	1.42203	1
142	75	1	2	1	2	998.20	1590.64	97.10	B	998.45	1674.51	97.10	1.00025	1.05273	1
143	77	1	1	1	1	981.05	1054.33	62.70	A	981.05	1561.37	62.70	1.00000	1.48090	1
144	77	1	2	1	2	825.21	894.62	57.20	B	824.16	1767.43	57.20	0.99872	1.97561	1
145	78	2	1	1	2	979.25	1230.89	62.40	B	979.25	1815.20	62.40	1.00000	1.47471	1
146	78	2	2	1	1	1135.45	1204.54	91.10	A	1135.45	1684.89	91.10	1.00000	1.39878	1
147	79	1	1	1	1	1382.28	1512.87	74.64	A	1382.92	1945.75	74.64	1.00046	1.28613	1
148	79	1	2	1	2	1380.24	1536.26	82.91	B	1380.24	.	82.91	1.00000	.	1
149	80	2	1	1	2	796.82	851.29	55.80	B	796.82	1574.68	55.80	1.00000	1.84977	1
150	80	2	2	1	1	777.10	1380.97	66.09	A	777.10	1163.04	66.09	1.00000	0.84219	1
151	81	1	1	1	1	1095.90	1410.91	67.91	A	1095.90	1833.26	67.91	1.00000	1.29935	1
152	81	1	2	1	2	1079.80	1588.17	78.40	B	1079.80	2074.41	78.40	1.00000	1.30617	1
153	82	2	1	1	2	679.79	879.38	102.40	B	679.79	1286.58	102.40	1.00000	1.46306	1
154	82	2	2	1	1	854.18	915.73	85.10	A	854.22	1184.64	85.10	1.00005	1.29366	1
155	83	2	1	1	2	692.81	1456.70	45.79	B	692.81	1326.32	45.79	1.00000	0.91050	1
156	83	2	2	1	1	800.62	876.06	76.88	A	800.62	1112.54	76.88	1.00000	1.26994	1
157	84	1	1	1	1	916.85	965.80	74.79	A	916.85	1584.91	74.79	1.00000	1.64103	1
158	84	1	2	1	2	1038.40	1115.83	74.40	B	1038.40	1262.42	74.40	1.00000	1.13137	1
159	86	1	1	1	1	1283.94	1390.90	113.79	A	1283.94	2121.37	113.79	1.00000	1.52518	1
160	86	1	2	1	2	1233.80	1303.05	123.00	B	1233.31	1745.42	123.00	0.99960	1.33949	1

091028 FED FIRM TO REVIEWER RATIO- Free DHA Baseline-Adjusted)

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
1	1	2	1	1	2	12.8140	12.905	3.4670	B	12.8140	.	3.4670	1.00000	.	1
2	1	2	2	1	1	9.4020	10.230	1.6610	A	9.4020	.	1.6610	1.00000	.	1
3	2	1	1	1	1	10.4515	11.815	1.8260	A	10.4636	.	1.8260	1.00116	.	1
4	2	1	2	1	2	15.7035	16.091	3.1400	B	15.7035	.	3.1400	1.00000	.	1
5	3	2	1	1	2	12.6355	12.987	1.8890	B	12.6355	.	1.8890	1.00000	.	1
6	3	2	2	1	1	9.7845	10.567	1.3250	A	9.7845	.	1.3250	1.00000	.	1
7	4	1	1	1	1	21.2425	21.565	2.8790	A	21.2425	21.6435	2.8790	1.00000	1.00363	1
8	4	1	2	1	2	21.9150	23.282	1.4050	B	21.9150	.	1.4050	1.00000	.	1
9	5	2	1	1	2	16.8010	17.250	2.9450	B	16.8010	.	2.9450	1.00000	.	1
10	5	2	2	1	1	21.8155	22.164	2.4940	A	21.8155	22.3067	2.4940	1.00000	1.00645	1
11	6	1	1	1	1	12.0875	19.623	2.6120	A	12.0875	.	2.6120	1.00000	.	1
12	6	1	2	1	2	11.8890	13.616	3.0510	B	11.8903	.	3.0510	1.00011	.	1

Reference ID: 3227106

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
13	7	2	1	1	2	23.7835	25.372	4.2560	B	23.7835	.	4.2560	1.00000	.	1
14	7	2	2	1	1	24.8645	113.163	4.5730	A	24.8645	.	4.5730	1.00000	.	1
15	8	1	1	1	1	12.5120	14.443	4.2270	A	12.5120	.	4.2270	1.00000	.	1
16	8	1	2	1	2	12.7215	19.054	2.3330	B	12.7215	.	2.3330	1.00000	.	1
17	9	2	1	1	2	13.3720	14.418	2.6240	B	13.3720	.	2.6240	1.00000	.	1
18	9	2	2	1	1	9.7670	10.913	1.7500	A	9.7670	.	1.7500	1.00000	.	1
19	10	1	1	1	1	14.4375	14.477	1.9690	A	14.4375	.	1.9690	1.00000	.	1
20	10	1	2	1	2	15.9895	16.373	2.6320	B	15.9895	.	2.6320	1.00000	.	1
21	11	1	1	1	1	15.5510	17.016	4.4520	A	15.5510	.	4.4520	1.00000	.	1
22	11	1	2	1	2	14.6580	49.206	5.0310	B	14.6580	.	5.0310	1.00000	.	1
23	12	2	1	1	2	10.3720	10.493	1.8050	B	10.3737	.	1.8050	1.00016	.	1
24	12	2	2	1	1	13.9050	14.394	1.9460	A	13.9193	.	1.9460	1.00103	.	1
25	13	2	1	1	2	8.0930	8.719	2.9870	B	8.0930	.	2.9870	1.00000	.	1
26	13	2	2	1	1	14.2080	14.331	2.3880	A	14.2846	.	2.3880	1.00539	.	1
27	16	1	1	1	1	16.2005	17.390	4.3400	A	16.2005	.	4.3400	1.00000	.	1
28	16	1	2	1	2	15.5605	15.830	2.6490	B	15.5605	.	2.6490	1.00000	.	1
29	17	2	1	1	2	16.3635	16.448	2.7190	B	16.3635	.	2.7190	1.00000	.	1
30	17	2	2	1	1	18.2750	29.596	3.3480	A	18.2750	.	3.3480	1.00000	.	1
31	18	1	1	1	1	17.0800	17.853	3.7220	A	17.0800	.	3.7220	1.00000	.	1
32	18	1	2	1	2	11.4550	12.693	1.5840	B	11.4550	.	1.5840	1.00000	.	1
33	19	1	1	1	1	12.9720	13.665	3.3560	A	12.9720	.	3.3560	1.00000	.	1
34	19	1	2	1	2	17.2275	17.295	3.2400	B	17.2275	.	3.2400	1.00000	.	1
35	20	2	1	1	2	12.0405	12.937	1.9280	B	12.0405	.	1.9280	1.00000	.	1
36	20	2	2	1	1	14.9735	17.069	2.8430	A	14.9735	.	2.8430	1.00000	.	1
37	21	1	1	1	1	9.7685	11.465	1.3390	A	9.7685	.	1.3390	1.00000	.	1
38	21	1	2	1	2	9.7840	16.206	3.1400	B	9.7840	.	3.1400	1.00000	.	1
39	22	2	1	1	2	11.7855	12.791	3.9030	B	11.7855	.	3.9030	1.00000	.	1
40	22	2	2	1	1	15.4500	20.549	3.8270	A	15.4500	.	3.8270	1.00000	.	1
41	23	1	1	1	1	18.4920	18.801	3.6630	A	18.4920	19.8878	3.6630	1.00000	1.05781	1
42	23	1	2	1	2	17.9340	20.549	2.1410	B	17.9340	.	2.1410	1.00000	.	1
43	24	2	1	1	2	16.0585	16.945	3.5280	B	16.0585	.	3.5280	1.00000	.	1
44	24	2	2	1	1	12.1445	13.128	1.6520	A	12.1527	.	1.6520	1.00068	.	1
45	25	1	1	1	1	12.2595	12.675	2.6600	A	12.2595	.	2.6600	1.00000	.	1
46	25	1	2	1	2	7.5815	76.289	1.9280	B	7.5815	.	1.9280	1.00000	.	1
47	26	2	1	1	2	7.8050	7.999	1.4900	B	7.8050	.	1.4900	1.00000	.	1
48	26	2	2	1	1	8.3560	9.408	1.1590	A	8.3560	.	1.1590	1.00000	.	1
49	27	2	1	1	2	11.4040	11.619	2.6140	B	11.4040	.	2.6140	1.00000	.	1
50	27	2	2	1	1	10.2730	10.452	1.5170	A	10.2730	.	1.5170	1.00000	.	1

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
51	28	1	1	1	1	1.1685	2.482	0.2990	A	1.1685	.	0.2990	1.00000	.	1
52	28	1	2	1	2	9.4135	11.285	1.0820	B	9.4135	.	1.0820	1.00000	.	1
53	29	2	1	1	2	11.6415	11.790	1.9710	B	11.6415	.	1.9710	1.00000	.	1
54	29	2	2	1	1	9.1440	10.834	2.0560	A	9.1440	.	2.0560	1.00000	.	1
55	30	2	1	1	2	11.0960	11.582	2.7830	B	11.0960	.	2.7830	1.00000	.	1
56	30	2	2	1	1	11.9385	13.239	2.9660	A	11.9385	.	2.9660	1.00000	.	1
57	31	1	1	1	1	14.9982	15.164	3.9660	A	14.9982	.	3.9660	1.00000	.	1
58	31	1	2	1	2	15.4097	15.669	2.8380	B	15.4097	.	2.8380	1.00000	.	1
59	32	1	1	1	1	12.3385	12.583	2.5530	A	12.3385	.	2.5530	1.00000	.	1
60	32	1	2	1	2	14.9920	15.317	1.7880	B	14.9920	15.4518	1.7880	1.00000	1.00883	1
61	33	2	1	1	2	12.5905	14.021	3.3750	B	12.5905	.	3.3750	1.00000	.	1
62	33	2	2	1	1	15.3305	15.755	2.4350	A	15.3305	15.9033	2.4350	1.00000	1.00942	1
63	34	1	1	1	1	7.4810	7.624	1.4910	A	7.4810	.	1.4910	1.00000	.	1
64	34	1	2	1	2	6.0680	6.176	1.3010	B	6.0680	.	1.3010	1.00000	.	1
65	37	2	1	1	2	15.9140	15.969	1.4800	B	15.9140	.	1.4800	1.00000	.	1
66	37	2	2	1	1	19.2170	19.358	2.9200	A	19.2170	.	2.9200	1.00000	.	1
67	38	2	1	1	2	16.1780	16.473	2.9920	B	16.1780	.	2.9920	1.00000	.	1
68	38	2	2	1	1	13.1900	14.139	3.8070	A	13.1900	.	3.8070	1.00000	.	1
69	39	1	1	1	1	18.0650	18.645	3.3640	A	18.0650	.	3.3640	1.00000	.	1
70	39	1	2	1	2	18.8120	19.700	2.4170	B	18.8120	.	2.4170	1.00000	.	1
71	40	1	1	1	1	15.8140	16.403	2.9860	A	15.8140	.	2.9860	1.00000	.	1
72	40	1	2	1	2	19.0985	24.158	4.1580	B	19.0985	.	4.1580	1.00000	.	1
73	41	2	1	1	2	10.5065	18.794	3.8030	B	10.5065	.	3.8030	1.00000	.	1
74	41	2	2	1	1	11.7690	19.195	3.3370	A	11.7690	.	3.3370	1.00000	.	1
75	42	2	1	1	2	12.3592	13.397	3.1000	B	12.3592	.	3.1000	1.00000	.	1
76	42	2	2	1	1	12.4700	13.607	2.1970	A	12.4700	.	2.1970	1.00000	.	1
77	43	1	1	1	1	12.2510	12.546	1.8080	A	12.2571	.	1.8080	1.00050	.	1
78	43	1	2	1	2	11.8615	12.398	2.9670	B	11.8358	.	2.9670	0 99784	.	1
79	44	1	1	1	1	11.4693	12.095	2.2610	A	11.4693	.	2.2610	1.00000	.	1
80	44	1	2	1	2	8.7682	9.579	2.2860	B	8.7593	.	2.2860	0 99899	.	1
81	45	1	1	1	1	19.8585	20.288	4.3730	A	19.8585	.	4.3730	1.00000	.	1
82	45	1	2	1	2	17.0210	17.895	3.8240	B	17.0101	.	3.8240	0 99936	.	1
83	46	2	1	1	2	12.3230	14.537	3.8280	B	12.3230	.	3.8280	1.00000	.	1
84	46	2	2	1	1	12.7105	13.639	3.7990	A	12.7105	.	3.7990	1.00000	.	1
85	47	1	1	1	1	15.9381	17.887	4.5780	A	15.9381	.	4.5780	1.00000	.	1
86	47	1	2	1	2	15.6060	18.092	3.4760	B	15.6116	.	3.4760	1.00036	.	1
87	48	2	1	1	2	11.7380	13.985	2.7150	B	11.7380	.	2.7150	1.00000	.	1
88	48	2	2	1	1	11.4070	13.281	3.9040	A	11.4070	.	3.9040	1.00000	.	1

Reference ID: 3227106

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
89	49	1	1	1	1	10.8368	11.396	1.7750	A	10.8368	.	1.7750	1.00000	.	1
90	49	1	2	1	2	13.9915	18.938	5.5330	B	13.9915	.	5.5330	1.00000	.	1
91	50	1	1	1	1	2.6934	4.217	0.3806	A	2.6934	.	0.3806	1.00000	.	1
92	50	1	2	1	2	6.3570	6.893	1.6400	B	6.3585	.	1.6400	1.00024	.	1
93	51	2	1	1	2	11.9770	12.516	2.4060	B	11.9648	.	2.4060	0 99898	.	1
94	51	2	2	1	1	13.1195	30.282	3.4340	A	13.0792	.	3.4340	0 99693	.	1
95	52	2	1	1	2	13.5058	13.840	2.7170	B	13.5058	.	2.7170	1.00000	.	1
96	52	2	2	1	1	14.3325	14.774	2.5140	A	14.2914	16.1163	2.5140	0 99713	1.09085	1
97	53	2	1	1	2	14.5855	15.760	2.5510	B	14.5818	.	2.5510	0 99975	.	1
98	53	2	2	1	1	16.6150	16.812	3.4710	A	16.6150	.	3.4710	1.00000	.	1
99	54	1	1	1	1	21.1357	23.019	3.5630	A	21.1357	21.3482	3.5630	1.00000	0.92741	1
100	54	1	2	1	2	13.6120	13.879	1.8640	B	13.6120	.	1.8640	1.00000	.	1
101	55	2	1	1	2	9.2565	21.334	1.9370	B	9.2554	.	1.9370	0 99988	.	1
102	55	2	2	1	1	3.3865	3.473	1.0410	A	3.3858	.	1.0410	0 99981	.	1
103	56	1	1	1	1	4.9800	5.375	0.7930	A	4.9800	.	0.7930	1.00000	.	1
104	56	1	2	1	2	6.2901	6.803	0.7780	B	6.2901	.	0.7780	1.00000	.	1
105	57	1	1	1	1	9.0360	566.965	1.5140	A	9.0360	.	1.5140	1.00000	.	1
106	57	1	2	1	2	8.0700	8.459	2.2130	B	8.0651	.	2.2130	0 99940	.	1
107	58	1	1	1	1	15.9100	16.174	2.7820	A	15.9225	.	2.7820	1.00079	.	1
108	58	1	2	1	2	14.0820	15.086	3.3400	B	14.0820	.	3.3400	1.00000	.	1
109	59	2	1	1	2	11.9105	12.632	2.7360	B	11.9105	.	2.7360	1.00000	.	1
110	59	2	2	1	1	12.7560	16.996	2.2370	A	12.7560	.	2.2370	1.00000	.	1
111	60	2	1	1	2	18.4155	19.149	2.5840	B	18.4155	.	2.5840	1.00000	.	1
112	60	2	2	1	1	13.8915	17.587	2.4840	A	13.8756	.	2.4840	0 99886	.	1
113	61	1	1	1	1	22.5395	22.691	4.7510	A	22.5395	.	4.7510	1.00000	.	1
114	61	1	2	1	2	11.7858	20.743	2.5290	B	11.7858	.	2.5290	1.00000	.	1
115	62	2	1	1	2	12.6720	12.839	1.9680	B	12.6720	.	1.9680	1.00000	.	1
116	62	2	2	1	1	16.9570	17.259	2.1240	A	16.9570	.	2.1240	1.00000	.	1
117	63	2	1	1	2	12.7210	13.003	3.7800	B	12.7210	.	3.7800	1.00000	.	1
118	63	2	2	1	1	7.1490	7.998	0.6340	A	7.1490	.	0.6340	1.00000	.	1
119	64	1	1	1	1	18.6940	21.224	3.4610	A	18.6940	.	3.4610	1.00000	.	1
120	64	1	2	1	2	20.7980	24.445	3.7710	B	20.7980	.	3.7710	1.00000	.	1
121	65	1	1	1	1	10.4615	10.593	3.0730	A	10.4615	12.6438	3.0730	1.00000	1.19359	1
122	65	1	2	1	2	14.9415	15.974	4.3780	B	14.8961	.	4.3780	0 99696	.	1
123	66	2	1	1	2	11.2150	11.639	1.4580	B	11.2150	.	1.4580	1.00000	.	1
124	66	2	2	1	1	15.7760	28.166	3.6500	A	15.7760	.	3.6500	1.00000	.	1
125	67	2	1	1	2	13.7175	14.140	2.4110	B	13.7175	.	2.4110	1.00000	.	1
126	67	2	2	1	1	16.2785	16.816	3.2820	A	16.2785	17.2541	3.2820	1.00000	1.02606	1

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
127	68	1	1	1	1	12.7430	12.838	2.9530	A	12.7430	12.7934	2.9530	1.00000	0.99652	1
128	68	1	2	1	2	15.2160	15.431	2.0820	B	15.2160	.	2.0820	1.00000	.	1
129	69	2	1	1	2	10.4585	12.636	2.6960	B	10.4585	.	2.6960	1.00000	.	1
130	69	2	2	1	1	8.4525	8.880	1.1510	A	8.4525	.	1.1510	1.00000	.	1
131	70	2	1	1	2	13.7980	14.375	2.4050	B	13.7980	.	2.4050	1.00000	.	1
132	70	2	2	1	1	6.8885	17.391	0.7910	A	6.8885	.	0.7910	1.00000	.	1
133	71	1	1	1	1	10.9140	11.374	3.1440	A	10.9140	.	3.1440	1.00000	.	1
134	71	1	2	1	2	12.9630	13.712	2.9350	B	12.9630	.	2.9350	1.00000	.	1
135	72	1	1	1	1	15.7830	16.343	3.6340	A	15.7830	.	3.6340	1.00000	.	1
136	72	1	2	1	2	11.3020	12.242	2.2940	B	11.3020	.	2.2940	1.00000	.	1
137	73	1	1	1	1	10.3048	10.622	1.5120	A	10.2914	.	1.5120	0 99870	.	1
138	73	1	2	1	2	7.2250	10.481	0.9220	B	7.2250	.	0.9220	1.00000	.	1
139	74	2	1	1	2	11.7350	11.834	3.5200	B	11.7350	.	3.5200	1.00000	.	1
140	74	2	2	1	1	13.3000	13.423	3.9150	A	13.3000	.	3.9150	1.00000	.	1
141	75	1	1	1	1	14.1910	14.839	3.9610	A	14.1910	.	3.9610	1.00000	.	1
142	75	1	2	1	2	10.9638	15.809	3.5380	B	10.9629	.	3.5380	0 99992	.	1
143	77	1	1	1	1	13.9266	14.262	1.9100	A	13.9266	.	1.9100	1.00000	.	1
144	77	1	2	1	2	7.2372	7.343	1.6000	B	7.2173	7.4085	1.6000	0 99725	1.00893	1
145	78	2	1	1	2	16.5945	17.047	3.7330	B	16.5945	.	3.7330	1.00000	.	1
146	78	2	2	1	1	11.7120	12.068	1.6150	A	11.7120	.	1.6150	1.00000	.	1
147	79	1	1	1	1	12.4250	12.844	2.0960	A	12.4284	.	2.0960	1.00027	.	1
148	79	1	2	1	2	8.8805	9.535	1.1680	B	8.8805	.	1.1680	1.00000	.	1
149	80	2	1	1	2	12.5448	12.664	2.7770	B	12.5448	.	2.7770	1.00000	.	1
150	80	2	2	1	1	8.3543	9.995	1.4777	A	8.3543	.	1.4777	1.00000	.	1
151	81	1	1	1	1	15.7135	15.969	2.5430	A	15.7135	.	2.5430	1.00000	.	1
152	81	1	2	1	2	12.9985	13.843	1.9270	B	12.9985	.	1.9270	1.00000	.	1
153	82	2	1	1	2	18.8115	19.386	4.5830	B	18.8115	.	4.5830	1.00000	.	1
154	82	2	2	1	1	17.0575	17.280	4.3550	A	17.0561	.	4.3550	0 99992	.	1
155	83	2	1	1	2	14.5450	15.205	2.0130	B	14.5450	.	2.0130	1.00000	.	1
156	83	2	2	1	1	12.9620	14.106	2.1400	A	12.9620	.	2.1400	1.00000	.	1
157	84	1	1	1	1	14.7695	15.562	2.6290	A	14.7695	.	2.6290	1.00000	.	1
158	84	1	2	1	2	16.9870	18.277	2.2140	B	16.9835	.	2.2140	0 99979	.	1
159	86	1	1	1	1	21.1415	21.668	3.2900	A	21.1415	.	3.2900	1.00000	.	1
160	86	1	2	1	2	16.2280	17.922	3.3030	B	16.2200	.	3.3030	0 99951	.	1

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
1	1	2	1	1	2	559.60	590.41	70.3	B	559.60	.	70.3	1.00000	.	1
2	1	2	2	1	1	295.00	333.58	48.3	A	295.00	.	48.3	1.00000	.	1
3	2	1	1	1	1	228.60	243.87	33.1	A	228.81	259.98	33.1	1.00094	1.06606	1
4	2	1	2	1	2	524.25	544.25	75.6	B	524.25	550.20	75.6	1.00000	1.01093	1
5	3	2	1	1	2	520.50	554.69	54.4	B	520.50	858.91	54.4	1.00000	1.54844	1
6	3	2	2	1	1	843.95	863.98	86.0	A	843.95	974.04	86.0	1.00000	1.12738	1
7	4	1	1	1	1	761.80	769.84	96.5	A	761.80	.	96.5	1.00000	.	1
8	4	1	2	1	2	1353.20	1376.27	106.2	B	1353.20	.	106.2	1.00000	.	1
9	5	2	1	1	2	644.75	653.33	95.3	B	644.75	.	95.3	1.00000	.	1
10	5	2	2	1	1	818.75	846.19	92.8	A	818.75	.	92.8	1.00000	.	1
11	6	1	1	1	1	393.35	665.90	60.6	A	393.35	.	60.6	1.00000	.	1
12	6	1	2	1	2	245.60	336.91	77.9	B	245.60	.	77.9	1.00000	.	1
13	7	2	1	1	2	580.70	625.98	63.1	B	580.70	.	63.1	1.00000	.	1
14	7	2	2	1	1	728.25	743.04	84.8	A	728.25	741.74	84.8	1.00000	0.99825	1
15	8	1	1	1	1	203.50	322.62	65.7	A	203.50	.	65.7	1.00000	.	1
16	8	1	2	1	2	485.65	2954.49	68.5	B	485.65	.	68.5	1.00000	.	1
17	9	2	1	1	2	445.10	533.28	63.8	B	445.10	.	63.8	1.00000	.	1
18	9	2	2	1	1	432.35	977.15	47.8	A	432.35	.	47.8	1.00000	.	1
19	10	1	1	1	1	396.85	418.47	52.0	A	396.85	.	52.0	1.00000	.	1
20	10	1	2	1	2	542.10	587.44	57.7	B	542.10	.	57.7	1.00000	.	1
21	11	1	1	1	1	366.75	490.96	69.7	A	366.75	.	69.7	1.00000	.	1
22	11	1	2	1	2	503.00	553.66	89.2	B	503.00	.	89.2	1.00000	.	1
23	12	2	1	1	2	307.70	331.84	23.7	B	307.74	.	23.7	1.00013	.	1
24	12	2	2	1	1	256.35	259.04	32.8	A	256.89	.	32.8	1.00211	.	1
25	13	2	1	1	2	128.80	191.11	37.3	B	128.80	.	37.3	1.00000	.	1
26	13	2	2	1	1	355.55	487.32	29.5	A	355.84	.	29.5	1.00081	.	1
27	16	1	1	1	1	431.60	465.01	81.3	A	431.60	.	81.3	1.00000	.	1
28	16	1	2	1	2	352.40	370.51	87.7	B	352.40	.	87.7	1.00000	.	1
29	17	2	1	1	2	290.85	305.04	33.0	B	290.85	.	33.0	1.00000	.	1
30	17	2	2	1	1	267.70	299.86	55.0	A	267.70	.	55.0	1.00000	.	1
31	18	1	1	1	1	156.05	165.58	29.3	A	156.05	.	29.3	1.00000	.	1
32	18	1	2	1	2	145.30	147.94	41.6	B	145.30	.	41.6	1.00000	.	1
33	19	1	1	1	1	287.80	314.61	71.7	A	287.80	.	71.7	1.00000	.	1
34	19	1	2	1	2	351.70	364.02	88.3	B	351.70	.	88.3	1.00000	.	1
35	20	2	1	1	2	307.40	408.23	57.8	B	307.40	.	57.8	1.00000	.	1
36	20	2	2	1	1	232.30	387.59	57.7	A	232.30	.	57.7	1.00000	.	1
37	21	1	1	1	1	12.85	41.34	3.8	A	12.85	.	3.8	1.00000	.	1
38	21	1	2	1	2	24.50	31.02	10.2	B	24.50	.	10.2	1.00000	.	1

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
39	22	2	1	1	2	64.70	75.87	10.6	B	64.70	.	10.6	1.00000	.	1
40	22	2	2	1	1	8.10	10.63	4.1	A	8.10	.	4.1	1.00000	.	1
41	23	1	1	1	1	293.50	301.04	42.0	A	293.50	.	42.0	1.00000	.	1
42	23	1	2	1	2	591.30	620.43	76.4	B	591.30	.	76.4	1.00000	.	1
43	24	2	1	1	2	160.80	173.10	47.3	B	160.80	.	47.3	1.00000	.	1
44	24	2	2	1	1	218.30	225.71	36.2	A	218.33	.	36.2	1.00014	.	1
45	25	1	1	1	1	233.35	238.71	44.7	A	233.35	.	44.7	1.00000	.	1
46	25	1	2	1	2	169.20	178.06	61.9	B	169.20	.	61.9	1.00000	.	1
47	26	2	1	1	2	256.35	276.58	35.6	B	256.35	.	35.6	1.00000	.	1
48	26	2	2	1	1	414.15	417.37	64.9	A	414.15	416.83	64.9	1.00000	0.99871	1
49	27	2	1	1	2	246.80	255.12	23.1	B	246.80	.	23.1	1.00000	.	1
50	27	2	2	1	1	354.65	382.11	47.9	A	354.65	.	47.9	1.00000	.	1
51	28	1	1	1	1	124.60	200.36	13.4	A	124.60	.	13.4	1.00000	.	1
52	28	1	2	1	2	366.05	395.94	27.4	B	366.05	.	27.4	1.00000	.	1
53	29	2	1	1	2	437.25	442.59	88.9	B	437.25	.	88.9	1.00000	.	1
54	29	2	2	1	1	335.60	341.88	101.8	A	335.60	.	101.8	1.00000	.	1
55	30	2	1	1	2	210.10	247.64	52.8	B	210.10	.	52.8	1.00000	.	1
56	30	2	2	1	1	241.85	254.76	68.2	A	241.85	.	68.2	1.00000	.	1
57	31	1	1	1	1	248.65	299.77	21.4	A	248.65	.	21.4	1.00000	.	1
58	31	1	2	1	2	146.85	181.94	13.6	B	146.85	.	13.6	1.00000	.	1
59	32	1	1	1	1	260.85	294.26	23.7	A	260.85	.	23.7	1.00000	.	1
60	32	1	2	1	2	317.40	377.51	24.3	B	317.40	433.30	24.3	1.00000	1.14777	1
61	33	2	1	1	2	315.10	337.27	57.2	B	315.10	.	57.2	1.00000	.	1
62	33	2	2	1	1	441.10	459.87	81.3	A	441.10	.	81.3	1.00000	.	1
63	34	1	1	1	1	283.30	311.56	24.0	A	283.30	.	24.0	1.00000	.	1
64	34	1	2	1	2	144.50	186.22	24.4	B	144.50	.	24.4	1.00000	.	1
65	37	2	1	1	2	2006.15	2022.20	153.3	B	2006.15	2044.02	153.3	1.00000	1.01079	1
66	37	2	2	1	1	2146.00	3082.11	223.0	A	2146.00	2349.38	223.0	1.00000	0.76226	1
67	38	2	1	1	2	621.50	686.29	68.4	B	621.50	.	68.4	1.00000	.	1
68	38	2	2	1	1	572.70	1051.12	68.7	A	572.70	648.87	68.7	1.00000	0.61732	1
69	39	1	1	1	1	335.20	386.86	56.3	A	335.20	.	56.3	1.00000	.	1
70	39	1	2	1	2	122.30	151.98	26.5	B	122.30	165.10	26.5	1.00000	1.08633	1
71	40	1	1	1	1	139.85	141.70	29.3	A	139.85	141.11	29.3	1.00000	0.99587	1
72	40	1	2	1	2	73.95	88.00	26.2	B	73.95	.	26.2	1.00000	.	1
73	41	2	1	1	2	142.60	185.36	45.9	B	142.60	.	45.9	1.00000	.	1
74	41	2	2	1	1	145.30	158.62	51.3	A	145.30	.	51.3	1.00000	.	1
75	42	2	1	1	2	415.85	695.40	79.8	B	415.85	.	79.8	1.00000	.	1
76	42	2	2	1	1	447.00	490.77	64.8	A	447.00	522.82	64.8	1.00000	1.06532	1

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
77	43	1	1	1	1	301.80	332.37	38.2	A	301.83	.	38.2	1.00008	.	1
78	43	1	2	1	2	265.80	289.54	82.4	B	265.59	.	82.4	0.99921	.	1
79	44	1	1	1	1	445.55	469.83	47.0	A	445.55	.	47.0	1.00000	.	1
80	44	1	2	1	2	264.80	281.38	47.2	B	264.86	.	47.2	1.00023	.	1
81	45	1	1	1	1	304.80	306.14	22.6	A	304.80	305.75	22.6	1.00000	0.99873	1
82	45	1	2	1	2	304.00	314.43	46.9	B	303.89	307.22	46.9	0.99962	0.97708	1
83	46	2	1	1	2	354.10	415.50	62.1	B	354.10	.	62.1	1.00000	.	1
84	46	2	2	1	1	368.85	370.12	66.4	A	368.85	.	66.4	1.00000	.	1
85	47	1	1	1	1	464.35	548.25	93.6	A	464.35	.	93.6	1.00000	.	1
86	47	1	2	1	2	533.80	557.15	103.0	B	534.30	.	103.0	1.00093	.	1
87	48	2	1	1	2	160.55	171.81	61.8	B	160.55	.	61.8	1.00000	.	1
88	48	2	2	1	1	178.40	370.55	61.5	A	178.40	.	61.5	1.00000	.	1
89	49	1	1	1	1	196.50	202.37	46.9	A	196.45	202.08	46.9	0.99974	0.99858	1
90	49	1	2	1	2	213.45	248.80	39.3	B	213.45	.	39.3	1.00000	.	1
91	50	1	1	1	1	295.20	382.83	16.3	A	295.20	.	16.3	1.00000	.	1
92	50	1	2	1	2	224.10	257.78	16.9	B	224.00	.	16.9	0.99957	.	1
93	51	2	1	1	2	219.95	236.73	20.9	B	219.95	.	20.9	0.99998	.	1
94	51	2	2	1	1	259.70	273.82	47.5	A	259.44	317.73	47.5	0.99899	1.16038	1
95	52	2	1	1	2	414.70	462.09	26.5	B	414.70	.	26.5	1.00000	.	1
96	52	2	2	1	1	525.30	575.03	53.1	A	526.49	.	53.1	1.00226	.	1
97	53	2	1	1	2	355.00	363.08	53.7	B	354.92	.	53.7	0.99977	.	1
98	53	2	2	1	1	543.65	628.06	90.3	A	543.65	.	90.3	1.00000	.	1
99	54	1	1	1	1	549.20	580.54	41.1	A	549.20	747.27	41.1	1.00000	1.28721	1
100	54	1	2	1	2	404.75	447.88	41.8	B	404.75	.	41.8	1.00000	.	1
101	55	2	1	1	2	186.70	193.87	30.8	B	186.65	.	30.8	0.99973	.	1
102	55	2	2	1	1	7.80	25.18	5.2	A	7.80	.	5.2	1.00000	.	1
103	56	1	1	1	1	352.20	361.09	42.4	A	352.20	.	42.4	1.00000	.	1
104	56	1	2	1	2	465.70	489.23	33.3	B	465.70	493.23	33.3	1.00000	1.00818	1
105	57	1	1	1	1	72.60	85.27	32.2	A	72.60	.	32.2	1.00000	.	1
106	57	1	2	1	2	87.65	89.57	20.0	B	87.70	.	20.0	1.00057	.	1
107	58	1	1	1	1	112.90	127.05	27.0	A	112.75	.	27.0	0.99865	.	1
108	58	1	2	1	2	93.10	106.13	31.9	B	93.10	.	31.9	1.00000	.	1
109	59	2	1	1	2	338.45	351.41	78.6	B	338.45	374.05	78.6	1.00000	1.06441	1
110	59	2	2	1	1	256.85	293.44	59.0	A	256.85	.	59.0	1.00000	.	1
111	60	2	1	1	2	105.20	119.82	15.6	B	105.20	.	15.6	1.00000	.	1
112	60	2	2	1	1	138.75	140.38	19.5	A	138.75	.	19.5	1.00000	.	1
113	61	1	1	1	1	588.95	602.85	52.4	A	588.95	675.84	52.4	1.00000	1.12109	1
114	61	1	2	1	2	483.80	505.08	32.5	B	483.80	549.30	32.5	1.00000	1.08755	1

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
115	62	2	1	1	2	818.90	860.06	122.1	B	818.90	1002.92	122.1	1.00000	1.16610	1
116	62	2	2	1	1	1758.20	1796.38	218.8	A	1758.20	2548.36	218.8	1.00000	1.41861	1
117	63	2	1	1	2	126.05	129.75	21.8	B	126.05	129.51	21.8	1.00000	0.99810	1
118	63	2	2	1	1	124.35	133.44	10.1	A	124.35	.	10.1	1.00000	.	1
119	64	1	1	1	1	529.90	546.43	90.0	A	529.90	544.98	90.0	1.00000	0.99735	1
120	64	1	2	1	2	672.60	683.21	90.2	B	672.60	686.16	90.2	1.00000	1.00432	1
121	65	1	1	1	1	230.85	236.09	40.5	A	230.85	309.46	40.5	1.00000	1.31081	1
122	65	1	2	1	2	172.90	178.02	48.1	B	172.26	211.41	48.1	0.99627	1.18752	1
123	66	2	1	1	2	390.80	435.75	25.3	B	390.80	.	25.3	1.00000	.	1
124	66	2	2	1	1	324.10	324.68	34.4	A	324.10	.	34.4	1.00000	.	1
125	67	2	1	1	2	254.55	257.19	16.4	B	254.55	.	16.4	1.00000	.	1
126	67	2	2	1	1	415.95	435.88	21.3	A	415.95	435.68	21.3	1.00000	0.99952	1
127	68	1	1	1	1	348.80	366.67	69.7	A	348.80	.	69.7	1.00000	.	1
128	68	1	2	1	2	141.90	301.04	26.1	B	141.90	.	26.1	1.00000	.	1
129	69	2	1	1	2	281.50	306.02	48.1	B	281.50	.	48.1	1.00000	.	1
130	69	2	2	1	1	211.25	362.20	25.8	A	211.25	.	25.8	1.00000	.	1
131	70	2	1	1	2	479.90	481.62	48.9	B	479.90	.	48.9	1.00000	.	1
132	70	2	2	1	1	258.95	279.64	30.5	A	258.95	.	30.5	1.00000	.	1
133	71	1	1	1	1	464.55	519.60	72.2	A	464.55	546.08	72.2	1.00000	1.05096	1
134	71	1	2	1	2	632.00	705.12	77.7	B	632.00	.	77.7	1.00000	.	1
135	72	1	1	1	1	304.20	334.76	64.3	A	304.20	.	64.3	1.00000	.	1
136	72	1	2	1	2	394.35	424.76	65.4	B	394.35	.	65.4	1.00000	.	1
137	73	1	1	1	1	303.00	321.95	18.0	A	302.94	.	18.0	0.99981	.	1
138	73	1	2	1	2	335.45	367.10	27.4	B	335.45	400.45	27.4	1.00000	1.09084	1
139	74	2	1	1	2	108.10	118.56	49.1	B	108.10	.	49.1	1.00000	.	1
140	74	2	2	1	1	33.85	50.29	27.5	A	33.85	.	27.5	1.00000	.	1
141	75	1	1	1	1	457.95	501.20	47.8	A	457.95	.	47.8	1.00000	.	1
142	75	1	2	1	2	342.45	385.74	53.0	B	342.41	.	53.0	0.99987	.	1
143	77	1	1	1	1	450.65	481.80	42.3	A	450.65	.	42.3	1.00000	.	1
144	77	1	2	1	2	251.50	265.29	28.1	B	250.78	.	28.1	0.99714	.	1
145	78	2	1	1	2	305.15	323.16	43.3	B	305.15	.	43.3	1.00000	.	1
146	78	2	2	1	1	537.45	555.23	76.6	A	537.45	578.26	76.6	1.00000	1.04147	1
147	79	1	1	1	1	656.85	699.25	51.0	A	657.13	752.57	51.0	1.00043	1.07626	1
148	79	1	2	1	2	582.05	664.36	59.3	B	582.05	.	59.3	1.00000	.	1
149	80	2	1	1	2	301.65	338.38	47.0	B	301.65	.	47.0	1.00000	.	1
150	80	2	2	1	1	342.70	357.12	50.9	A	342.70	450.06	50.9	1.00000	1.26025	1
151	81	1	1	1	1	299.05	314.94	39.6	A	299.05	.	39.6	1.00000	.	1
152	81	1	2	1	2	421.20	424.51	51.5	B	421.20	423.76	51.5	1.00000	0.99825	1

Reference ID: 3227106

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
153	82	2	1	1	2	208.65	235.44	76.8	B	208.65	.	76.8	1.00000	.	1
154	82	2	2	1	1	508.25	550.39	62.1	A	508.21	.	62.1	0.99993	.	1
155	83	2	1	1	2	147.10	197.46	24.9	B	147.10	.	24.9	1.00000	.	1
156	83	2	2	1	1	444.30	465.79	66.2	A	444.30	466.91	66.2	1.00000	1.00241	1
157	84	1	1	1	1	532.25	577.65	61.8	A	532.25	.	61.8	1.00000	.	1
158	84	1	2	1	2	483.45	539.01	51.7	B	483.45	.	51.7	1.00001	.	1
159	86	1	1	1	1	933.20	1003.95	78.7	A	933.20	1074.39	78.7	1.00000	1.07016	1
160	86	1	2	1	2	654.10	666.41	89.5	B	654.01	663.02	89.5	0.99986	0.99491	1

4.8.4 Fed Study Output

FED STATISTICAL OUTPUT- FREE EPA (BASELINE-NON-ADJUSTED)

The GLM Procedure

Class Level Information		
Class	**Levels**	**Values**
sub	80	1 2 3 4 5 6 7 8 9 10 11 12 13 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 77 78 79 80 81 82 83 84 86
trt	2	1 2
per	2	1 2
seq	2	1 2

Number of Observations Read	160
Number of Observations Used	160

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	81	10.22416248	0.12622423	6.57	<.0001
Error	78	1.49780070	0.01920257		
Corrected Total	159	11.72196318			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.872223	1.534502	0.138573	9.030512

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.00953652	0.00953652	0.50	0.4831
sub(seq)	78	10.05459187	0.12890502	6.71	<.0001
per	1	0.13129847	0.13129847	6.84	0.0107
trt	1	0.02873563	0.02873563	1.50	0.2249

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00953652	0.00953652	0.50	0.4831
sub(seq)	78	10.05459187	0.12890502	6.71	<.0001
per	1	0.12816411	0.12816411	6.67	0.0116

Reference ID: 3227106

Source	DF	Type III SS	Mean Square	F Value	Pr > F
trt	1	0.02873563	0.02873563	1.50	0.2249

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00953652	0.00953652	0.07	0.7863

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.02681119	0.02191722	-1.22	0.2249

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	81	10.82152092	0.13359902	4.90	<.0001
Error	78	2.12850817	0.02728857		
Corrected Total	159	12.95002910			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.835637	1.799667	0.165193	9.179060

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.00260610	0.00260610	0.10	0.7581
sub(seq)	78	10.54153331	0.13514786	4.95	<.0001
per	1	0.16399479	0.16399479	6.01	0.0165
trt	1	0.11338672	0.11338672	4.16	0.0449

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00260610	0.00260610	0.10	0.7581
sub(seq)	78	10.54153331	0.13514786	4.95	<.0001
per	1	0.15714714	0.15714714	5.76	0.0188
trt	1	0.11338672	0.11338672	4.16	0.0449

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00260610	0.00260610	0.02	0.8899

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.05325825	0.02612740	-2.04	0.0449

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	81	21.27649873	0.26267282	2.78	<.0001
Error	78	7.38056701	0.09462265		
Corrected Total	159	28.65706574			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.742452	4.524868	0.307608	6.798164

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.02198414	0.02198414	0.23	0.6311
sub(seq)	78	20.79267577	0.26657277	2.82	<.0001
per	1	0.21075735	0.21075735	2.23	0.1396
trt	1	0.25108148	0.25108148	2.65	0.1074

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.02198414	0.02198414	0.23	0.6311
sub(seq)	78	20.79267577	0.26657277	2.82	<.0001
per	1	0.22228083	0.22228083	2.35	0.1294
trt	1	0.25108148	0.25108148	2.65	0.1074

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.02198414	0.02198414	0.08	0.7747

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.07925252	0.04865229	-1.63	0.1074

FED STATISTICAL OUTPUT- FREE EPA (BASELINE-ADJUSTED)

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	80	1 2 3 4 5 6 7 8 9 10 11 12 13 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 77 78 79 80 81 82 83 84 86
trt	2	1 2
per	2	1 2
seq	2	1 2

Number of Observations Read	160
Number of Observations Used	160

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	81	13.08260198	0.16151360	4.31	<.0001
Error	78	2.92585863	0.03751101		
Corrected Total	159	16.00846061			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.817230	11.64468	0.193678	1.663229

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.01302780	0.01302780	0.35	0.5573
sub(seq)	78	12.95817169	0.16613041	4.43	<.0001
per	1	0.00487684	0.00487684	0.13	0.7194
trt	1	0.10652565	0.10652565	2.84	0.0959

Source	DF	Type III SS	Mean Square	F Value	Pr > F

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.01302780	0.01302780	0.35	0.5573
sub(seq)	78	12.95817169	0.16613041	4.43	<.0001
per	1	0.00607966	0.00607966	0.16	0.6884
trt	1	0.10652565	0.10652565	2.84	0.0959

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.01302780	0.01302780	0.08	0.7802

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.05162177	0.03063269	-1.69	0.0959

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	81	47.86138166	0.59088126	1.16	0.2560
Error	78	39.74701929	0.50957717		
Corrected Total	159	87.60840095			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.546310	34.88576	0.713847	2.046241

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.41335938	0.41335938	0.81	0.3705
sub(seq)	78	45.78963342	0.58704658	1.15	0.2667
per	1	0.38011577	0.38011577	0.75	0.3904
trt	1	1.27827309	1.27827309	2.51	0.1173

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.41335938	0.41335938	0.81	0.3705
sub(seq)	78	45.78963342	0.58704658	1.15	0.2667
per	1	0.41551920	0.41551920	0.82	0.3693
trt	1	1.27827309	1.27827309	2.51	0.1173

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.41335938	0.41335938	0.70	0.4040

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.17882062	0.11290437	-1.58	0.1173

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	81	24.15326513	0.29818846	2.73	<.0001
Error	78	8.52490580	0.10929366		
Corrected Total	159	32.67817093			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.739125	-188.2895	0.330596	-0.175579

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.01334449	0.01334449	0.12	0.7277
sub(seq)	78	23.65578035	0.30327924	2.77	<.0001
per	1	0.22570442	0.22570442	2.07	0.1547
trt	1	0.25843586	0.25843586	2.36	0.1282

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.01334449	0.01334449	0.12	0.7277
sub(seq)	78	23.65578035	0.30327924	2.77	<.0001
per	1	0.23779692	0.23779692	2.18	0.1442
trt	1	0.25843586	0.25843586	2.36	0.1282

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.01334449	0.01334449	0.04	0.8344

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.08040483	0.05228815	-1.54	0.1282

FED STATISTICAL OUTPUT- TOTAL EPA (BASELINE –NON-ADJUSTED)

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	80	1 2 3 4 5 6 7 8 9 10 11 12 13 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 77 78 79 80 81 82 83 84 86
trt	2	1 2
per	2	1 2
seq	2	1 2

Number of Observations Read	160
Number of Observations Used	160

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	81	13.52585532	0.16698587	10.16	<.0001
Error	78	1.28193032	0.01643500		
Corrected Total	159	14.80778564			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.913429	1.726546	0.128199	7.425177

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.09890640	0.09890640	6.02	0.0164
sub(seq)	78	12.45769413	0.15971403	9.72	<.0001
per	1	0.96632884	0.96632884	58.80	<.0001
trt	1	0.00292595	0.00292595	0.18	0.6742

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.09890640	0.09890640	6.02	0.0164
sub(seq)	78	12.45769413	0.15971403	9.72	<.0001
per	1	0.96838456	0.96838456	58.92	<.0001
trt	1	0.00292595	0.00292595	0.18	0.6742

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.09890640	0.09890640	0.62	0.4337

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	0.00855538	0.02027639	0.42	0.6742

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	81	48.87229072	0.60336161	2.92	<.0001
Error	78	16.14279308	0.20695889		
Corrected Total	159	65.01508380			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.751707	5.412009	0.454927	8.405887

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.59152575	0.59152575	2.86	0.0949
sub(seq)	78	48.25918790	0.61870754	2.99	<.0001
per	1	0.01674684	0.01674684	0.08	0.7768
trt	1	0.00483024	0.00483024	0.02	0.8790

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.59152575	0.59152575	2.86	0.0949
sub(seq)	78	48.25918790	0.61870754	2.99	<.0001
per	1	0.01718894	0.01718894	0.08	0.7740
trt	1	0.00483024	0.00483024	0.02	0.8790

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.59152575	0.59152575	0.96	0.3312

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	0.01099233	0.07195282	0.15	0.8790

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	81	20.74331043	0.25609025	7.32	<.0001
Error	78	2.72911641	0.03498867		
Corrected Total	159	23.47242684			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.883731	4.187324	0.187053	4.467115

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.43493858	0.43493858	12.43	0.0007
sub(seq)	78	19.46211000	0.24951423	7.13	<.0001
per	1	0.82209072	0.82209072	23.50	<.0001
trt	1	0.02417114	0.02417114	0.69	0.4084

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.43493858	0.43493858	12.43	0.0007
sub(seq)	78	19.46211000	0.24951423	7.13	<.0001
per	1	0.81454602	0.81454602	23.28	<.0001
trt	1	0.02417114	0.02417114	0.69	0.4084

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.43493858	0.43493858	1.74	0.1906

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.02458976	0.02958486	-0.83	0.4084

FED STATISTICAL OUTPUT- TOTAL EPA (BASELINE-ADJUSTED)

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	80	1 2 3 4 5 6 7 8 9 10 11 12 13 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 77 78 79 80 81 82 83 84 86
trt	2	1 2
per	2	1 2
seq	2	1 2

Number of Observations Read	160
Number of Observations Used	160

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	81	12.72015405	0.15703894	4.92	<.0001
Error	78	2.49060084	0.03193078		
Corrected Total	159	15.21075489			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.836261	2.604906	0.178692	6.859820

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.09045449	0.09045449	2.83	0.0964
sub(seq)	78	12.60507475	0.16160352	5.06	<.0001
per	1	0.01852344	0.01852344	0.58	0.4486
trt	1	0.00610137	0.00610137	0.19	0.6632

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.09045449	0.09045449	2.83	0.0964
sub(seq)	78	12.60507475	0.16160352	5.06	<.0001
per	1	0.01798429	0.01798429	0.56	0.4552
trt	1	0.00610137	0.00610137	0.19	0.6632

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.09045449	0.09045449	0.56	0.4566

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.01235434	0.02826250	-0.44	0.6632

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	81	18.25303404	0.22534610	2.70	<.0001
Error	78	6.52174204	0.08361208		
Corrected Total	159	24.77477608			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.736759	3.883143	0.289158	7.446482

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.10643580	0.10643580	1.27	0.2627
sub(seq)	78	17.78502886	0.22801319	2.73	<.0001
per	1	0.34575039	0.34575039	4.14	0.0454
trt	1	0.01581899	0.01581899	0.19	0.6648

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.10643580	0.10643580	1.27	0.2627
sub(seq)	78	17.78502886	0.22801319	2.73	<.0001
per	1	0.34184756	0.34184756	4.09	0.0466
trt	1	0.01581899	0.01581899	0.19	0.6648

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.10643580	0.10643580	0.47	0.4965

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	0.01989277	0.04573411	0.43	0.6648

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	81	24.05572381	0.29698424	5.37	<.0001
Error	78	4.31047137	0.05526245		
Corrected Total	159	28.36619518			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.848042	5.462792	0.235080	4.303288

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.49593909	0.49593909	8.97	0.0037
sub(seq)	78	23.02647519	0.29521122	5.34	<.0001
per	1	0.47783245	0.47783245	8.65	0.0043
trt	1	0.05547707	0.05547707	1.00	0.3195

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.49593909	0.49593909	8.97	0.0037
sub(seq)	78	23.02647519	0.29521122	5.34	<.0001
per	1	0.46943027	0.46943027	8.49	0.0046
trt	1	0.05547707	0.05547707	1.00	0.3195

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.49593909	0.49593909	1.68	0.1988

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.03725311	0.03718098	-1.00	0.3195

FED STATISTICAL OUTPUT- FREE DHA (BASELINE-NON-ADJUSTED)

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	80	1 2 3 4 5 6 7 8 9 10 11 12 13 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 77 78 79 80 81 82 83 84 86
trt	2	1 2
per	2	1 2
seq	2	1 2

Number of Observations Read	160
Number of Observations Used	160

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	81	9.89946120	0.12221557	9.38	<.0001
Error	78	1.01662585	0.01303366		
Corrected Total	159	10.91608705			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.906869	1.093882	0.114165	10.43669

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.03916510	0.03916510	3.00	0.0870
sub(seq)	78	9.85730418	0.12637569	9.70	<.0001
per	1	0.00262523	0.00262523	0.20	0.6548
trt	1	0.00036669	0.00036669	0.03	0.8672

Reference ID: 3227106

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.03916510	0.03916510	3.00	0.0870
sub(seq)	78	9.85730418	0.12637569	9.70	<.0001
per	1	0.00257478	0.00257478	0.20	0.6579
trt	1	0.00036669	0.00036669	0.03	0.8672

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.03916510	0.03916510	0.31	0.5793

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.00302870	0.01805673	-0.17	0.8672

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	81	24.24971530	0.29937920	1.61	0.0182
Error	78	14.53436085	0.18633796		
Corrected Total	159	38.78407615			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.625249	4.062605	0.431669	10.62542

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.45644611	0.45644611	2.45	0.1216
sub(seq)	78	23.66628988	0.30341397	1.63	0.0164
per	1	0.00415191	0.00415191	0.02	0.8817
trt	1	0.12282740	0.12282740	0.66	0.4193

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.45644611	0.45644611	2.45	0.1216
sub(seq)	78	23.66628988	0.30341397	1.63	0.0164
per	1	0.00535485	0.00535485	0.03	0.8658
trt	1	0.12282740	0.12282740	0.66	0.4193

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.45644611	0.45644611	1.50	0.2237

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.05543109	0.06827417	-0.81	0.4193

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	81	16.33997774	0.20172812	2.52	<.0001
Error	78	6.24799607	0.08010251		
Corrected Total	159	22.58797380			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.723393	3.551308	0.283024	7.969567

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.00110901	0.00110901	0.01	0.9066
sub(seq)	78	15.86463942	0.20339281	2.54	<.0001
per	1	0.34171393	0.34171393	4.27	0.0422
trt	1	0.13251538	0.13251538	1.65	0.2022

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00110901	0.00110901	0.01	0.9066
sub(seq)	78	15.86463942	0.20339281	2.54	<.0001
per	1	0.35221968	0.35221968	4.40	0.0392
trt	1	0.13251538	0.13251538	1.65	0.2022

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00110901	0.00110901	0.01	0.9413

Reference ID: 3227106

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.05757566	0.04476399	-1.29	0.2022

FED STATISTICAL OUTPUT- FREE DHA (BASELINE- ADJUSTED)

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	80	1 2 3 4 5 6 7 8 9 10 11 12 13 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 77 78 79 80 81 82 83 84 86
trt	2	1 2
per	2	1 2
seq	2	1 2

Data for Analysis of AUCT CMAX LAUCT LCMAX	
Number of Observations Read	160
Number of Observations Used	160

Data for Analysis of AUCI LAUCI	
Number of Observations Read	160
Number of Observations Used	147

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	81	17.63664693	0.21773638	2.95	<.0001
Error	78	5.75374572	0.07376597		
Corrected Total	159	23.39039265			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.754012	10.74441	0.271599	2.527815

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.01045205	0.01045205	0.14	0.7076

Source	DF	Type I SS	Mean Square	F Value	Pr > F
sub(seq)	78	17.58580769	0.22545907	3.06	<.0001
per	1	0.01415501	0.01415501	0.19	0.6626
trt	1	0.02623218	0.02623218	0.36	0.5527

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.01045205	0.01045205	0.14	0.7076
sub(seq)	78	17.58580769	0.22545907	3.06	<.0001
per	1	0.01512574	0.01512574	0.21	0.6519
trt	1	0.02623218	0.02623218	0.36	0.5527

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.01045205	0.01045205	0.05	0.8301

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.02561669	0.04295699	-0.60	0.5527

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	81	14.31993170	0.17678928	1.17	0.2516
Error	65	9.78444622	0.15052994		
Corrected Total	146	24.10437792			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.594080	14.29979	0.387982	2.713200

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.08684597	0.08684597	0.58	0.4503
sub(seq)	78	14.11145374	0.18091607	1.20	0.2232
per	1	0.04672285	0.04672285	0.31	0.5794
trt	1	0.07490913	0.07490913	0.50	0.4831

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.09496029	0.09496029	0.63	0.4299
sub(seq)	78	14.04879803	0.18011280	1.20	0.2287
per	1	0.04496334	0.04496334	0.30	0.5866
trt	1	0.07490913	0.07490913	0.50	0.4831

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.09496029	0.09496029	0.53	0.4699

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.04729262	0.06704053	-0.71	0.4831

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	81	24.68325420	0.30473153	2.24	0.0002
Error	78	10.62666512	0.13623930		
Corrected Total	159	35.30991933			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.699046	41.42473	0.369106	0.891028

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.01930275	0.01930275	0.14	0.7076
sub(seq)	78	24.14480645	0.30954880	2.27	0.0002
per	1	0.36438936	0.36438936	2.67	0.1060
trt	1	0.15475564	0.15475564	1.14	0.2898

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.01930275	0.01930275	0.14	0.7076
sub(seq)	78	24.14480645	0.30954880	2.27	0.0002
per	1	0.37612805	0.37612805	2.76	0.1006
trt	1	0.15475564	0.15475564	1.14	0.2898

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.01930275	0.01930275	0.06	0.8035

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.06221986	0.05837904	-1.07	0.2898

FED STATISTICAL OUTPUT- TOTAL DHA (BASELINE- NON-ADJUSTED)

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	80	1 2 3 4 5 6 7 8 9 10 11 12 13 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 77 78 79 80 81 82 83 84 86
trt	2	1 2
per	2	1 2
seq	2	1 2

Number of Observations Read	160
Number of Observations Used	160

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	81	14.36598675	0.17735786	23.66	<.0001
Error	78	0.58466211	0.00749567		
Corrected Total	159	14.95064885			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.960894	1.066167	0.086578	8.120443

Reference ID: 3227106

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.33923251	0.33923251	45.26	<.0001
sub(seq)	78	13.35834166	0.17126079	22.85	<.0001
per	1	0.65916956	0.65916956	87.94	<.0001
trt	1	0.00924303	0.00924303	1.23	0.2702

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.33923251	0.33923251	45.26	<.0001
sub(seq)	78	13.35834166	0.17126079	22.85	<.0001
per	1	0.66266493	0.66266493	88.41	<.0001
trt	1	0.00924303	0.00924303	1.23	0.2702

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.33923251	0.33923251	1.98	0.1633

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	0.01520593	0.01369339	1.11	0.2702

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	81	112.3304854	1.3867961	1.24	0.1665
Error	78	86.9360633	1.1145649		
Corrected Total	159	199.2665487			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.563720	10.86744	1.055730	9.714610

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	1.6710073	1.6710073	1.50	0.2245
sub(seq)	78	100.9749032	1.2945500	1.16	0.2551
per	1	6.1132461	6.1132461	5.48	0.0217
trt	1	3.5713287	3.5713287	3.20	0.0773

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	1.6710073	1.6710073	1.50	0.2245
sub(seq)	78	100.9749032	1.2945500	1.16	0.2551
per	1	6.3452102	6.3452102	5.69	0.0195
trt	1	3.5713287	3.5713287	3.20	0.0773

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	1.67100735	1.67100735	1.29	0.2594

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	0.29889639	0.16697769	1.79	0.0773

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	81	17.24808100	0.21293927	11.36	<.0001
Error	78	1.46263214	0.01875169		
Corrected Total	159	18.71071314			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.921829	2.966995	0.136937	4.615337

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.35485719	0.35485719	18.92	<.0001
sub(seq)	78	16.34416483	0.20954057	11.17	<.0001
per	1	0.53579580	0.53579580	28.57	<.0001
trt	1	0.01326318	0.01326318	0.71	0.4029

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.35485719	0.35485719	18.92	<.0001
sub(seq)	78	16.34416483	0.20954057	11.17	<.0001
per	1	0.53968286	0.53968286	28.78	<.0001
trt	1	0.01326318	0.01326318	0.71	0.4029

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.35485719	0.35485719	1.69	0.1970

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	0.01821502	0.02165838	0.84	0.4029

FED STATISTICAL OUTPUT- TOTAL DHA (BASELINE -ADJUSTED)

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	80	1 2 3 4 5 6 7 8 9 10 11 12 13 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 77 78 79 80 81 82 83 84 86
trt	2	1 2
per	2	1 2
seq	2	1 2

Data for Analysis of AUCT CMAX LAUCT LCMAX	
Number of Observations Read	160
Number of Observations Used	160

Data for Analysis of AUCI LAUCI	
Number of Observations Read	160
Number of Observations Used	152

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	81	89.8135780	1.1088096	5.48	<.0001
Error	78	15.7751757	0.2022458		
Corrected Total	159	105.5887537			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.850598	7.929405	0.449718	5.671516

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.00142310	0.00142310	0.01	0.9334
sub(seq)	78	89.80686727	1.15137009	5.69	<.0001
per	1	0.00525779	0.00525779	0.03	0.8723
trt	1	0.00002979	0.00002979	0.00	0.9903

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00142310	0.00142310	0.01	0.9334
sub(seq)	78	89.80686727	1.15137009	5.69	<.0001
per	1	0.00523474	0.00523474	0.03	0.8726
trt	1	0.00002979	0.00002979	0.00	0.9903

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00142310	0.00142310	0.00	0.9720

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	0.00086330	0.07112881	0.01	0.9903

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	80	55.03615103	0.68795189	4.64	<.0001
Error	71	10.51987910	0.14816731		
Corrected Total	151	65.55603013			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.839528	6.456497	0.384925	5.961825

Source	DF	Type I SS	Mean Square	F Value	Pr > F

Reference ID: 3227106

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.18797433	0.18797433	1.27	0.2638
sub(seq)	77	54.63849573	0.70959085	4.79	<.0001
per	1	0.15206110	0.15206110	1.03	0.3145
trt	1	0.05761988	0.05761988	0.39	0.5349

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.19173260	0.19173260	1.29	0.2591
sub(seq)	77	54.00531367	0.70136771	4.73	<.0001
per	1	0.16441042	0.16441042	1.11	0.2957
trt	1	0.05761988	0.05761988	0.39	0.5349

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.19173260	0.19173260	0.27	0.6026

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	0.03982546	0.06386323	0.62	0.5349

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	81	58.30365199	0.71979817	6.31	<.0001
Error	78	8.89482020	0.11403616		
Corrected Total	159	67.19847219			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.867634	8.901312	0.337692	3.793737

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.17180952	0.17180952	1.51	0.2233
sub(seq)	78	57.89895117	0.74229425	6.51	<.0001
per	1	0.22012547	0.22012547	1.93	0.1687
trt	1	0.01276583	0.01276583	0.11	0.7388

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.17180952	0.17180952	1.51	0.2233
sub(seq)	78	57.89895117	0.74229425	6.51	<.0001
per	1	0.21734619	0.21734619	1.91	0.1714
trt	1	0.01276583	0.01276583	0.11	0.7388

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.17180952	0.17180952	0.23	0.6318

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.01787024	0.05341055	-0.33	0.7388

Following this page, 6 Pages Withheld in Full as (b)(4)

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 091028

APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Omega-3-Acid Ethyl Esters Capsules, 1 g

The Division of Bioequivalence I (DBI) has completed its review of your submission acknowledged on the cover sheet and the following deficiencies have been identified:

Deficiencies Related to Bioequivalence (BE) Studies

1. The DBI has reviewed the test formulation using the criteria on active pharmaceutical ingredient and antioxidant as stated in the draft Individual Product BE Guidance for Omega-3-Acid Ethyl Esters Capsules, posted on September, 2012, (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM320011.pdf), and considers that your test product meets the criteria. The test and reference products are similar and the bioequivalence (BE) may be established based solely on an *in vitro* method (Quantitative Capsule Rupture Test, also described in the draft guidance).

2. However, per the draft Guidance aforementioned, if you wish to choose *In Vivo* BE Study Option for your application, please conduct both new fasting and fed BE studies for Omega-3-Acid Ethyl Esters Capsules, 1 g.

   According to that current BE Guidance for Omega-3-Acid Ethyl Esters Capsules posted on September 2012, the 90% confidence intervals (CIs) for the BE fed study are based on**:** (1) Eicosapentaenoic Acid (EPA) ethyl esters and (2) Docosahexaenoic Acid (DHA) ethyl esters. In addition, a fasting BE study is recommended and its 90% CIs for BE are based on: (1) baseline-adjusted EPA total lipids and (2) baseline-adjusted DHA total lipids.

3. Based on your pre-study validation data in your currently submitted fed study (Study No. 2008-1829), the percent of average recovery for the free eicosapentaenoic acid (EPA) (e.g. QC A, B and C: 131.9 % to 140.0 %) and docosahexaenoic acid (DHA) (e.g. QC A, B and C: 130.2 % to 135.8 %) and that of Internal Standard [IS (b) (4) 124.1%] are very high. Please provide your explanation(s) about such high values of average recovery of the above mentioned analytes and the internal standard.

For your future submissions, please be advised of the following:

4. Please submit complete (100%) raw numerical data of **all** assay and reassay runs for **all subjects**, including the data of peak area/height for the drug, peak area/height for

the internal standard, ratio of the peak area/height for the drug to the peak area/height for the internal standard, dilution factor (if any), and the corresponding concentration for each assayed and reassayed sample of all subject samples, calibration standard concentration samples, and quality control samples for each of your BE study. For your pilot study (Study No. 2008-1779) and fed study (Study No. 2008-1829) currently submitted, you only submitted the raw numerical data of **approximately 50% and 22.5%** of the subjects, respectively.

5. Regarding Compliance with Section 508 of the Rehabilitation Act of 1973: The images included in your submission do not contain alternate text and are therefore unsearchable and not in compliance with Section 508 of the Rehabilitation Act of 1973, which requires that Federal agencies' electronic and information technology is accessible to people with disabilities. Please ensure that future submissions are in compliance with Section 508 and contain images with alternate text so that the images are searchable. Instructions for adding alternate text should be provided in the software used to construct/view the PDF file. Please refer to the website http://www.section508.gov for further information.

Deficiencies Related to *In Vitro* Drug Release Testing

6. The quantitative capsule rupture (QCR) testing conducted using your proposed method, in 900 mL of 10% Labrasol in 0.1N HCl using USP Apparatus 2 (Paddle) with (b) (4) rpm at 37°C ± 0.5°C, is not sufficiently discriminatory, based on the release profile submitted for your test product, Omega-3-Acid Ethyl Esters Capsules, 1 g, comparing it with the reference product, GlaxoSmithKline's Lovaza® Capsules, 1 g.

   Based on the QCR data submitted by you for your test product, the DBI suggests you modify your proposed method by using (b) (4) paddle speeds such as 50 rpm, 75 rpm and 100 rpm, and/or lower Labrasol concentration, as follows:

Medium:	Labrasol in 0.1N HCl at 1%, 2%, 5%, 8%, 10% etc.
Apparatus:	USP Apparatus 2 (Paddle)
Speed:	**50**, **75** and **100** rpm
Volume:	900 mL
Temperature:	37°C ± 0.5°C
Sampling times:	5, 10, 15, 30, 45, and 60 minutes until at least 80% of the drug is released from the dosage form.

   Please be advised that for USP Apparatus 2, when used for this dosage form, the sampling probes should remain immersed in the dissolution medium throughout the duration of testing in order to obtain reproducible results. The use of a sinker with USP Apparatus 2 may be considered in preventing the capsules from floating to the top.

   Alternatively, you may consider using different surfactants and/or the USP Apparatus 4 (flow-through cell) as suggested in the draft guidance.

7. The DBI will evaluate the method development and optimization data as well as the complete data of the test and reference products obtained for 12 units per product, based on the most appropriate procedure, and determine the most suitable QCR method and specification for your test product.

Deficiency Related to the Test Product Formulation

8. Please provide the quantitative amount of each component of your Soft Gelatin Capsule Shell and White Printing Ink [redacted] (b) (4) per capsule in your test formulation.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

4.10 Outcome Page

ANDA: 091028

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
18257	11/10/2008	Bioequivalence Study (REGULAR)	Fasting & Fed Study (Pilot)	1	1
18257	11/10/2008	Bioequivalence Study (REGULAR)	Fed Study (Pivotal)	1	1
18257	10/02/2009	Other (REGULAR)	Dissolution Amendment	1	1
				Bean Total:	3

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LI GONG
12/06/2012

APRIL C BRADDY
12/10/2012

HOAINHON N CARAMENICO
12/10/2012

DALE P CONNER
12/14/2012

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	91-028	
Drug Product Name	Omega-3-Acid Ethyl Esters Capsules	
Strength (s)	1 g	
Applicant Name	Teva Pharmaceuticals USA	
Address	1090 Horsham Road PO BOX 1090 North Wales, PA 19454	
Applicant's Point of Contact	Philip Erickson	
Contact's Phone Number	215-591-3141	
Contact's Fax Number	215-591-8812	
Submission Date(s)	November 10, 2008	
First Generic	Yes	
Reviewer	Ke Ren, Ph.D.	
Study Number (s)	2008-1779	2008-1829
Study Type (s)	Fasting and Fed study (RLD only)	Fed Study (Test and RLD)
Strength(s)	4 X 1 g	4 X 1 g
Clinical Site	Pharma Medica Research Inc.	
Clinical Site Address	4770 Sheppard Avenue East Toronto, Ontario, Canada M1S 3V6	
Analytical Site	(b) (4)	
Analytical Site Address		
OUTCOME DECISION	**INCOMPLETE**	

I. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

There is no USP method for this product, but the DBE recommends a quantitative capsule rupture test method for such dosage form. However, there is no specific DBE-recommended quantitative capsule rupture test method currently available in the public or internal dissolution database on the Office of Generic Drugs website (http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm).

The firm conducted its disintegration testing using the following: 500 mL of water using Apparatus II (paddle) at 50 rpm per USP <711>. The firm's proposed specification of "all capsules rupture in not more than (b) (4) for its disintegration test. The disintegration testing is not the current DBE-recommended method.

DBE recommends the firm to develop a **quantitative capsule rupture** test to evaluate the in-vitro performance of Omega-3-acid Ethyl Esters Capsules. The quantitative capsule rupture method should be discriminating to detect potential differences between the test and reference products. The firm should measure drug release of two key components of the drug product, Eicosapentaenoic acid (EPA) and Docosahecaenoic acid (DHA) as percentage of the labeled amounts. The firm may consider trying the following method:

Apparatus:	USP apparatus I (basket)
Speed:	100 rpm
Medium:	Water with a low concentration of surfactant
Volume:	900 mL
Sampling:	Once every 15 minutes until at least 80% of the labeled amount of Eicosapentaenoic acid (EPA) and Docosahecaenoic acid (DHA) is dispersed in the media

If necessary, the firm can try varying the media volume, increasing the rotational speed, increasing the concentration of surfactant, and/or using USP Apparatus II (paddles) instead of Apparatus I. If all capsules tested rupture in less than one hour, it may be necessary to sample more frequently to adequately characterize the capsule rupture rate and profile.

The Long Term Storage Stability (LTSS) for free eicosapentaenoic acid, free docosahexaenoic acid, eicosapentaenoic acid and docosahexaenoic acid are **under process**. The firm should submit LTSS for free eicosapentaenoic acid and free docosahexaenoic acid that are sufficient to cover the maximum storage time of the study samples for free eicosapentaenoic acid and free docosahexaenoic acid, which is at least 104 days. The firm should also submit LTSS for eicosapentaenoic acid and docosahexaenoic acid that are sufficient to cover the maximum storage time of the study samples for eicosapentaenoic acid and docosahexaenoic acid, which is at least 80 days.

The DBE requested Division of Scientific Investigations (DSI) inspection for clinical sit (new site). The analytical site was last inspected in (b) (4) and outcome was (b) (4) (b) (4)

The DBE will review the fasting and fed BE studies at a later date.

Table 1: SUBMISSION CONTENT CHECKLIST

Information			YES	NO	N/A
Did the firm use the FDA-recommended dissolution method			☐	☒	☐
Did the firm use the USP dissolution method			☐	☐	☒
Did the firm use 12 units of both test and reference in dissolution testing			☒	☐	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)			☒	☐	☐
Did the firm conduct dissolution testing with its own proposed method			☒	☐	☐
Is FDA method in the public dissolution database (on the web)			☐	☐	☒
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Fed BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Other study	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
Are the DBE Summary Tables present an in either PDF and/or MS Word Format?			☒	☐	☐
If any of the tables are missing or incomplete please indicate that in the comments and request the firm to provide the complete DBE Summary Tables 1-16.					
Is the Long Term Storage Stability (LTSS) sufficient to cover the maximum storage time of the study samples*?			☐	☒	☐
If the LTSS is NOT sufficient please request the firm to provide the necessary data.					

* The Long Term Storage Stability (LTSS) for free eicosapentaenoic acid, free docosahexaenoic acid, eicosapentaenoic acid and docosahexaenoic acid are **under process.**

Reviewer's Notes:

1. There is no USP method for Omega-3-acid ethyl esters capsules, but the DBE recommends a quantitative capsule rupture test method for such dosage form. However, there is no specific DBE- recommended quantitative capsule rupture test method currently available in the public dissolution database on the Office of Generic Drugs (OGD) websites: http://www. fda.gov/cder/ogd.index.htm, nor in the DBE internal dissolution database.

2. The DBE recommends that the firm should develop their own quantitative capsule rupture method[1]. This method should be discriminating to detect potential differences between the test and reference products. The firm should measure drug release of two key components of the drug product, Eicosapentaenoic acid (EPA) and Docosahecaenoic acid (DHA) as percentage of the labeled amounts. The firm may consider trying the following method:

Apparatus:	USP apparatus I (basket)
Speed:	100 rpm
Medium:	Water with a low concentration of surfactant
Volume:	900 mL
Sampling:	Once every 15 minutes until at least 80% of the labeled amount of Eicosapentaenoic acid (EPA) and Docosahecaenoic acid (DHA) is dispersed in the media

   If necessary, the firm can try varying the media volume, increasing the rotational speed, increasing the concentration of surfactant, and/or using USP Apparatus II (paddles) instead of Apparatus I. If all capsules tested rupture in less than one hour, it may be necessary to sample more frequently to adequately characterize the capsule rupture rate and profile.

3. As background information, the reviewer also checked the OCPB review of NDA 21-654 which listed a disintegration method[2] and specifications[3] for Omega-3-Acid Ethyl Esters capsules as follows:

   Two-tier disintegration test:

   Tier 1 Testing: The disintegration test is conducted in water in accordance with the current USP <701>.

[1] V:\FirmsNZ\ (b) (4) \Protocols\07012P0707.doc
[2] Chemistry review DFS N 021654 SCS 008 11-Apr-2006, page 3
[3] Chemistry review DFS N 021654 SCM 007 07-Feb-2006, page 13

Specification: Disintegration release NMT [redacted] min
Disintegration shelf life* NMT 30 min

* Note is made that the stability acceptance criteria is more relaxed at NMT [redacted] minutes [redacted]

If the capsules do not confirm to the acceptance criteria when tested in water, repeat the test in simulated gastric fluid.

Tier 2 Testing: The disintegration test is conducted in simulated gastric fluid (SGF)* in accordance with the current USP <701>.

[redacted] However, per the USP, Simulated Gastric Fluid is prepared by dissolving 2.0 g of sodium chloride and 3.2 g of ***purified pepsin***, which is derived from porcine stomach mucosa, with an activity of 800 to 2500 units per mg of protein, in 7.0 mL of hydrochloric acid and sufficient water to make 1000 mL. [redacted]

4. Currently, there is no control document review or Bioequivalence Recommendation Guidance for Omega-3-acid ethyl esters capsules. OGD Science Staff has **drafted** the bioequivalence recommendations for this product (see attachment for details). It recommends the disintegration testing be conducted according to the current USP <701>. Data should be provided for 12 capsules each of test and reference products. The acceptance limit for release is [redacted] min and the limit for shelf-life is 30 min.

Table 2: SUMMARY OF IN VITRO DISSOLUTION DATA

Dissolution Conditions	**Apparatus:**	USP Apparatus II (Paddles)
	Speed of Rotation:	50 RPM
	Medium:	Purified Water
	Volume:	500 mL
	Temperature:	37.0°C ± 0.5°C
Firm's Proposed Specifications	All capsules rupture in not more than (b) (4)	
Dissolution Testing Site (Name, Address)	Teva Pharmaceuticals USA 8-10 Gloria Lane Fairfield, NJ 07004	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Rupture Times (seconds)**	**Study Report Location**
Study Report #: QDP0004605	7/29/08	Omega-3-Acid Ethyl Esters Capsules Lot P080602 June 24, 2008	1 g Capsule	12	Mean	117	Module 5.3.1.3 of the original ANDA
					Range	(b) (4)	
	7/29/08	Lovaza Capsules Lot 7HH0014 Nov 2010	1 g Capsule	12	Mean	103	
					Range	(b) (4)	

II. COMMENTS:

1. The firm conducted its disintegration testing using the following method: 500 mL of water using Apparatus II (paddle) at 50 rpm per USP <711>. The firm's proposed specification of "all capsules rupture in not more than (b) (4) The disintegration testing is not the current DBE-recommended method.

2. DBE recommends the firm to develop a **quantitative capsule rupture** test to evaluate the in-vitro performance of Omega-3-Acid Ethyl Esters Capsules. The quantitative capsule rupture method should be discriminating to detect potential differences between the test and reference products. The firm should measure drug release of Eicosapentaenoic acid (EPA) and Docosahecaenoic acid (DHA). The firm may consider trying the following method:

Apparatus:	USP apparatus I (basket)
Speed:	100 rpm
Medium:	Water with a low concentration of surfactant
Volume:	900 mL
Sampling:	Once every 15 minutes until at least 80% of the labeled amount of Eicosapentaenoic acid (EPA) and Docosahecaenoic acid (DHA) is dispersed in the media

   If necessary, the firm can try varying the media volume, increasing the rotational speed, increasing the concentration of surfactant, and/or using USP Apparatus II (paddles) instead of Apparatus I. If all capsules tested rupture in less than one hour, it may be necessary to sample more frequently to adequately characterize the capsule rupture rate and profile.

3. The firm did not submit the LTSS for free eicosapentaenoic acid, free docosahexaenoic acid, eicosapentaenoic acid and docosahexaenoic acid.

4. The DSI inspection of the clinical facility has been requested.

III. DEFICIENCY COMMENTS:

1. The firm should develop a **quantitative capsule rupture** test to evaluate the in-vitro performance of Omega-3-Acid Ethyl Esters Capsules.

2. The firm should submit LTSS for free eicosapentaenoic acid and free docosahexaenoic acid that are sufficient to cover the maximum storage time of the study samples for free eicosapentaenoic acid and free docosahexaenoic acid (104 days). The firm should also submit LTSS for eicosapentaenoic acid and docosahexaenoic acid that are sufficient to cover the maximum storage time of the study samples for eicosapentaenoic acid and docosahexaenoic acid (80 days).

3. The DSI inspection of the clinical facility has been requested.

IV. RECOMMENDATIONS:

The disintegration testing conducted by Teva Pharmaceuticals on its test products, Omega-3-acid ethyl esters Capsules, 1 g, comparing them to Smithkline Beecham's Lovaza® Capsules, 1 g, is **incomplete** due to the deficiencies cited in the deficiency comments section**.**

The firm should develop a **quantitative capsule rupture** test to evaluate the in-vitro performance of Omega-3-acid Ethyl Esters Capsules. The firm should measure drug release of Eicosapentaenoic acid (EPA) and Docosahecaenoic acid (DHA). The firm may consider trying the following method:

Apparatus:	USP apparatus I (basket)
Speed:	100 rpm
Medium:	Water with a low concentration of surfactant
Volume:	900 mL
Sampling:	Once every 15 minutes until at least 80% of the labeled amount of Eicosapentaenoic acid (EPA) and Docosahecaenoic acid (DHA) is dispersed in the media

If necessary, the firm can try varying the media volume, increasing the rotational speed, increasing the concentration of surfactant, and/or using USP Apparatus II (paddles) instead of Apparatus I. If all capsules tested rupture in less than one hour, it may be necessary to sample more frequently to adequately characterize the capsule rupture rate and profile..

The firm should submit LTSS for free eicosapentaenoic acid and free docosahexaenoic acid that are sufficient to cover the maximum storage time of the study samples for free eicosapentaenoic acid and free docosahexaenoic acid (104 days). The firm should also submit LTSS for eicosapentaenoic acid and docosahexaenoic acid that are sufficient to cover the maximum storage time of the study samples for eicosapentaenoic acid and docosahexaenoic acid (80 days).

Following this page, 3 Pages Withheld in Full as (b)(4)

Dissolution Test Method and Sampling Times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.fda.gov/cder/ogd/index.htm. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 91-028

APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Omega-3-acid Ethyl Esters Capsules, 1 g

The Division of Bioequivalence (DBE) has completed its review of the disintegration testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted at a later date. The following deficiency has been identified:

1. Currently, the DBE recommends a quantitative rupture test method be used to evaluate the *in vitro* performance of the drug product. Please develop your own quantitative capsule rupture method which should be discriminating to detect potential differences between the test and reference products. Please measure drug release of Eicosapentaenoic acid (EPA) and Docosahecaenoic acid (DHA). You may consider trying the following method:

Apparatus:	USP apparatus I (basket)
Speed:	100 rpm
Medium:	Water with a low concentration of surfactant
Volume:	900 mL
Sampling:	Once every 15 minutes until at least 80% of the labeled amount of Eicosapentaenoic acid (EPA) and Docosahecaenoic acid(DHA)is dispersed in the media

Number of Units Tested: 12

If necessary, we suggest you try varying the medium volume, changing the rotational speed, adjusting the concentration of surfactant used, and/or using USP Apparatus II (paddles) instead of Apparatus I. If all capsules tested rupture in less than one hour, it may be necessary to sample more frequently to adequately characterize the capsule rupture rate and profile. Please provide individual capsule data as well as the test summary data such as mean, range, % coefficient of variation (CV) at each time point. The summary of the

quantitative rupture testing data should also be provided in eCTD-formatted tables.

2. Please provide long term storage stability data of free eicosapentaenoic acid and free docosahexaenoic acid in frozen plasma to cover the maximum storage time of the study samples for free eicosapentaenoic acid and free docosahexaenoic acid assay, which is at least 104 days. Please also provide long term storage stability data of eicosapentaenoic acid and docosahexaenoic acid in frozen plasma to cover the maximum storage time of the study samples for eicosapentaenoic acid and docosahexaenoic acid assay, which is at least 80 days.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

VI. OUTCOME

ANDA: 91-028

Reviewer: Ren, Ke **Date Completed:**

Verifier: **Date Verified:**

Division: Division of Bioequivalence

Description: Omega-3-acid Ethyl Esters Capsules, 1 g, Teva Pharmaceuticals USA

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
8048	11/10/2008	Dissolution Data	Dissolution Review	1	1
				Bean Total:	1

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ke Ren
5/1/2009 05:30:13 PM
BIOPHARMACEUTICS

Bing Li
5/1/2009 05:58:45 PM
BIOPHARMACEUTICS

Hoainhon T. Nguyen
5/4/2009 11:57:10 AM
BIOPHARMACEUTICS
For Dale P. Conner, Pharm. D., Director, Division of Bioequivalence I

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 91028

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ROUTING SHEET

☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ CGMP

Division: III	Team: 34	PM: Chinyelum Olele

Electronic ANDA: Yes ☒ No ☐

ANDA #:091028
Firm Name:Teva Pharmaceuticals USA
ANDA Name:Omega-3-Acid Ethyl Esters Capsules USP, 1 gram
RLD Name:Lovaza

Electronic AP Routing Summary Located:
V:\Chemistry Division III\Team 34\Electronic AP Summary\091028_APRV_ROUT_SUMRY

AP/TA Letter Located:
V:\Chemistry Division III\Team 34\Final Version For DARRTS Folder\091028_apltr

Project Manager Evaluation: **Date: 4/3/14 Initials:** CO

☐ Previously reviewed and tentatively approved --- Date _____
☐ Previously reviewed and CGMP Complete Response issued -- Date _____

Original Rec'd date 11/10/08	Date of Application 11/10/08	Date Acceptable for Filing 11/10/08
Patent Certification (type) P-IV	Date Patent/Excl. expires 4/10/17	Citizens' Petition/Legal Case? Yes☐ No ☐ (If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☐ **DMF#:** (b) (4) (provide MF Jackets)	Priority Approval (Top 100, PEPFAR, etc.)? Yes ☐ No ☐ Comment: Prepared Draft Press Release sent to Cecelia Parise Yes ☐ No ☐ Date:	
☐ Suitability Petition/Pediatric Waiver	Pediatric Waiver Request: Accepted ☐ Rejected ☐ Pending ☐	

GDUFA User Fee Obligation Status: ☒ Met ☐ Unmet**:** ☐ Facility Fee not paid, ☐ Backlog fee not paid
EER Status: ☐ Pending ☐☐ ☒ Acceptable ☐ OAI *EES Date Acceptable: 4/8/14* ☐ Warning Letter Issued; Date:
Has there been an amendment providing for a Major change in formulation since filling? Yes ☐ No ☐ Comment:
Date of Acceptable Quality (Chemistry) 03/28/14 Addendum Needed: Yes ☐ No ☒ Comment:
Date of Acceptable Bio 4/3/14 Bio reviews in DARRTS: Yes ☒ No ☐ (Volume location:)
Date of Acceptable Labeling 1/10/14 Attached labeling to Letter: Yes ☐ No ☐ Comment:
Date of Acceptable Sterility Assurance (Micro) _____

Methods Val. Samples Pending: Yes ☐ No ☐**;** Commitment Rcvd. from Firm: Yes ☐ No ☐

Post Marketing Agreement (PMA): Yes ☐ No ☒ (If yes, email PM Coordinator) Comment:

Modified-release dosage form: Yes ☐ No ☒ (If yes, enter dissolution information in Letter)

Routing:

☒ Labeling Endorsement, Date emailed: 4/3/14 REMS Required: Yes ☐ No ☒ REMS Acceptable: Yes ☐ No ☐

☒ Regulatory Support

☐ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: _____

☐ Division

☐ Bob West / Peter Rickman

☐ Kathleen Uhl

☐ Filed AP Routing Summary in DARRTs	☐ Notified Firm and Faxed Copy of Approval Letter	☐ Sent Email to "CDER-OGDAPPROVALS" distribution list

OGD APPROVAL ROUTING SUMMARY

1. ***Regulatory Support Branch Evaluation***

Martin Shimer **Date: 4/4/2014**

Chief, Reg. Support Branch **Initials:** MHS

Contains GDEA certification: Yes ☒ No ☐	Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92)	Pediatric Exclusivity System
	RLD = Lovaza NDA# 21-654 Date Checked 4/7/14 Nothing Submitted ☒ Written request issued ☐ Study Submitted ☐
Patent/Exclusivity Certification: Yes ☒ No ☐ If Para. IV Certification- did applicant: Notify patent holder/NDA holder Yes ☒ No ☐ Was applicant sued w/in 45 days:Yes ☒ No ☐ Has case been settled: Yes ☒ No ☐ Date settled: Is applicant eligible for 180 day Yes Is a forfeiture memo needed: Yes ☒ No ☐ If yes, has it been completed	
Generic Drugs Exclusivity for each strength: Yes ☒ No ☐	
Date of latest Labeling Review/Approval Summary _____	

Any filing status changes requiring addition Labeling Review Yes ☐ No ☒☐

Type of Letter:
☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐CGMP ☐ OTHER:

Comments:ANDA submitted on 11/10/2008, BOS=Lovaza NDA 21-654, PIII to the '594, PIV to the '077 and '667 patents, NCE exp. 11/10/2009-this was an NCE minus one submission. ANDA ack for filing on 11/10/2008 (LO dated 3/9/2009).
Patent Amendment rec'd on 6/3/2009-revised cert to take into account expiration date of the '667.
Patent Amendment rec'd on 6/16/2009-CA 09-286 filed in the D of DE for infringement of the '077 and '667 patents.
Patent Amendment rec'd on 8/13/2010-PIV to the '488, TEVA maintains PIV certs to the '077 and '667, PII to the expired '594
Patent Amendment rec'd on 7/15/2011-notice related to the '488 patent was sent via (b) (4) to SmithKline Beecham in RTP, NC with notice delivered on 8/16/2010, notice sent via (b) (4) to GlaxoSmithKline in Phila PA with notice delivered on 8/16/2010, notice sent via (b) (4) to Pronova Biopharma Norge AS in Lysaker Norway with notice delivered on 8/18/2010, CA 10 CV 0800 filed on 9/20/2010 in the D of DE for infringement of the '488 patent. Since this patent was not listed in the OB at the time this ANDA was submitted there is no 30 month stay of approval associated with this CA.
Patent Amendment rec'd on 8/1/2012- Judgment for CA 09 CV 0286 pending in the D of DE entered on 5/29/2012-Judgment entered in favor of Pronova Biopharma and against TEVA and Par. Also copy of Stipulation of Dismissal without Prejudice and Order entered on 7/22/2011 dismissing CA 10-800 related to the '930, '698 and '488 patents. Cover letter of this amendment indicates that TEVA filed a Notice of Appeal on 6/25/2012.
Patent Amendment rec'd on 12/27/2012-TEVA reinserting claims related to M-87 which expired on 9/16/2012.
Patent Amendment rec'd on 1/30/2014-copy of Decision from the CAFC which reversed the District Court ruling and found that the asserted claims of the '667 patent are invalid under 102(b). The case was remanded back to the DC. As the '077 patent was expired at the time of the CAFC's order. Petition for hearing En Banc was denied on 1/16/2014, this denial stated that the Mandate associated with the CAFC Order will issue on 1/23/2014. Copy of Mandate which was issued on 1/23/2014 also included in this amendment.

The issuance of the Mandate on 1/23/2014 triggered the 75 day period under 505(j)(5)(D)(i)(I)(bb)(AA). This 75 day period expires on April 8, 2014. If this ANDA is not approved on or before 4/8/2014 there will be events both under 505(j)(5)(D)(i)(I)(bb)(AA) and under 505(j)(5)(D)(i)(I)(aa)(BB). This would mean that TEVA and any other applicant that submitted an ANDA on the NCE minus one date would forfeit eligibility for 180 day exclusivity.

At this point the only unexpired patent listed in the OB for Lovaza is the '667 patent. The '594 and '077 patents expired and the later listed '488 patent was delisted per the NDA holders request-since the '488 would not have been a placeholder of 180 day exclusivity this delisting would have been acceptable.

ANDA is eligible for Full Approval.

2. ***Labeling Endorsement***

Reviewer, Betty Turner:
Date4/3/14

Labeling Team Leader: Angela Payne
Date4/7/14

REMS required?
☐Yes ☒No

REMS acceptable?
☐Yes ☐No ☒n/a

Comments:

From: Payne, Angela
Sent: Monday, April 07, 2014 1:12 PM
To: Wu, Ruby (Chi-Ann); Olele, Chinyelum
Cc: Turner, Betty
Subject: RE: ANDA 091028

I concur.

Angela
ATL

From: Wu, Ruby (Chi-Ann)
Sent: Thursday, April 03, 2014 12:47 PM
To: Payne, Angela
Cc: Turner, Betty
Subject: FW: ANDA 091028

Hi Angela,

Please endorse.

Thanks!

From: Turner, Betty
Sent: Thursday, April 03, 2014 12:19 PM
To: Olele, Chinyelum; Wu, Ruby (Chi-Ann)
Subject: FW: ANDA 091028

Hi Chi Chi,
Labeling:
There are no changes for the labeling review since the last review was completed.

Letter
Please delete the extra space between "that is/are".
Please delete the extra space between "IV certification to . Therefore,"

Thanks,
Betty

From: Olele, Chinyelum
Sent: Thursday, April 03, 2014 11:45 AM
To: Turner, Betty; Wu, Ruby (Chi-Ann)
Subject: ANDA 091028

Hi Ruby and Betty,

This ANDA is ready for AP. Please provide labeling endorsement.

Thanks

Chi-Chi

3. ***Paragraph IV Evaluation*** **PIV's Only**

David Read **Date 7Apr2014**

OGD Regulatory Counsel **InitialsDTR**

Pre-MMA Language included ☐

Post-MMA Language Included ☐

Comments:Changes to AP letter saved to V drive. This ANDA is subject to TWO possible forfeitures of 180-day exclusivity. First, they failed to obtain TAwith 30 months of their ANDA being received, i.e., by May 10, 2011. Second, due to the Ct of Appeals mandate issuing on Jan 23, 2014, they must commence marketing NLT April 8, 2014, or else forfeit under the Failure to Market provision. With respect to failure to obtain TA, we are punting - no subsequent appplicant is close to approval, and Teva has said they will commence marketing immediately.

4. ***Quality Division Director /Deputy Director Evaluation*** **Date 4/3/14**

Chemistry Div. **III (Sayeed)** **InitialsCO for**

Comments: Chemistry Review # 4 concluding that the CMC section of this ANDA is acceptable for approval was endorsed by Vilayat Sayeed, Ph.D., Director, Division of Chemistry III on 3//28/14.

OGD Office Management Evaluation

5. Peter Rickman **Date 4/7/14**

Director, DLPS **Initials rlw/for**

Para.IV Patent Cert: Yes☐ ☐ ☐ No☐

Pending Legal Action: Yes☐ ☐ No☐

Petition: Yes☐ No☐

Entered to APTrack database ☐

GDUFA User Fee Obligation Status Met☐ Unmet☐

Press Release Acceptable ☐

Date PETS checked for first generic drug _____

Comments: There are two options proposed to establish bioequivalence for this drug product in the draft guidance for Omega-3-Acid Ethyl Esters Capsules. One is an in-vivo approach and the other is an in-vitro approach. Teva has selected the in-vitro approach. This is based upon the composition of the innovator and Teva's capsule to be quantitatively and qualitatively the same and the determination by DBE that the comparative dissolution testing (in-vitro quantitative capsule rupture testing (QCRT) is acceptable. Office-level bio endorsed 4/4/14.

Final-printed labeling (FPL) found acceptable for approval 1/10/14, as endorsed 4/3/14. No REMS is required.

CMC found acceptable for approval (Chemistry Review #4) 3/28/14.

OR

6. Robert L. West **Date 4/7/14**

Deputy Director, OGD **Initials RLWest**

Para.IV Patent Cert: Yes☒ ☐ ☐ No☐

Pending Legal Action: Yes☐ ☐ No☒

Petition: Yes☐ No☒

Entered to APTrack database ☒

GDUFA User Fee Obligation Status Met☒ Unmet☐

Press Release Acceptable ☐

Date PETS checked for first generic drug _____

Comments: Acceptable EES dated 2/3/14 (Verified 4/7/14). No "OAI" Alerts noted. Reevaluation date 4/8/14.

Teva provided a paragraph IV certification to the '667 patent. Teva was sued on the '667 patent (an other unlisted patents) within the 45- day period. Teva lost the patent infringement case regarding the '667 patent at the district level. Teva appealed and was successful at the appeals court level as the appeals court overturned the district court decision. The appeals court ruled that the claims of the '667 patent were invalid. The mandate of the appeals court's decision was issued on 1/23/14. The issuance of this mandate triggered a 75-day deadline for Teva to begin marketing of this product.

Currently, there are no additional patents or exclusivity listed in the "Orange Book" for this drug product.

Teva may be eligible to share 180-day generic drug exclusivity for this drug product. As no other ANDA applicant for Omega-3-Acid Ethyl Esters Capsules USP is eligible for approval at this time, a formal exclusivity decision will be deferred.

This ANDA is recommended for approval.

7. ***OGD Director Evaluation***

Kathleen Uhl

Comments: RLWSest for Kathleen Uhl, M.D., Acting Director, Office of Generic Drugs, 4/7/14.
First Generic Approval ☐
PD or Clinical for BE ☐
Special Scientific or Reg. Issue ☐
Press Release Acceptable ☐

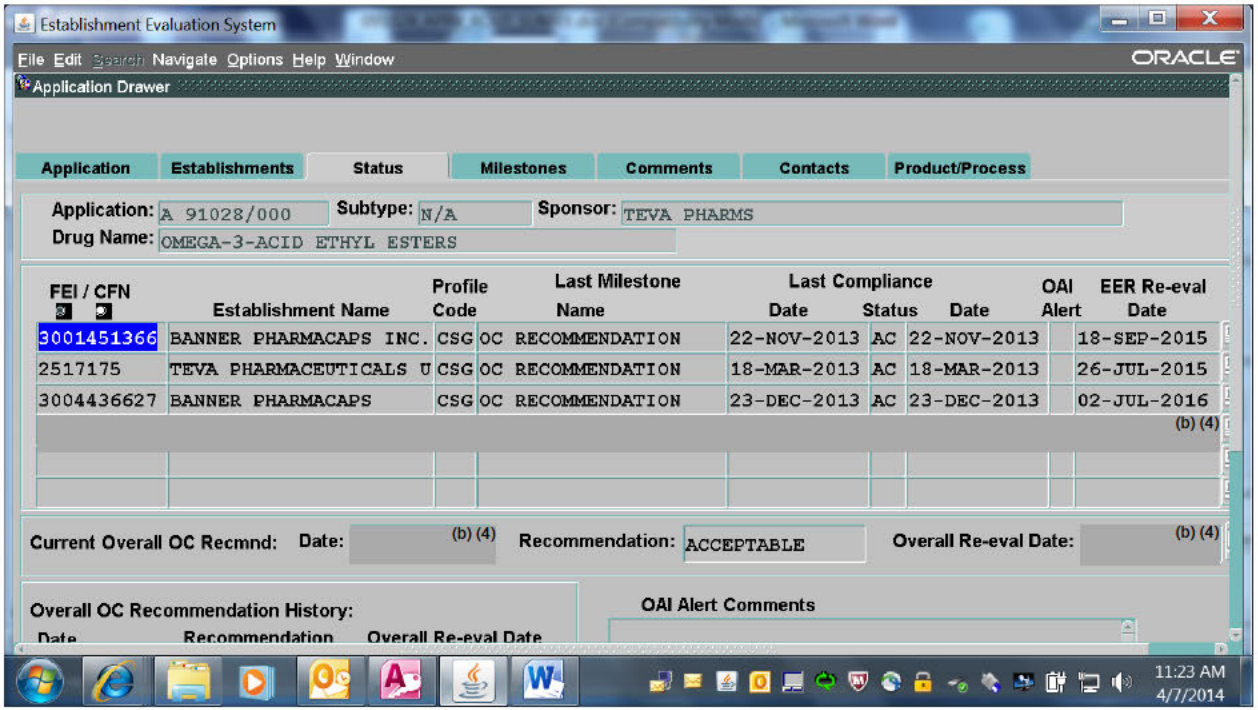
Comments:

8. Project Manager **Date 4/7/14**
Initials CO

Comments:

Check Communication and Routing Summary into DARRTS

EES DATA:


Establishment Evaluation System
File Edit Search Navigate Options Help Window
ORACLE
Application Drawer
Application
Establishments
Status
Milestones
Comments
Contacts
Product/Process
Application: A 91028/000
Subtype: N/A
Sponsor: TEVA PHARMS
Drug Name: OMEGA-3-ACID ETHYL ESTERS
FEI / CFN
Establishment Name
Profile Code
Last Milestone Name
Last Compliance Date
Status
Date
OAI Alert
EER Re-eval Date
3001451366 BANNER PHARMACAPS INC. CSG OC RECOMMENDATION 22-NOV-2013 AC 22-NOV-2013 18-SEP-2015
2517175 TEVA PHARMACEUTICALS U CSG OC RECOMMENDATION 18-MAR-2013 AC 18-MAR-2013 26-JUL-2015
3004436627 BANNER PHARMACAPS CSG OC RECOMMENDATION 23-DEC-2013 AC 23-DEC-2013 02-JUL-2016
(b) (4)
Current Overall OC Recmnd:
Date: (b) (4)
Recommendation: ACCEPTABLE
Overall Re-eval Date: (b) (4)
Overall OC Recommendation History:
Date
Recommendation
Overall Re-eval Date
OAI Alert Comments
11:23 AM
4/7/2014

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Patent and Exclusivity Search Results from query on Appl No 021654 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N021654	001	5656667	Apr 10, 2017	Y	Y	U - 822	

Exclusivity Data

There is no unexpired exclusivity for this product.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHINYELUM A OLELE
04/07/2014

EASILY CORRECTABLE DEFICIENCY FAX

ANDA 091028

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Teva Pharmaceuticals USA TEL: (215) 591-3142

ATTN: Scott D. Tomsky FAX: (215) 591-8812

FROM: Chinyelum Olele FDA CONTACT PHONE: (240) 276-9778

Dear Sir:

This communication is in reference to your abbreviated new drug application (ANDA) dated November 10, 2008, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Omega-3-Acid Ethyl Esters Capsules USP, 1 gram.

Reference is also made to your amendment dated March 20, 2014.

The deficiencies presented below represent *EASILY CORRECTABLE DEFICIENCIES* identified during the review and the current review cycle will remain open. You should provide a complete response to these deficiencies within ten (10) U.S. business days.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

EASILY CORRECTABLE DEFICIENCY
BIOEQUIVALENCE

If you do not submit a complete response within ten (10) U.S. business days, the review will be closed and the listed deficiencies will be incorporated in the next COMPLETE RESPONSE. Please provide your response after that complete response communication is received along with your response to any other issued comments.

If you are unable to submit a complete response within ten (10) U.S. business days, please contact the Regulatory Project Manager immediately so a complete response may be issued if appropriate.

Please submit official archival copies of your response to the ANDA, facsimile or e-mail responses will not be accepted. A partial response to this communication will not be processed as an amendment and will not start a review.

If you have questions regarding these deficiencies please contact the Regulatory Project Manager, Chinyelum Olele at (240) 276-9778.

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We have completed our review, as amended, and have the following comments:

DISSOLUTION

The Division of Bioequivalence I (DBI) has completed its review of the drug release testing portion of your submission acknowledged on the cover sheet. The following deficiency has been identified:

1. Your quantitative capsule rupture testing (QCRT) data, using the method stated below, are acceptable. However, your proposed specifications of "NLT (b)(4)% (Q) in (b)(4) minutes" for both Docosahexaenoic Acid (DHA) and Eicosapentaenoic Acid (EPA) components are not acceptable. Based on the submitted data, DBI recommends the specifications below for the test product. Please acknowledge the following QCRT method and specifications for your product:

Apparatus:	USP II (paddle) with (b)(4) Helix Coil sinkers
Speed of Rotation:	100 rpm
Medium:	Tier I: 8% Labrasol in 0.1 N HCl without enzyme Tier II: 8% Labrasol in 0.1 N HCl with pepsin (750,000 units/L)
Volume:	900 mL
Temperature:	37°C ± 0.5°C
Specifications	NLT (b)(4)% (Q) in 90 minutes for EPA and DHA

2. The date of the QCRT studies (October 2013) was prior to the approval date for dissolution method validation (project IDO013; Code: 2000040, approval date of December 2013). In future submissions, please be advised that the validation should be completed prior to comparative QCRT studies.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HOAINHON N CARAMENICO on behalf of DALE P CONNER
04/03/2014

DIVISION OF BIOEQUIVALENCE

Date:	March 13, 2014
ANDA:	091028
Drug Product Name:	Omega 3- Acid Ethyl Esters Capsules
Strength:	1 gram
Applicant Name:	Teva Pharmaceuticals USA
Submission Dates:	November 10, 2008 (Original) March 11, 2014 (Complete Response)
RE:	Post CR Clarification

Comments:

Teva Pharmaceuticals USA requested clarification following the Complete Response (CR) letter dated 3/11/2014. On March, 13 2014, the Division of Bioequivalence I (DBI) communicated the following response to the RPM:

From: Yoon, Martin
Sent: Thursday, March 13, 2014 5:07 PM
To: Gaines, Robert; Olele, Chinyelum
Cc: Yoon, Martin
Subject: RE: Question related to CRL received for ANDA 091028

Hello Bob,

Please see Bio response to Teva's inquiries:

Firm's Question 1:
The 2nd paragraph at the top of page 2 of the CRL discusses the Quantitative Capsule Rupture Test (QCRT) which is "used for the purpose of confirming bioequivalence". In the 2nd sentence of this paragraph, however- the letter states "Please note that these deficiencies are the same as those identified for the QCRT method used for the regulatory release and stability testing purpose, as the two methods are identical for the current ANDA."

Our current release and stability specification includes Disintegration testing per USP <701> and Dissolution testing per USP <711> (as provided in Sequence 0013), but does not include the QCRT, which we believed to be strictly for the purpose of demonstrating bioequivalence.

FDA Response to Question 1:
Currently there is no drug release testing method for this drug product in USP for the release and stability testing purpose (Please note that the active ingredients are not soluble in the

testing medium, therefore, “dissolution” is not appropriate term that can be applied to these active ingredients). DBI recommends that the firm use a QCRT method for the release and stability purpose as well as for the purpose of demonstrating bioequivalence. The firm may propose a QCRT method for release and stability testing that is different from QCRT method used for BE demonstration, but disintegration testing of this drug product is not acceptable to the Agency for release and stability testing purpose.

Firm’s Question 2:
Can clarification be provided by what was meant in the sentence highlighted above? Was this statement possibly in error?

FDA Response to Question 2:
No, the statement is not an error. Please see the clarification above.

Thank you,
Martin

From: Yoon, Martin
Sent: Thursday, March 13, 2014 4:10 PM
To: Gaines, Robert
Cc: Olele, Chinyelum
Subject: RE: Question related to CRL received for ANDA 091028

Hello Bob,

Bio can provide a response via email if needed by the Office. The review team is drafting the response at this moment.

Thank you,
Martin

From: Gaines, Robert
Sent: Thursday, March 13, 2014 2:54 PM
To: Yoon, Martin
Cc: Olele, Chinyelum
Subject: FW: Question related to CRL received for ANDA 091028
Importance: High

Good afternoon Martin.

Please see the below email from Teva regarding the CR we just issued for ANDA 91028. Please let me know if we will be able to provide a response via email. Per a recent legal decision, this product has to be approved on/before 4/7/14.

Thanks
Bob

Robert Gaines, PharmD
CDR, United States Public Health Service
Regulatory Project Manager
Office of Generic Drugs
Food and Drug Administration
7500 Standish Place Room E145
Rockville, MD 20855
Phone: 240-276-8495
Fax: 240-276-8474

From: Jill Pastore [mailto:Jill.Pastore@tevapharm.com]
Sent: Thursday, March 13, 2014 1:48 PM
To: Gaines, Robert
Cc: Scott Tomsky
Subject: Question related to CRL received for ANDA 091028

Dear Bob,

This email is in follow up to a voice message I left for you a few moments ago. Teva is in receipt of the CRL that issued on 3/11/14 for Omega-3-Acid Ethyl Esters Capsules (ANDA 091028), and we are hoping to get clarification of a statement made on page 2 of the letter (page 3 of the fax), under the Bioequivalence section. I thought it might be easier if I explained our question via the voice message I left, but I have outlined it below as well:
The 2nd paragraph at the top of page 2 of the CRL discusses the Quantitative Capsule Rupture Test (QCRT) which is "used for the purpose of confirming bioequivalence". In the 2nd sentence of this paragraph, however- the letter states "Please note that these deficiencies are the same as those identified for the QCRT method used for the regulatory release and stability testing purpose, as the two methods are identical for the current ANDA."
Our current release and stability specification includes Disintegration testing per USP <701> and Dissolution testing per USP <711> (as provided in Sequence 0013), but does not include the QCRT, which we believed to be strictly for the purpose of demonstrating bioequivalence. Can clarification be provided by what was meant in the sentence highlighted above? Was this statement possibly in error?

Many thanks for any clarification you can provide.

Best regards,

Jill

Jill Pastore Senior Director, Generics Regulatory Affairs
Tel: 215-591-3150
Jill.Pastore@tevapharm.com sip:Jill.Pastore@tevapharm.com www.tevapharm.com

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARTIN YOON
03/14/2014

COMPLETE RESPONSE
ANDA 091028

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

TO: Teva Pharmaceuticals USA

TEL: 215-591-3142

ATTN: Scott Tomsky

FAX: 215-591-8812

FROM: Robert Gaines

FDA CONTACT PHONE: 240-276-8495

Dear Sir:

This facsimile is in reference to your abbreviated new drug application, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

We have completed the review and have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachments (____ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.
If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 091028

COMPLETE RESPONSE

Teva Pharmaceuticals USA
Attention: Scott D. Tomsky
VP US Generics Regulatory Affairs
425 Privet Road
Horsham, PA 19044

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated November 10, 2008, received November 10, 2008, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Omega-3-Acid Ethyl Esters Capsules USP, 1 gram.

Reference is also made to the Complete Response letter issued by the Agency on August 13, 2013 and to the Easily Correctable Bioequivalence Deficiency issued by the Agency on February 7, 2014. We acknowledge receipt of your amendment dated December 30, 2013.

We have completed our review of this application, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

The deficiencies presented below represent Minor deficiencies.

Deficiencies

1. The drug master file # (b) (4) for Omega-3acid ethyl esters is currently inadequate. The DMF holder, (b) (4) has been notified. Please do not respond to this letter until the DMF holder has informed you that they have responded to all the deficiencies. Please update your drug substance specifications in consultation with your DMF holder and provide updated methods and validations as applicable.

2. We acknowledge that you have updated your drug product release and stability specification to comply with the current USP monograph. (b) (4)

Please update the release and stability specifications accordingly.

BIOEQUIVALENCE

The Division of Bioequivalence I (DBI) has completed its review of your submission(s) acknowledged on the cover sheet and has identified the following deficiencies.

The *in vitro* quantitative capsule rupture testing (QCRT) method used for the purpose of confirming bioequivalence (BE) of the test product is inadequate for the reasons listed below. Please note that these deficiencies are the same as those identified for the QCRT method used for the regulatory release and stability testing purpose, as the two methods are identical for the current ANDA.

1. With respect to the Quantitative Capsule Rupture Testing (QCRT) and *in vitro* bioequivalence (BE) studies submitted on December 30, 2013, you have referenced two different analytical methods. Specifically, the analytical method used in your method validation (Project ID O013; Code: 2000040) differs from that used in the QCRT [Report No. QDP0060815] and in the *in vitro* BE testing (POPV_0313_0791, POPV_0313_0852, POPV_0313_0853, POPV_0313_0892, POPV_0313_0891), as follows:

   Analytical method used in your method validation (Project ID O013; Code: 2000040):

   Column:

   Detection:
   Flow Rate:
   Injection Volume:
   Column Temperature:
   Run Time:

   (b) (4)

   Analytical method used in your quantitative capsule rupture testing (QCRT) using USP Apparatus II (paddles) or USP apparatus IV [Report No. QDP0060815] and in the *in vitro* bioequivalence (BE) testing (POPV_0313_0791, POPV_0313_0852, POPV_0313_0853, POPV_0313_0892, POPV_0313_0891):

   Column:

   Detection:
   Flow Rate:
   Injection Volume:
   Column Temperature:
   Auto sampler Temperature:
   Run Time (Apparatus II):

   (b) (4)

Run Time (Apparatus IV): (b) (4)

Please clearly identify which instrument conditions were used during the QCRT testing [Report No. QDP0060815] and the *in vitro* BE testing. If the method used in these studies differs from that already validated, then please provide additional validation as necessary. Also, please provide your Standard Operating Procedure (SOP) for each of the above methods as well as for the method validation procedure.

2. In your QCRT testing [Report No. QDP0060815] and In vitro BE testing submitted December 30, 2013, you submitted data reflecting the sum of Eicosapentaenoic Acid Ethyl Ester (EPA) + Docosahexaenoic Acid Ethyl Ester (DHA) release. Please submit the release data from the referenced studies for each individual component rather than for the sum of the two components. Please submit the data from 12 individual dosage units of the Test and Reference products from the referenced studies. In addition, please submit all mean data, range, %CV, and the dates of these studies in eCTD format (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120957.pdf). Finally, please submit the temperature and humidity at which the test and reference product lots were stored between manufacture of the test product (or acquisition of the reference product) and the time of the aforementioned studies.

3. You did not provide your Standard Operating Procedures (SOPs) for the QCR testing and *in vitro* BE studies. Please submit these documents/information.

4. You have used sinkers in study #s QDP0068549, QDP0069171, QDP0068622, QDP0068624, QDP0060815, and study # POPV_0313_0791. Please provide the following information for the sinkers: 1) a detailed description of the sinker used in the dissolution method (including a diagram, dimensions and manufacturing information) and 2) confirmation that the sinker is consistent with those described in USP Chapter <711> with respect to composition and dimensions.

Please note that Deficiency #s 1 and 2 above have been changed from those issued in the Easily Correctible Deficiency (ECD) letter dated 2/7/2014. In addition, please note that Deficiency #s 3 and 4 are new deficiencies that were not issued in the above-mentioned ECD letter. We communicate the above deficiencies in the current letter since you did not respond to the 2/7/2014 ECD letter within 10 business days.

Please also note that the bioequivalence comments provided in this communication are comprehensive as of issuance. These comments are subject to revision if additional concerns by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

LABELING

The Labeling Review Branch has no further questions/comments at this time based on your labeling submission dated December 30, 2013.

Please continue to monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book and the NF-USP online for recent updates, and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17.

FACILITY INSPECTIONS

Office of Compliance has no further questions at this time. The compliance status of each facility named in the application may be re-evaluated upon re-submission.

OTHER

A partial response to this letter will not be processed as a resubmission and will not start a new review cycle. The resubmission to this will be considered to represent a Minor AMENDMENT. The designation as a **RESUBMISSION/AFTER ACTION- *MINOR AMENDMENT*** should appear prominently in your cover letter. In addition, please designate in bold on your cover letter each review discipline (Chemistry, Labeling, Bioequivalence, Microbiology, Clinical) you are providing responses to.

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the ANDA under 21 CFR 314.65. You may also request an extension of time in which to resubmit the ANDA. A resubmission response must fully address all the deficiencies listed.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dose form (FDFs) or active pharmaceutical ingredient (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees

when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

The drug product may not be legally marketed until you have been notified in writing that this ANDA is approved.

If you have any questions, call Robert Gaines, Regulatory Project Manager, at 240-276-8495.

Sincerely yours,

{See appended electronic signature page}

Kathleen Uhl, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT L WEST

03/11/2014

Deputy Director, Office of Generic Drugs, for
Kathleen Uhl, M.D.

EASILY CORRECTABLE DEFICIENCY FAX

ANDA 091028

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Teva Pharmaceuticals USA TEL: (215) 591-3142

ATTN: Scott D. Tomsky FAX: (215) 591-8812

FROM: Robert Gaines FDA CONTACT PHONE: (240) 276-8495

Dear Sir:

This communication is in reference to your abbreviated new drug application (ANDA) dated November 10, 2008, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Omega-3-Acid Ethyl Esters Capsules USP, 1 gram.

Reference is also made to your amendment dated December 30, 2013

The deficiencies presented below represent *EASILY CORRECTABLE DEFICIENCIES* identified during the review and the current review cycle will remain open. You should provide a complete response to these deficiencies within ten (10) U.S. business days.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

EASILY CORRECTABLE DEFICIENCY
BIOEQUIVALENCE

If you do not submit a complete response within ten (10) U.S. business days, the review will be closed and the listed deficiencies will be incorporated in the next COMPLETE RESPONSE. Please provide your response after that complete response communication is received along with your response to any other issued comments.

If you are unable to submit a complete response within ten (10) U.S. business days, please contact the Regulatory Project Manager immediately so a complete response may be issued if appropriate.

Please submit official archival copies of your response to the ANDA, facsimile or e-mail responses will not be accepted. A partial response to this communication will not be processed as an amendment and will not start a review.

If you have questions regarding these deficiencies please contact the Regulatory Project Manager, Robert Gaines at (240) 276-8495.

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If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

We have completed our review, as amended, and have the following comments:

BIOEQUIVALENCE

1. With respect to the Quantitative Capsule Rupture Testing (QCRT) and in vitro bioequivalence (BE) studies submitted on December 30, 2013, you have referenced two different analytical methods. Specifically, the analytical method used in your method validation (Project ID O013; Code: 2000040) differs from that used in the QCRT [Report No. QDP0060815] and in the in vitro BE testing (POPV_0313_0791), as follows:

   Analytical method used in your method validation (Project ID O013; Code: 2000040):

   Detection:
   Flow Rate:
   Injection Volume:
   Column Temperature:
   Run Time:

   (b) (4)

   Analytical method used in your quantitative capsule rupture testing (QCRT) using USP Apparatus II (paddles) [Report No. QDP0060815] and in the in vitro bioequivalence (BE) testing (POPV_0313_0791):

   Detection:
   Flow Rate:
   Injection Volume:
   Column Temperature:
   Auto sampler Temperature:
   Run Time:

   (b) (4)

   Please clearly identify which instrument conditions were used during the QCRT testing [Report No. QDP0060815] and the in vitro BE testing (POPV_0313_0791). If the method used in these studies differs from that already validated, then please provide additional validation as necessary. Also, please provide your Standard Operating Procedure (SOP) for each of the above methods as well as for the method validation procedure.

2. In your QCRT testing [Report No. QDP0060815] and In vitro BE testing (POPV_0313_0791) submitted December 30, 2013, you submitted data reflecting the sum of Eicosapentaenoic Acid (EPA) + Docosahexaenoic Acid (DHA) release. Please submit the release data from the referenced studies for each individual component rather than for the sum of the two components. Please submit the data from 12 individual dosage units of the Test and Reference products from the referenced studies. In addition, please submit all mean data, range, %CV, and the dates of these studies in eCTD format (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120957.pdf). Finally, please submit the temperature and humidity at which the test and reference product lots were stored between manufacture of the test product (or acquisition of the reference product) and the time of the aforementioned studies.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HOAINHON N CARAMENICO on behalf of DALE P CONNER
02/07/2014

COMPLETE RESPONSE
ANDA 091028

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

TO: Teva Pharmaceuticals USA TEL: 215-591-8725

ATTN: Jean Zwicker FAX: 215-591-8812

FROM: Robert Gaines FDA CONTACT PHONE: 240-276-8495

Dear Madam:

This facsimile is in reference to your abbreviated new drug application, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

We have completed the review and have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachments (____ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.
If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 091028

COMPLETE RESPONSE

Teva Pharmaceuticals USA
Attention: Jean Zwicker
Senior Director, Regulatory Affairs
425 Privet Road
Horsham, PA 19044

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated November 10, 2008, received November 10, 2008, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Omega-3-Acid Ethyl Esters Capsules USP, 1 gram.

We acknowledge receipt of your amendments dated June 3, and October 1, 2009; March 8, 2010; March 4, and October 27, 2011; and December 27, 2012.

We have completed our review of this application, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

The deficiencies presented below represent Minor deficiencies.

A. Deficiencies

1. The drug master file # (b) (4) for Omega-3acid ethyl esters is currently inadequate. The DMF holder, (b) (4) has been notified. Please do not respond to this letter until the DMF holder has informed you that they have responded to all the deficiencies. Please update your drug substance specifications in consultation with your DMF holder and provide updated methods and validations as applicable.

(b) (4)

(b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please list the API and other excipients in the composition table as USP or NF grade as applicable.

2. For future ANDA submissions, please provide answer to all Question-based Review questions. If the question is not applicable, please provide a response that the question is not applicable and why it is not applicable.

3. Please make all applicable changes to your drug product release specifications to comply with the division of bioequivalence recommendations.

4. Please update the drug product name and other relevant information to comply with the current USP monograph for the drug product.

5. Please provide updated stability data at controlled room temperature using the revised stability specifications.

BIOEQUIVALENCE

The Division of Bioequivalence I (DBI) has completed its review of your submission acknowledged on the cover sheet and the following deficiencies have been identified:

Deficiencies Related to Bioequivalence (BE) Studies

1. The DBI has reviewed the test formulation using the criteria on active pharmaceutical ingredient and antioxidant as stated in the draft Individual Product BE Guidance for Omega-3-Acid Ethyl Esters Capsules, posted on September, 2012, (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM320011.pdf), and considers that your test product meets the criteria. The test and reference products are similar and the bioequivalence (BE) may be established based solely on an *in vitro* method (Quantitative Capsule Rupture Test, also described in the draft guidance).

2. However, per the draft Guidance aforementioned, if you wish to choose *In Vivo* BE Study Option for your application, please conduct both new fasting and fed BE studies for Omega-3-Acid Ethyl Esters Capsules, 1 g.

   According to that current BE Guidance for Omega-3-Acid Ethyl Esters Capsules posted on September 2012, the 90% confidence intervals (CIs) for the BE fed study are based on: (1) Eicosapentaenoic Acid (EPA) ethyl esters and (2) Docosahexaenoic Acid (DHA) ethyl esters. In addition, a fasting BE study is recommended and its 90% CIs for BE

are based on: (1) baseline-adjusted EPA total lipids and (2) baseline- adjusted DHA total lipids.

3. Based on your pre-study validation data in your currently submitted fed study (Study No. 2008-1829), the percent of average recovery for the free eicosapentaenoic acid (EPA) (e.g. QC A, B and C: 131.9 % to 140.0 %) and docosahexaenoic acid (DHA) (e.g. QC A, B and C: 130.2 % to 135.8 %) and that of Internal Standard [IS (b) (4) 124.1%] are very high. Please provide your explanation(s) about such high values of average recovery of the above mentioned analytes and the internal standard.

For your future submissions, please be advised of the following:

4. Please submit complete (100%) raw numerical data of **all** assay and reassay runs for **all subjects**, including the data of peak area/height for the drug, peak area/height for the internal standard, ratio of the peak area/height for the drug to the peak area/height for the internal standard, dilution factor (if any), and the corresponding concentration for each assayed and reassayed sample of all subject samples, calibration standard concentration samples, and quality control samples for each of your BE study. For your pilot study (Study No. 2008-1779) and fed study (Study No. 2008-1829) currently submitted, you only submitted the raw numerical data of **approximately 50% and 22.5%** of the subjects, respectively.

5. Regarding Compliance with Section 508 of the Rehabilitation Act of 1973: The images included in your submission do not contain alternate text and are therefore unsearchable and not in compliance with Section 508 of the Rehabilitation Act of 1973, which requires that Federal agencies' electronic and information technology is accessible to people with disabilities. Please ensure that future submissions are in compliance with Section 508 and contain images with alternate text so that the images are searchable. Instructions for adding alternate text should be provided in the software used to construct/view the PDF file. Please refer to the website http://www.section508.gov for further information.

Deficiencies Related to *In Vitro* Drug Release Testing

6. The quantitative capsule rupture (QCR) testing conducted using your proposed method, in 900 mL of 10% Labrasol in 0.1N HCl using USP Apparatus 2 (Paddle) with (b) (4) rpm at 37°C ± 0.5°C, is not sufficiently discriminatory, based on the release profile submitted for your test product, Omega-3-Acid Ethyl Esters Capsules, 1 g, comparing it with the reference product, GlaxoSmithKline's Lovaza® Capsules, 1 g.

   Based on the QCR data submitted by you for your test product, the DBI suggests you modify your proposed method by using (b) (4) paddle speeds such as 50 rpm, 75 rpm and 100 rpm, and/or lower Labrasol concentration, as follows:

Medium:	Labrasol in 0.1N HCl at 1%, 2%, 5%, 8%, 10% etc.
Apparatus:	USP Apparatus 2 (Paddle)

Speed: 50, 75 and 100 rpm
Volume: 900 mL
Temperature: 37°C ± 0.5°C
Sampling times: 5, 10, 15, 30, 45, and 60 minutes until at least 80% of the drug is released from the dosage form.

Please be advised that for USP Apparatus 2, when used for this dosage form, the sampling probes should remain immersed in the dissolution medium throughout the duration of testing in order to obtain reproducible results. The use of a sinker with USP Apparatus 2 may be considered in preventing the capsules from floating to the top.

Alternatively, you may consider using different surfactants and/or the USP Apparatus 4 (flow-through cell) as suggested in the draft guidance.

7. The DBI will evaluate the method development and optimization data as well as the complete data of the test and reference products obtained for 12 units per product, based on the most appropriate procedure, and determine the most suitable QCR method and specification for your test product.

Deficiency Related to the Test Product Formulation

8. Please provide the quantitative amount of each component of your Soft Gelatin Capsule Shell and White Printing Ink ((b) (4)) per capsule in your test formulation.

LABELING

Labeling Deficiencies determined on August 9, 2013 based on your submission dated March 8, 2010, March 4, 2011 and December 27, 2012:

1. CONTAINER
   a. Upon further consideration, please add the expression of strength "1 gram*" to the principal display panel and add an asterisk immediately before the "*Each capsule contains…" statement on the side panel.

   b. Revise "Each capsule contains 1 g…" to read "*Each capsule contains 1 gram…"

   c. Add "Protect from light" to the storage statement.

2. PHYSICIAN INSERT
   a. GENERAL COMMENT: Due to changes in the insert labeling for the reference listed drug Lovaza® (omega-3-acid ethyl esters) Capsules by GlaxoSmithKline, (NDA 021654/S-037) approved June 26, 2013, please revise your labeling to be in accordance with the reference listed drug labeling. If you are unable to obtain this labeling at the Drugs@FDA website

(http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm), please contact the labeling reviewer, Betty Turner (betty.turner@fda.hhs.gov).

b. Please revise "1 g" to read "1 gram" throughout your insert.

c. Please confirm if the following statement accurately reflects your drug product: These are predominantly a combination of ethyl esters of eicosapentaenoic acid (EPA- approximately 465 mg) and docosahexaenoic acid (DHA- approximately 375 mg).

3. PATIENT INFORMATION LEAFLET
Please ensure that your leaflet is in accordance with the RLD approved on June 26, 2013.

4. SPL
Please submit your labeling in SPL format. Please also update to be in accordance with the most recently approved labeling for the RLD.

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug's labeling with all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the Electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

FACILITY INSPECTIONS

We have not yet completed inspection(s)/compliance evaluation of your manufacturing facility(s) named or referenced in this ANDA. We must perform a complete evaluation of the information associated with the inspection before determining that the site(s) are satisfactory and this ANDA may be approved.

OTHER

A partial response to this letter will not be processed as a resubmission and will not start a new review cycle. The resubmission to this will be considered to represent a Minor AMENDMENT. The designation as a **RESUBMISSION/AFTER ACTION- *MINOR AMENDMENT*** should appear prominently in your cover letter. In addition, please designate in bold on your cover letter each review discipline (Chemistry, Labeling, Bioequivalence, Microbiology, Clinical) you are providing responses to.

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your

lack of response a request to withdraw the ANDA under 21 CFR 314.65. You may also request an extension of time in which to resubmit the ANDA. A resubmission response must fully address all the deficiencies listed.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dose form (FDFs) or active pharmaceutical ingredient (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

The drug product may not be legally marketed until you have been notified in writing that this ANDA is approved.

If you have any questions, call Robert Gaines, Regulatory Project Manager, at 240-276-8495.

Sincerely yours,

{See appended electronic signature page}

Kathleen Uhl, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

ROBERT L WEST

08/13/2013

Deputy Director, Office of Generic Drugs, for
Kathleen Uhl, M.D.

QUALITY DEFICIENCY - MINOR

ANDA 091028

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Teva Pharmaceuticals USA

TEL: (215) 591-3141

ATTN: Philip Erickson

FAX: (215) 591-8812

FROM: Leigh Ann Sears

FDA CONTACT PHONE: (240) 276-8453

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated November 10, 2008, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Omega-3-Acid Ethyl Esters Capsules, 1 g.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **2** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.
If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

III. List of Deficiencies to be communicated:

ANDA: 091028
APPLICANT: TEVA Pharmaceuticals USA
DRUG PRODUCT: Omega-3-Acid Ethyl Esters Capsules, 1 g

The deficiencies presented below represent a Minor deficiency.

A. Deficiencies:

(b) (4)

Upon receiving the above requested data a complete CMC review of the application will be undertaken.

Sincerely yours,

{See appended electronic signature}

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

LEIGH A SEARS
06/07/2011

LAXMA R NAGAVELLI
06/07/2011
Signed for Vilayat A Sayeed, PhD

Telephone Fax

ANDA 91-028

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8986

TO: TEVA Pharmaceuticals USA TEL: (215) 591-3141

ATTN: Philip Erickson FAX: (215) 591-8812

FROM: Ann Vu

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Omega- 3 Acid Ethyl Esters Capsules, 1 gram

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

Labeling Comments

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 91-028 Date of Submission: June 3, 2009
Applicant's Name: TEVA Pharmaceuticals USA
Established Name: Omega 3-Acid Ethyl Esters Capsule, 1 gram

Labeling Deficiencies:

1. **GENERAL COMMENT**

   Please address the M-87 exclusivity.

2. **CONTAINER**: (30's, 120's)
   Please delete "1 g" from the principal display panel.

3. **INSERT:**
   Please revise your insert in accordance with the most recently approved RLD, Lovaza labeling (021654/S-022). Please refer to the Drugs@FDA website for the RLD labeling.

4. **PATIENT PACKAGE INSERT:**
   Acceptable in draft.

Submit labels and labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with the RLD labeling with all differences annotated and explained.

{See appended electronic signature page}

_____
Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91028	ORIG-1	TEVA PHARMACEUTICALS USA	OMEGA-3-ACID ETHYL ESTERS

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/s/

THUYANH VU
01/21/2010

JOHN F GRACE
01/25/2010

BIOEQUIVALENCE AMENDMENT

ANDA 91-028

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Teva Pharmaceuticals USA TEL: (215) 591-3141

ATTN: Philip Erickson FAX: (215) 591-8812

FROM: Nam J. Chun FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on November 10, 2008, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Omega-3-Acid Ethyl Esters Capsules, 1 gram.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **two** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalence Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format.
This will improve document availability to review staff.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.
If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 91-028

APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Omega-3-Acid Ethyl Esters Capsules, 1 gram

The Division of Bioequivalence (DBE) has completed its review of the disintegration testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted at a later date. The following deficiency has been identified:

1. Currently, the DBE recommends a quantitative rupture test method be used to evaluate the *in vitro* performance of the drug product. Please develop your own quantitative capsule rupture method which should be discriminating to detect potential differences between the test and reference products. Please measure drug release of Eicosapentaenoic acid (EPA) and Docosahecaenoic acid (DHA). You may consider trying the following method:

Apparatus:	USP apparatus I (basket)
Speed:	100 rpm
Medium:	Water with a low concentration of surfactant
Volume:	900 mL
Sampling:	Once every 15 minutes until at least 80% of the labeled amount of Eicosapentaenoic acid (EPA) and Docosahecaenoic acid (DHA) is dispersed in the media
Number of Units Tested:	12

   If necessary, we suggest you try varying the medium volume, changing the rotational speed, adjusting the concentration of surfactant used, and/or using USP Apparatus II (paddles) instead of Apparatus I. If all capsules tested rupture in less than one hour, it may be necessary to sample more frequently to adequately characterize the capsule rupture rate and profile. Please provide individual capsule data as well as the test summary data such as mean, range and % coefficient of variation (CV) at each time point. The summary of the quantitative rupture testing data should also be provided in eCTD-formatted tables.

2. Please provide long term storage stability data of free eicosapentaenoic acid and free docosahexaenoic acid in frozen plasma to cover the maximum storage time of the study samples for free eicosapentaenoic acid and free docosahexaenoic acid assay, which is at least 104 days. Please also provide long term storage stability data of eicosapentaenoic acid and docosahexaenoic acid in frozen plasma to cover the maximum storage time of the study samples for eicosapentaenoic acid and docosahexaenoic acid assay, which is at least 80 days.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Dale Conner

5/6/2009 02:18:52 PM

Telephone Fax

ANDA 91-028

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8986

TO: TEVA Pharmaceuticals USA

TEL: (215) 591-3141

ATTN: Philip Erickson

FAX: (215) 591-8812

FROM: Ann Vu

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Omega- 3 Acid Ethyl Esters Capsules, 1 gram

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

Labeling Comments

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 91-028 Date of Submission: November 10, 2008

Applicant's Name: TEVA Pharmaceuticals USA

Established Name: Omega 3-Acid Ethyl Esters Capsule, 1 gram

Labeling Deficiencies:

1. **CONTAINER**: (30's, 120's)

   a. The manufacturer of this product is Banner, yet there is no mention of Banner on the labels. According to 21 CFR 201.1(h)(2), "The appearance on a drug product label of a person's name without qualification is a representation that the named person is the sole manufacturer of the product. That representation is false and misleading, and the drug product is misbranded under section 502(a) of the act, if the person is not the manufacturer of the product in accordance to this section". Please revise your labels by adding "Manufactured for TEVA..." or "Manufactured by Banner..."

   b. We encourage adding the statement "Pharmacist: please dispense with patient package insert".

2. **INSERT:**

   a. DESCRIPTION: Please revise to read "4 mg alpha-tocopherol"

   b. CLINICAL STUDIES: Table 1, please format the rows correctly so that the numbers is shown on one line (e.g "137" vs. "13)

      7"

   c. Revise the subsection "DRUG ABUSE" to "DRUG ABUSE AND DEPENDENCE".

3. **PATIENT PACKAGE INSERT:**

   Please submit the patient package insert.

Submit final printed labeling electronically. We refer you to the http://www.fda.gov/oc/datacouncil/spl.html website for guidance.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

{See appended electronic signature page}

_____
Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

John Grace
4/21/2009 12:07:42 PM
for Wm Peter Rickman

COMPLETE RESPONSE -- MAJOR

ANDA 91-028

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Teva Pharmaceuticals USA TEL: (215) 591-3141

ATTN: Philip Erickson FAX: (215) 591-8812

FROM: Jeanne Skanchy FDA CONTACT PHONE: (240) 276-8467

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated November 10, 2008, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Omega-3-Acid Ethyl Esters Capsules, 1 g.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

We have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachments (**2** pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. Upon OGD's acceptance for filing of your ANDA, it was determined that an adequate amount of information was submitted to allow for review of your Bioequivalence and Microbiology data. You will be notified in a separate communication of any further deficiencies identified during our review of your Bioequivalence and Microbiology data. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.
If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 91-028 APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Omega-3-Acid Ethyl Esters Capsules, 1 g

The deficiencies presented below represent MAJOR deficiencies:

A. Deficiencies:

1. Please be informed that sufficient information has not been provided in your ANDA submission to facilitate a complete CMC review. We request that the following data be provided to facilitate the CMC review:

Sincerely yours,

(See appended electronic signature page)

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Robert Iser
3/10/2009 11:52:04 AM
signed for V. Sayeed

Memo to File

Date: 3/10/2009

To: ANDAs 90-973, 91-018 and 91-028
Omega 3 Acid Ethyl Ester Capsules, 1.0 gram
ANDA submissions (filed)

From: Robert Iser, Team Leader, CMC Review Team 12
RE: Major Amendment

After discussion with the Team, Division, Regulatory Support, and Science Group, it was decided that due to insufficient characterization of the active, as compared to the current RLD, all sponsors will receive a major amendment letter without a CMC review of the submitted ANDA or associated DMF(s).

The letter text will be as follows:

> Please be informed that sufficient information has not been provided in your ANDA submission to facilitate a complete CMC review. We request that the following data be provided to facilitate the CMC review:
>
> a. (b) (4)
>
> b.

The next review cycle will include a CMC review of the response to the above request and the previously submitted information, as applicable, as well as the associated DMF(s).

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/s/

Robert Iser

3/10/2009 08:06:05 AM

CHEMIST

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
**** For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
***** A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ *****

ANDA #: 91-028 **FIRM NAME**: TEVA PHARMACEUTICALS

PIV: YES **Electronic or Paper Submission:** CTD FORMAT PAPER

RELATED APPLICATION(S): NA

First Generic Product Received? NO

DRUG NAME: OMEGA 3- ACID ETHYL ESTER

DOSAGE FORM: CAPSULES, 1 GRAM

Random Queue: 12

Bio Assignments:		**Micro Review (No)**
☒ **BPH**	☐ **BCE**	
☐ **BST**	☒ **BDI**	

Chem Team Leader: Iser, Robert Chem PM: Jeanne Skanchy Labeling Reviewer: Ann Vu
Bio PM: Lizzie Sanchez (Acting PM)

Letter Date: NOVEMBER 10, 2008 **Received Date**: NOVEMBER 10, 2008

Comments: EC- 1 YES **On Cards:** YES
Therapeutic Code: 3031600 LIPID ALTERING AGENTS

Archival copy: CTD FORMAT PAPER **Sections** I
Review copy: YES E-Media Disposition: YES SENT TO EDR
Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Iain Margand Date 2/27/2009	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**

Supervisory Concurrence/Date: _____ **Date:** _____

ADDITIONAL COMMENTS REGARDING THE ANDA:
**** See Bio Filing Review below****

****Initially there had been discussion to Refuse Omega-3 applications based on the potential for Pharmaceutical Equivalence issues that may arise with this product. However, a decision has been made to allow the applications to be filed and the PE issue will become a review issue.**

Contact: Pilip Erickson

RE: PHARMACEUTICAL EQUIVALENCE ISSUE in Filing for ANDAs of Omega 3-Acid Ethyl Esters Capsule Drug Products and Bioequivalence Review of F...

File Edit View Insert Format Tools Actions Help Toolbars Adobe PDF

Reply | Reply to All | Forward

You forwarded this message on 2/3/2009 9:54 AM.

From: Li, Bing Sent: Mon 2/2/2009 4:22 PM

To: Nguyen, Hoainhon T; Shimer, Martin

Cc: Conner, Dale P; Yu, Lawrence; Adams, Wallace P; Sanchez, Aida L; Dandamudi, Suman*; Gong, Li; Chun, Nam; Margand, Iain; Howard, Eda; Li, Bing

Subject: RE: PHARMACEUTICAL EQUIVALENCE ISSUE in Filing for ANDAs of Omega 3-Acid Ethyl Esters Capsule Drug Products and Bioequivalence Review of First Generic Checklists

Please note that DBE has completed all four checklist reviews for Omega 3-Acid Ethyl Esters Capsule and loaded them in DFS. Please refer to the reviews at DFS for details.

Thanks,

Bing

From: Nguyen, Hoainhon T
Sent: Friday, January 23, 2009 10:56 AM
To: Shimer, Martin
Cc: Conner, Dale P; Yu, Lawrence; Adams, Wallace P; Li, Bing; Sanchez, Aida L; Dandamudi, Suman*; Gong, Li; Chun, Nam; Margand, Iain; Howard, Eda; Nguyen, Hoainhon T
Subject: PHARMACEUTICAL EQUIVALENCE ISSUE in Filing for ANDAs of Omega 3-Acid Ethyl Esters Capsule Drug Products and Bioequivalence Review of First Generic Checklists

Good morning Marty,

The DBE1 is currently requested by your division to review the Bioequivalence Checklists of the following ANDAs: 91018 (Par), 91028 (Teva), 90973 (Apotex), (b) (4) (b) (4) of the above drug product. The Science Team has recently drafted a guidance for evaluating the generic versions of the drug product (attached). Per the draft guidance, in addition to the in vivo bioequivalence study and dissolution testing recommendations, there are recommendations related to the PHARMACEUTICAL EQUIVALENCE for the generic drug products. Per Wally and Lawrence of the Science Team, the issue of PHARMACEUTICAL EQUIVALENCE is complex and very important for this drug product, and should be addressed satisfactorily in each application ***before it is accepted for filing***.

Per Dale, the DBE1/Team 8 will review only the portion of the applications related to the in vivo bioequivalence and dissolution/rupture testing to make sure the in vivo and in vitro data are sufficiently presented for the purpose of demonstrating bioequivalence. Please consult the Science Team for the portion of the applications related to the PHARMACEUTICAL EQUIVALENCE of the drug products before accepting the ANDAs for filing.

Thanks,
Hoai

<< File: Omega-3-acid ethyl esters Draft Option Recommendations042108 (2).doc >>

From: Li, Bing
Sent: Thursday, January 22, 2009 2:43 PM
To: Howard, Eda; Margand, Iain
Cc: Li, Bing; Dandamudi, Suman*; Nguyen, Hoainhon T
Subject: First Generic Checklist ANDA91018

RE: PHARMACEUTICAL EQUIVALENCE ISSUE in Filing for ANDAs of Omega 3-Acid Ethyl Esters Capsule Drug Products and Bioequivalence Review of F...

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Reply | Reply to All | Forward

You forwarded this message on 2/3/2009 9:54 AM.

From: Li, Bing Sent: Mon 2/2/2009 4:22 PM

To: Nguyen, Hoainhon T; Shimer, Martin

Cc: Conner, Dale P; Yu, Lawrence; Adams, Wallace P; Sanchez, Aida L; Dandamudi, Suman*; Gong, Li; Chun, Nam; Margand, Iain; Howard, Eda; Li, Bing

Subject: RE: PHARMACEUTICAL EQUIVALENCE ISSUE in Filing for ANDAs of Omega 3-Acid Ethyl Esters Capsule Drug Products and Bioequivalence Review of First Generic Checklists

From: Li, Bing
Sent: Thursday, January 22, 2009 2:43 PM
To: Howard, Eda; Margand, Iain
Cc: Li, Bing; Dandamudi, Suman*; Nguyen, Hoainhon T
Subject: First Generic Checklist ANDA91018

Hi, Eda and Iain,

This email is pertaining a first generic checklist (see below) our team reviewed recently. Initially, we found the application acceptable for filing and indicated so in our review (loaded on DFS on ~1/7/09). However, we realize that we need to re-evaluate it. Please DO NOT send the letter to the firm at this moment. We will let you know the updates as soon as possible.

First Generic Checklist 91018
Omega 3 - Acid Ethyl Esters
Capsules
1 gm
Par Pharmaceutical, Inc.
Letter Date(s) November 10, 2008

.

Thanks,

Bing

Bing V. Li, Ph. D.

Lead Pharmacologist, Team Leader
Division of Bioequivalence

MODULE 1
ADMINISTRATIVE

ACCEPTABLE

1.1	**1.1.2 Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) RX YES	☒
1.2	**Cover Letter** Dated: NOVEMBER 10, 2008	☒
1.2.1	**Form FDA 3674 (PDF) YES** Box "B"	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** YES **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature) YES	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) YES Disclosure Statement (Form FDA 3455, submit copy to Regulatory Branch Chief) NA	☒
1.3.5	**1.3.5.1 Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2 Patent Certification** 1. Patent number(s) PIII '594 exp. 8/4/09 PIV '077 exp. 3/26/2013 2. Paragraph: (Check all certifications that apply) '667 exp. 8/27/2018 MOU ☐ PI ☐ PII ☐ PIII ☐ PIV ☒ (Statement of Notification) ☐ 3. Expiration of Patent(s): 8-27-2018 a. Pediatric exclusivity submitted? b. Expiration of Pediatric Exclusivity? 4. Exclusivity Statement: YES M-64 exp. 6/12/2010 NCE exp. 11/10/09	☒
1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient Y b. Type III DMF authorization letter(s) for container closure Y 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) N/A	☒
1.12.11	**Basis for Submission** NDA# : 21-654 Ref Listed Drug: LOVAZA Firm: SMITH KLINE BEECHAM ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use Same 2. Active ingredients Omega-3-acid ethyl esters 3. Inactive ingredients 4. Route of administration Oral 5. Dosage Form Gel Capsule 6. Strength 1 g	☒
1.12.14	**Environmental Impact Analysis Statement** YES	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): NA	☐
1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) Y **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained Y **1.14.1.3** 1 package insert (content of labeling) submitted electronically Y ***Was a proprietary name request submitted? No (If yes, send email to Labeling Reviewer indicating such.)	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained Y **1.14.3.3** 1 RLD label and 1 RLD container label Y	☒

MODULE 2
SUMMARIES ACCEPTABLE

2.3	**Quality Overall Summary (QOS)** **E-Submission: PDF** Y **Word Processed e.g., MS Word** Y A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www fda.gov/cder/ogd/ **Question based Review (QbR)** Y **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient)** **2.3.S.1 General Information** **2.3.S.2 Manufacture** **2.3.S.3 Characterization** **2.3.S.4 Control of Drug Substance** **2.3.S.5 Reference Standards or Materials** **2.3.S.6 Container Closure System** **2.3.S.7 Stability** **2.3.P** **Drug Product** **2.3.P.1 Description and Composition of the Drug Product** **2.3.P.2 Pharmaceutical Development** **2.3.P.2.1 Components of the Drug Product** **2.3.P.2.1.1 Drug Substance** **2.3.P.2.1.2 Excipients** **2.3.P.2.2 Drug Product** **2.3.P.2.3 Manufacturing Process Development** **2.3.P.2.4 Container Closure System** **2.3.P.3 Manufacture** **2.3.P.4 Control of Excipients** **2.3.P.5 Control of Drug Product** **2.3.P.6 Reference Standards or Materials** **2.3.P.7 Container Closure System** **2.3.P.8 Stability**	☒
2.7	**Clinical Summary (Bioequivalence)** **Model Bioequivalence Data Summary Tables** **E-Submission: PDF** Y **Word Processed e.g., MS Word** Y **2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1 Background and Overview** Table 1. Submission Summary Table 4. Bioanalytical Method Validation Table 6. Formulation Data **2.7.1.2 Summary of Results of Individual Studies** Table 5. Summary of In Vitro Dissolution **2.7.1.3 Comparison and Analyses of Results Across Studies** Table 2. Summary of Bioavailability (BA) Studies Table 3. Statistical Summary of the Comparative BA Data **2.7.1.4 Appendix** **2.7.4.1.3 Demographic and Other Characteristics of Study Population** Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study **2.7.4.2.1.1 Common Adverse Events** Table 8. Incidence of Adverse Events in Individual Studies	☒

MODULE 3

3.2.S DRUG SUBSTANCE ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1 Nomenclature** **3.2.S.1.2 Structure** **3.2.S.1.3 General Properties**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Name and Full Address(es)of the Facility(ies) Y 2. Function or Responsibility Y 3. Type II DMF number for API DMF# (b) (4) 4. CFN or FEI numbers	☒
3.2.S.3	**Characterization** Refer to DMF# (b) (4)	☐
3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1 Specification** Testing specifications and data from drug substance manufacturer(s) Y **3.2.S.4.2 Analytical Procedures** Y **3.2.S.4.3 Validation of Analytical Procedures** Y 1. Spectra and chromatograms for reference standards and test samples Y 2. Samples-Statement of Availability and Identification of: a. Drug Substance Y b. Same lot number(s) Y **3.2.S.4.4 Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) Y 2. Applicant certificate of analysis Y **3.2.S.4.5 Justification of Specification** Y	☒
3.2.S.5	**Reference Standards or Materials**	☒
3.2.S.6	**Container Closure Systems** Refer to DMF# (b) (4)	☐
3.2.S.7	**Stability** Refer to DMF# (b) (4)	☐

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1. Unit composition Y 2. Inactive ingredients and amounts are appropriate per IIG see attached Refer to DMF# 14194 for information on Gelatin Capsules	☒
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report	☒
3.2.P.3	**Manufacture** **3.2.P.3.1 Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) YES 2. CGMP Certification: YES 3. Function or Responsibility YES 4. CFN or FEI numbers **3.2.P.3.2 Batch Formula** Y **3.2.P.3.3 Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process Y 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified (b) (4) capsules 3. If sterile product: Aseptic fill / Terminal sterilization N/A 4. Reprocessing Statement Y **3.2.P.3.4 Controls of Critical Steps and Intermediates** Y **3.2.P.3.5 Process Validation and/or Evaluation** N/A 1. Microbiological sterilization validation 2. Filter validation (if aseptic fill)	☒
3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified Y **3.2.P.4.1 Specifications** 1. Testing specifications (including identification and characterization) Y 2. Suppliers' COA (specifications and test results) Y **3.2.P.4.2 Analytical Procedures** Y **3.2.P.4.3 Validation of Analytical Procedures** N/A/ - USP/NF **3.2.P.4.4 Justification of Specifications** Applicant COA Y	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1 Specification(s)** Y **3.2.P.5.2 Analytical Procedures** Y **3.2.P.5.3 Validation of Analytical Procedures** see 3.2.R.3.P Samples - Statement of Availability and Identification of: 1. Finished Dosage Form Y 2. Same lot numbers Y **3.2.P.5.4 Batch Analysis** Certificate of Analysis for Finished Dosage Form lot# P080602 **3.2.P.5.5 Characterization of Impurities** Y **3.2.P.5.6 Justification of Specifications** Y	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) Y 2. Components Specification and Test Data Y 3. Packaging Configuration and Sizes 120 cc and 400 cc plastic bottles 4. Container/Closure Testing Y 5. Source of supply and suppliers address Y	☒
3.2.P.8	**3.2.P.8.1 Stability (Finished Dosage Form)** 1. Stability Protocol submitted Y 2. Expiration Dating Period 24 months **3.2.P.8.2 Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments Y **3.2.P.8.3 Stability Data** 1. 3 month accelerated stability data Y – no long term data provided 2. Batch numbers on stability records the same as the test batch lot# P080602	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S Executed Batch Records for drug substance (if available) N/A** **3.2.R.2.S Comparability Protocols N/A** **3.2.R.3.S Methods Validation Package YES** Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) Batch Reconciliation and Label Reconciliation see attached Theoretical Yield Actual Yield Packaged Yield **3.2.R.1.P.2 Information on Components** N/A **3.2.R.2.P Comparability Protocols** N/A **3.2.R.3.P Methods Validation Package** see 3.2.R.3.S Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 5

CLINICAL STUDY REPORTS

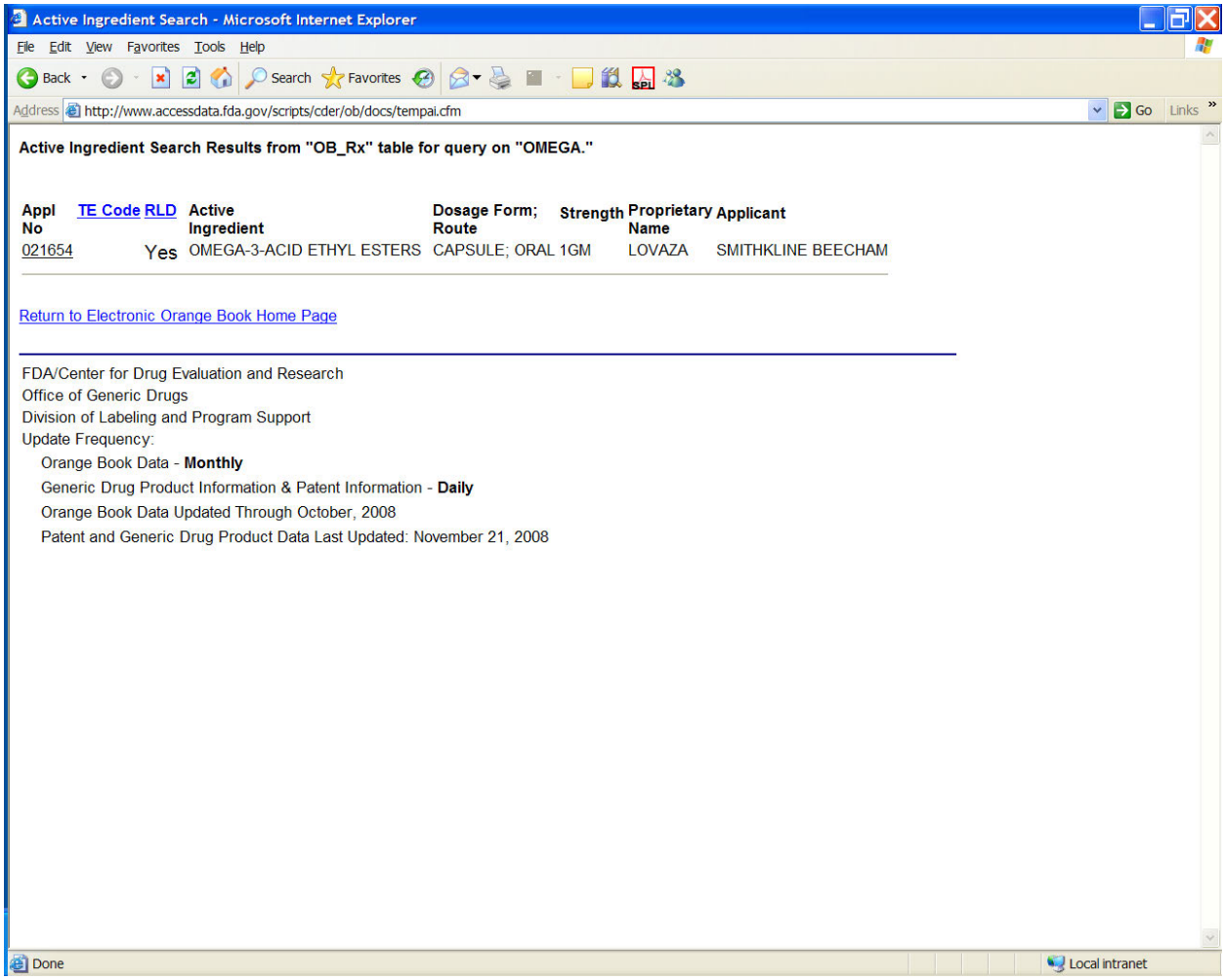
ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☐
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) N/A b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) N/A **2. Lot Numbers of Products used in BE Study(ies):** lot# P080602-B2 **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒

	5.3.1.2 Comparative BA/BE Study Reports 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. Summary Bioequivalence tables: Table 10. Study Information Table 12. Dropout Information Table 13. Protocol Deviations **5.3.1.3** **In Vitro-In-Vivo Correlation Study Reports** 1. Summary Bioequivalence tables: Table 11. Product Information Table 16. Composition of Meal Used in Fed Bioequivalence Study **5.3.1.4** **Reports of Bioanalytical and Analytical Methods for Human Studies** 1. Summary Bioequivalence table: Table 9. Reanalysis of Study Samples Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples **5.3.7** **Case Report Forms and Individual Patient Listing**	☒
5.4	**Literature References**	☐
	Possible Study Types:	
Study Type	**IN-VIVO BE STUDY(IES) with PK ENDPOINTS** (i.e., fasting/fed/sprinkle) FASTING AND FED ON 1 GRAM 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) see attached 2. EDR Email: Data Files Submitted: YES SENT TO EDR 3. In-Vitro Dissolution: YES	☒
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐

Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming)	☐
Study Type	**IN-VIVO BE STUDY(IES) with PD ENDPOINTS** (e.g., topical corticosteroid vasoconstrictor studies) 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

Updated 8/11/2008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TE Code
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Active Ingredient
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Strength
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CAPSULE; ORAL
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LOVAZA
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FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
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Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through October, 2008
Patent and Generic Drug Product Data Last Updated: November 21, 2008
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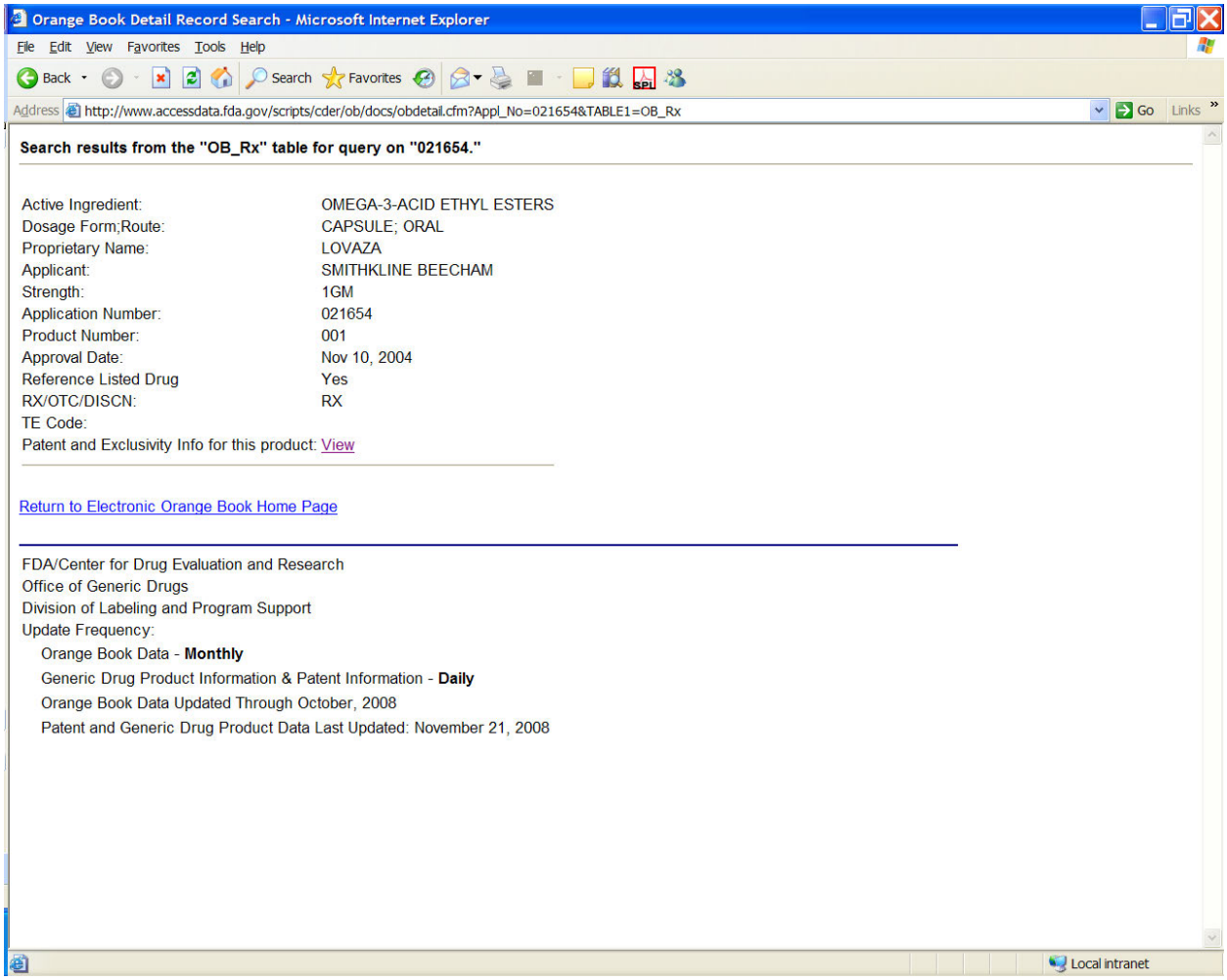
Orange Book Detail Record Search - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=021654&TABLE1=OB_Rx
Go Links
Search results from the "OB_Rx" table for query on "021654."
Active Ingredient: OMEGA-3-ACID ETHYL ESTERS
Dosage Form;Route: CAPSULE; ORAL
Proprietary Name: LOVAZA
Applicant: SMITHKLINE BEECHAM
Strength: 1GM
Application Number: 021654
Product Number: 001
Approval Date: Nov 10, 2004
Reference Listed Drug Yes
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: View
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
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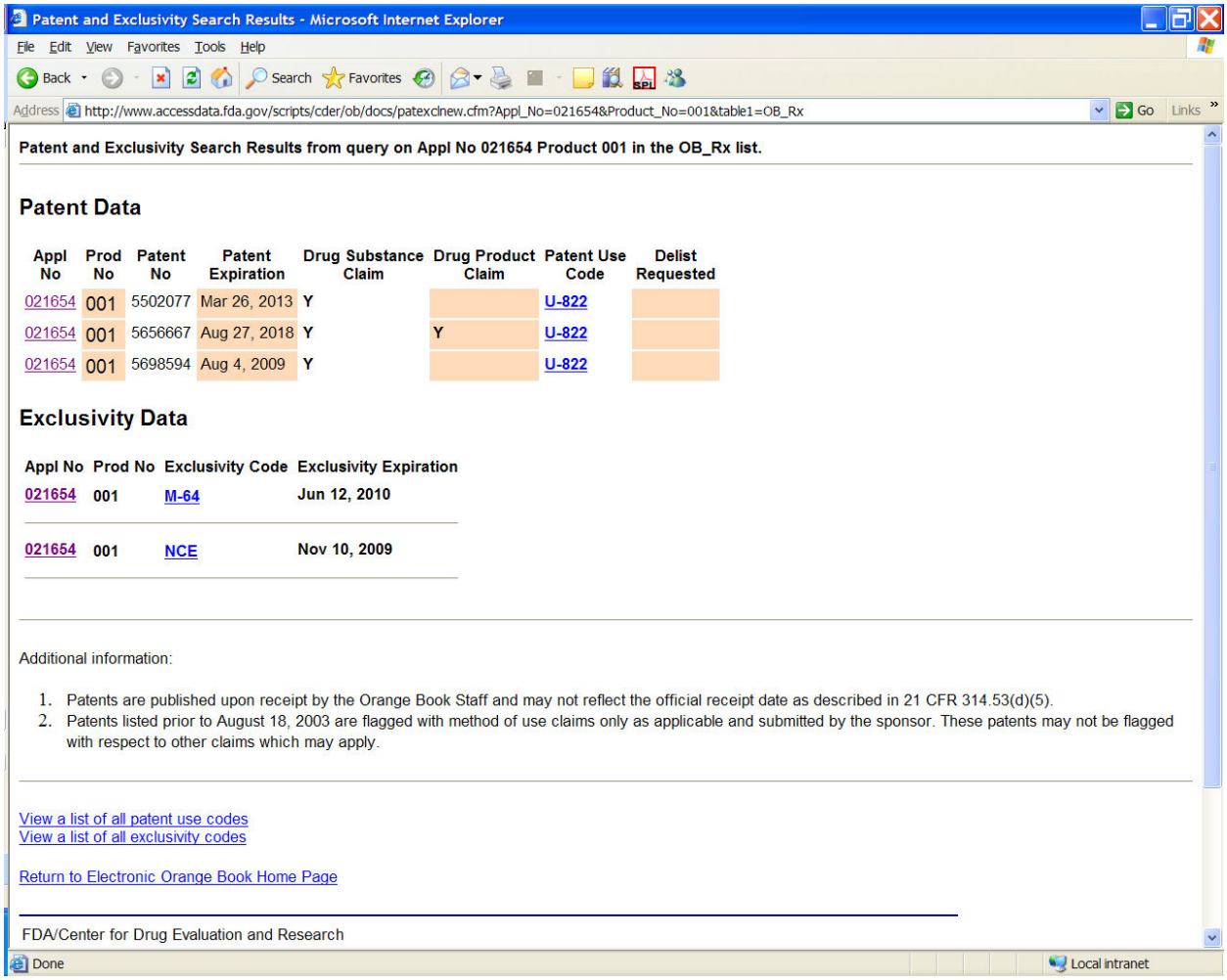

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Omega-3 Acid Ethyl Esters Dose (4 x 1000 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study (Study No. 2008-1829)				
Eicosapentaenoic acid (total lipids)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	947.91	959.65	98.78	94.24 - 103.53
Cmax	72.68	75.44	96.34	90.56 - 102.49
Docosahexaenoic acid (total lipids)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	290.59	290.30	100.10	88.92 - 112.68
Cmax	44.06	44.86	98.23	89.87 - 107.36
Eicosapentaenoic acid (free fatty acids)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	5.141	5.412	94.99	90.26 - 99.96
Cmax	0.806	0.873	92.27	84.58 - 100.67
Docosahexaenoic acid (free fatty acids)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	12.369	12.688	97.49	90.76 - 104.71
Cmax	2.364	2.515	93.97	85.27 - 103.56

Item Verified:	YES	NO	Information Sent/ Information Required	Comments/ Information to Request
Protocol	☒	☐		Appendix 16.1.1 Protocol and Consent Forms
Assay Methodology	☒	☐		Analytical Report, Section 6.1 Analytical Method
Procedure SOP	☒	☐		Appendix V Relevant SOPs
Methods Validation	☒	☐		Appendix 16.6 Validation Report
Study Results Ln/Lin	☒	☐		Module 5.3.1.2 Report Body: Synopsis
Adverse Events	☒	☐		Appendix 16.2.7 Adverse Event Listing; 12.2.1 Brief Summary of Adverse Events
IRB Approval	☒	☐		Appendix 16.1.3 Ethics Review Board
Dissolution Data	☒	☐		CTD Summary Tables-Table 5 Summary of In Vitro Dissolution Studies; Module 3.2.P.5.2 & 3.2.P.5.4 Rupture testing data for 12 individual units submitted
Pre-screening of Patients	☒	☐		Appendix 16.1.1 Protocol and Consent Forms, Section 9.3, Page 13
Chromatograms	☒	☐		Analytical Report, Page 81, Subjects 01, 02, 03 and Randomized Repeats
Consent Forms	☒	☐		Appendix 16.1.3 Ethics Review Board
Composition	☒	☐		Module 3.2.P.1 Description and Composition of the Drug

				Product
Summary of Study	☒	☐		Module 5.3.1.2 Report Body: Synopsis
Individual Data & Graphs, Linear & Ln	☒	☐		Appendix 16.2.6 Individual Efficacy Response Data
PK/PD Data Disk Submitted)	☒	☐		Datasets 2008-1779 & 2008-1829
Randomization Schedule	☒	☐		Appendix 16.1.7 Randomization Scheme
Protocol Deviations	☒	☐		Appendix 16.2.2 Protocol Deviations
Clinical Site	☒	☐		CTD Summary Tables-Table 10 Study Information
Analytical Site	☒	☐		CTD Summary Tables-Table 10 Study Information
Medical Records	☒	☐		Appendix 16.2.8 Clinically Significant Laboratory Results (b) (4) Adverse Event Listings
Clinical Raw Data	☒	☐		Appendix 16.2.8 Clinically Significant Laboratory Results (b) (4)
Test Article Inventory	☒	☐		Module 2.3 Quality Overall Summary
BIO Batch Size	☒	☐		CTD Summery Tables – Table 11 Product Information; Module 2.3 Quality Overall Summary

Assay of Active Content Drug	☒	☐		Analytical Report, Section 8.1 Subject Plasma Concentrations of Free Eicosapentaenoic Acid, Free Docosahexaenoic Acid, Eicosapentaenoic Acid and Docosahexaenoic Acid
Content Uniformity	☒	☐		CTD Summery Tables – Table 11 Product Information
Date of Manufacture	☒	☐		CTD Summery Tables – Table 11 Product Information
Exp. Date of RLD	☒	☐		CTD Summery Tables – Table 11 Product Information
BioStudy Lot Numbers	☒	☐		CTD Summery Tables – CTD Summery Tables – Table 11 Product Information
Statistics	☒	☐		CTD Summery Tables – Table 3.1 & 3.2 Statistical Summary of the Comparative Bioavailability Data; Module 5.3.1.2 Report Body: Synopsis; Appendix 16.1.1 Protocol and Consent Forms
Summary results provided by the firm indicate studies pass BE criteria	☒	☐		CTD Summery Tables – Table 3.1 & 3.2 Statistical Summary of the Comparative Bioavailability Data; Module 5.3.1.2 Report Body: Synopsis
Waiver requests for other strengths / supporting data	☐	☒		Not applicable

Lovaza® is a lipid regulating agent. It is indicated as an adjunct to diet to reduce triglyceride levels in adult patients with very high triglyceride levels. Each one gram capsule of Lovaza® (Omega 3-acid ethyl esters) contains at least 900 mg of the ethyl esters of omega-3 fatty acids. These are predominantly a combination of ethyl esters of Eicosapentaenoic acid (EPA- 465 mg) and Docosahexaenoic acid (DHA- 375 mg).

Additional Comments regarding the ANDA:

1. The test product is Omega-3 Acid Ethyl Esters Capsules, 1000 mg. Omega-3 Acid Ethyl Esters is an FDA-approved drug product to use as an adjunct to diet to reduce very high (≥ 500 mg/dL) triglyceride (TG) levels in adult patients.

2. The reference-listed drug (RLD) product is Lovaza® Capsules (brand of Omega-3 Acid Ethyl Esters Capsules), 1000 mg (NDA 21-654, Approval date: 11/10/2004) by GlaxoSmithKline.

3. The firm has conducted the pilot study on the RLD and submitted the results of Pharmacokinetic studies of Lovaza® 1000 mg capsules under fasting and fed conditions.

4. The RLD labeling of Lovaza® states that *"Patients should be placed on an appropriate lipid-lowering diet before receiving LOVAZA, and should continue this diet during treatment with LOVAZA. In clinical studies, LOVAZA was administered with meals."*

   Although the RLD labeling does not specify the drug product to be taken with meals, the DBE considers that a fed BE study is acceptable for this drug product for the following reasons:

   - In this application, Teva Pharmaceuticals USA conducted two pilot pharmacokinetic studies on the RLD under both fasting and fed conditions, and the results are as following:

EPA (Total lipids)

Parameter	Mean ± %CV	
	Lovaza® Capsules, 1000 mg	
	Fasting	Fed
AUC0-t (µg·hr/mL)	73.27 ± 104	1022.86 ± 34
Cmax (µg/mL)	5.22 ± 59	73.64 ± 11

DHA (Total lipids)

Parameter	Mean ± %CV	
	Lovaza® Capsules, 1000 mg	
	Fasting	Fed
AUC0-t (µg·hr/mL)	65.67 ± 91	348.99 ± 33
Cmax (µg/mL)	8.46 ± 43	50.53 ± 12

From the above results, very low level of EPA and DHA were observed in the fasting study, as compare to the fed study, which could render the fasting study results unreliable. The firm therefore performed the pivotal study under fed condition only.

- Similar results were observed in another application for Omega 3-Acid Ethyl Ester Capsules from Par Pharmaceuticals (ANDA 91-018). The overall absorption of the EPA and DHA appeared to be limited under fasting condition and thus the firm performed the pivotal study under fed condition.

- It is also noticed that the clinical studies for Lovaza® (Omega 3-Acid Ethyl Ester) Capsules by Smith Kline Beecham (NDA #: 21-654) were conducted only under fed condition.

Based on the above reasons, the DBE has recommended accepting for filing the fed BE study conducted for demonstration of bioequivalence.

5. The firm measured EPA and DHA levels from the free fatty acids of plasma and from the plasma total lipids. Since endogenous levels of EPA and DHA are present, so the firm measured the concentrations in 24 hours prior to dosing and were used to adjust for baseline post-dose levels time-point by time-point.

6. The Pharmacokinetic parameters were estimated based on baseline adjusted EPA and DHA levels from total lipids and from free fatty acids of plasma for each subject.

   EPA (total lipids), N= 80 (point estimate and 90% confidence intervals) are:
   LAUCT = 98.78% (94.24 - 103.53%), and LCmax = 96.34% (90.56 - 102.49%).

   EPA (free fatty acids), N= 80 (point estimate and 90% confidence intervals) are:
   LAUCT = 94.99% (90.26 - 99.96%), and LCmax = 92.27% (84.58 - 100.67%).

   DHA (total lipids), N= 80 (point estimate and 90% confidence intervals) are:
   LAUCT = 100.10% (88.92 - 112.68%), and LCmax = 98.23% (89.87 - 107.36%).

   DHA (free fatty acids), N= 80 (point estimate and 90% confidence intervals) are:
   LAUCT = 97.49% (90.76 - 104.71%), and LCmax = 93.97% (85.27 - 103.56%).

7. **There is currently no control document review or Bioequivalence Recommendation guidance for Omega 3-Acid Ethyl Ester Capsules. OGD Science Staff has drafted the bioequivalence recommendations for this product (shown below). However this is a "DRAFT ONLY" and not yet finalized.**

(b) (4)

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(b) (4)

[redacted]

Dissolution Test Method and Sampling Times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.fda.gov/cder/ogd/index.htm. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products.

(b) (4)

[redacted]

Additional Comments:

1. The draft guidance recommends for the BE studies, drug treatment be conducted for 7 days to reach the steady state i.e **multiple doses** should be administered. The appropriate parameters for BE statistics are increasing in maximum blood EPA and DHA concentration (Cmaxss) and increasing in area under the blood EPA and DHA concentration versus time curve [AUCss(0-tau)] from day prior to drug treatment to the day after reaching the steady state. These recommendations were made based on the NDA 21-654.

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4. Based on this rationale, DBE recommends that the Rupture Test should be conducted on this product, and accepts the firm's rupture test results.

Note to the Regulatory Support Staff: Please note that the DBE1/Team 8 has reviewed only the portion of the application related to the in vivo bioequivalence and dissolution/rupture testing to make sure the in vivo and in vitro data are sufficiently presented for the purpose of demonstrating bioequivalence. Please consult the Science Team for the portion of the application related to the PHARMACEUTICAL EQUIVALENCE of the drug products before accepting the ANDA for filing.

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/s/

Martin Shimer

3/9/2009 10:44:17 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 91-028

TEVA Pharmaceuticals USA
Attention: Philip Erickson
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Omega-3-Acid Ethyl Esters Capsules, 1 g

DATE OF APPLICATION: November 10, 2008

DATE (RECEIVED) ACCEPTABLE FOR FILING: November 10, 2008

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;

  2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a copy of a court order or judgment or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Martin Shimer, Chief, Regulatory Support Branch, at (240) 276-8419.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Jeanne Skanchy
Project Manager
240-276-8467

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Martin Shimer
3/9/2009 10:43:45 AM
Signing for Wm Peter Rickman

BIOEQUIVALENCE CHECKLIST
for Application Completeness of First Generic ANDA

ANDA# 91-028 **FIRM NAME** Teva Pharmaceuticals USA

DRUG NAME Omega-3 Acid Ethyl Esters Capsules, 1.0 gram

DOSAGE Capsule
SUBJ: Request for examination of Bioequivalence Study

	Summary of Findings by Division of Bioequivalence
☒	**Study meets statutory requirements**
☐	**Study does NOT meet statutory requirements**
	Reason:
☐	**Waiver meets statutory requirements**
☐	**Waiver does NOT meet statutory requirements**
	Reason:

RECOMMENDATION: ☒ **COMPLETE** ☐ **INCOMPLETE**

Reviewed by:

Li Gong
Reviewer Date: _____

Bing Li
Team Leader Date: _____

Item Verified:	**YES**	**NO**	**Information Sent/ Information Required**	**Comments/ Information to Request**
Protocol	☒	☐		Appendix 16.1.1 Protocol and Consent Forms
Assay Methodology	☒	☐		Analytical Report, Section 6.1 Analytical Method
Procedure SOP	☒	☐		Appendix V Relevant SOPs
Methods Validation	☒	☐		Appendix 16.6 Validation Report
Study Results Ln/Lin	☒	☐		Module 5.3.1.2 Report Body: Synopsis
Adverse Events	☒	☐		Appendix 16.2.7 Adverse Event Listing; 12.2.1 Brief Summary of Adverse Events
IRB Approval	☒	☐		Appendix 16.1.3 Ethics Review Board
Dissolution Data	☒	☐		CTD Summary Tables-Table 5 Summary of In Vitro Dissolution Studies; Module 3.2.P.5.2 & 3.2.P.5.4 Rupture testing data for 12 individual units submitted
Pre-screening of Patients	☒	☐		Appendix 16.1.1 Protocol and Consent Forms, Section 9.3, Page 13
Chromatograms	☒	☐		Analytical Report, Page 81, Subjects 01, 02, 03 and Randomized Repeats
Consent Forms	☒	☐		Appendix 16.1.3 Ethics Review Board
Composition	☒	☐		Module 3.2.P.1 Description and Composition of the Drug

				Product
Summary of Study	☒	☐		Module 5.3.1.2 Report Body: Synopsis
Individual Data & Graphs, Linear & Ln	☒	☐		Appendix 16.2.6 Individual Efficacy Response Data
PK/PD Data Disk Submitted)	☒	☐		Datasets 2008-1779 & 2008-1829
Randomization Schedule	☒	☐		Appendix 16.1.7 Randomization Scheme
Protocol Deviations	☒	☐		Appendix 16.2.2 Protocol Deviations
Clinical Site	☒	☐		CTD Summary Tables-Table 10 Study Information
Analytical Site	☒	☐		CTD Summary Tables-Table 10 Study Information
Medical Records	☒	☐		Appendix 16.2.8 Clinically Significant Laboratory Results (b) (4) Adverse Event Listings
Clinical Raw Data	☒	☐		Appendix 16.2.8 Clinically Significant Laboratory Results Outside of Normal (b) (4)
Test Article Inventory	☒	☐		Module 2.3 Quality Overall Summary
BIO Batch Size	☒	☐		CTD Summery Tables – Table 11 Product Information; Module 2.3 Quality Overall Summary

Assay of Active Content Drug	☒	☐		Analytical Report, Section 8.1 Subject Plasma Concentrations of Free Eicosapentaenoic Acid, Free Docosahexaenoic Acid, Eicosapentaenoic Acid and Docosahexaenoic Acid
Content Uniformity	☒	☐		CTD Summery Tables – Table 11 Product Information
Date of Manufacture	☒	☐		CTD Summery Tables – Table 11 Product Information
Exp. Date of RLD	☒	☐		CTD Summery Tables – Table 11 Product Information
BioStudy Lot Numbers	☒	☐		CTD Summery Tables – CTD Summery Tables – Table 11 Product Information
Statistics	☒	☐		CTD Summery Tables – Table 3.1 & 3.2 Statistical Summary of the Comparative Bioavailability Data; Module 5.3.1.2 Report Body: Synopsis; Appendix 16.1.1 Protocol and Consent Forms
Summary results provided by the firm indicate studies pass BE criteria	☒	☐		CTD Summery Tables – Table 3.1 & 3.2 Statistical Summary of the Comparative Bioavailability Data; Module 5.3.1.2 Report Body: Synopsis
Waiver requests for other strengths / supporting data	☐	☒		Not applicable

Lovaza® is a lipid regulating agent. It is indicated as an adjunct to diet to reduce triglyceride levels in adult patients with very high triglyceride levels. Each one gram capsule of Lovaza® (Omega 3-acid ethyl esters) contains at least 900 mg of the ethyl esters of omega-3 fatty acids. These are predominantly a combination of ethyl esters of Eicosapentaenoic acid (EPA- 465 mg) and Docosahexaenoic acid (DHA- 375 mg).

Additional Comments regarding the ANDA:

1. The test product is Omega-3 Acid Ethyl Esters Capsules, 1000 mg. Omega-3 Acid Ethyl Esters is an FDA-approved drug product to use as an adjunct to diet to reduce very high (≥ 500 mg/dL) triglyceride (TG) levels in adult patients.

2. The reference-listed drug (RLD) product is Lovaza® Capsules (brand of Omega-3 Acid Ethyl Esters Capsules), 1000 mg (NDA 21-654, Approval date: 11/10/2004) by GlaxoSmithKline.

3. The firm has conducted the pilot study on the RLD and submitted the results of Pharmacokinetic studies of Lovaza® 1000 mg capsules under fasting and fed conditions.

4. The RLD labeling of Lovaza® states that "*Patients should be placed on an appropriate lipid-lowering diet before receiving LOVAZA, and should continue this diet during treatment with LOVAZA. In clinical studies, LOVAZA was administered with meals.*"

Although the RLD labeling does not specify the drug product to be taken with meals, the DBE considers that a fed BE study is acceptable for this drug product for the following reasons:

- In this application, Teva Pharmaceuticals USA conducted two pilot pharmacokinetic studies on the RLD under both fasting and fed conditions, and the results are as following:

EPA (Total lipids)

Parameter	**Mean ± %CV**	
	Lovaza® Capsules, 1000 mg	
	Fasting	**Fed**
AUC0-t (µg·hr/mL)	73.27 ± 104	1022.86 ± 34
Cmax (µg/mL)	5.22 ± 59	73.64 ± 11

DHA (Total lipids)

Parameter	**Mean ± %CV**	
	Lovaza® Capsules, 1000 mg	
	Fasting	**Fed**
AUC0-t (µg·hr/mL)	65.67 ± 91	348.99 ± 33
Cmax (µg/mL)	8.46 ± 43	50.53 ± 12

From the above results, very low level of EPA and DHA were observed in the fasting study, as compare to the fed study, which could render the fasting study results unreliable. The firm therefore performed the pivotal study under fed condition only.

- Similar results were observed in another application for Omega 3-Acid Ethyl Ester Capsules from Par Pharmaceuticals (ANDA 91-018). The overall absorption of the EPA and DHA appeared to be limited under fasting condition and thus the firm performed the pivotal study under fed condition.

- It is also noticed that the clinical studies for Lovaza® (Omega 3-Acid Ethyl Ester) Capsules by Smith Kline Beecham (NDA #: 21-654) were conducted only under fed condition.

Based on the above reasons, the DBE has recommended accepting for filing the fed BE study conducted for demonstration of bioequivalence.

5. The firm measured EPA and DHA levels from the free fatty acids of plasma and from the plasma total lipids. Since endogenous levels of EPA and DHA are present, so the firm measured the concentrations in 24 hours prior to dosing and were used to adjust for baseline post-dose levels time-point by time-point.

6. The Pharmacokinetic parameters were estimated based on baseline adjusted EPA and DHA levels from total lipids and from free fatty acids of plasma for each subject.

EPA (total lipids), N= 80 (point estimate and 90% confidence intervals) are:
LAUCT = 98.78% (94.24 - 103.53%), and LCmax = 96.34% (90.56 - 102.49%).

EPA (free fatty acids), N= 80 (point estimate and 90% confidence intervals) are:
LAUCT = 94.99% (90.26 - 99.96%), and LCmax = 92.27% (84.58 - 100.67%).

DHA (total lipids), N= 80 (point estimate and 90% confidence intervals) are:
LAUCT = 100.10% (88.92 - 112.68%), and LCmax = 98.23% (89.87 - 107.36%).

DHA (free fatty acids), N= 80 (point estimate and 90% confidence intervals) are:
LAUCT = 97.49% (90.76 - 104.71%), and LCmax = 93.97% (85.27 - 103.56%).

7. **There is currently no control document review or Bioequivalence Recommendation guidance for Omega 3-Acid Ethyl Ester Capsules. OGD Science Staff has drafted the bioequivalence recommendations for this product (shown below). However this is a "DRAFT ONLY" and not yet finalized.**

(b) (4)

[redacted]

Following this page, 2 Pages Withheld in Full as (b)(4)

Dissolution Test Method and Sampling Times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.fda.gov/cder/ogd/index.htm. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products.

Additional Comments:

1. The draft guidance recommends for the BE studies, drug treatment be conducted for 7 days to reach the steady state i.e **multiple doses** should be administered. The appropriate parameters for BE statistics are increasing in maximum blood EPA and DHA concentration (Cmaxss) and increasing in area under the blood EPA and DHA concentration versus time curve [AUCss(0-tau)] from day prior to drug treatment to the day after reaching the steady state. These recommendations were made based on the NDA 21-654.

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Outcome Page

ANDA 91-028

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
7278	11/10/2008	Paragraph 4	Paragraph 4 Checklist	1	1
				Bean Total:	1

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/s/

Bing Li

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : December 10, 2008

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

SUBJECT: Examination of the bioequivalence study submitted with an ANDA 91-028 for Omega-3 Acid Ethyl Esters Capsules, 1 gram to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to 21 USC 355(j)(5)(B)(iv).

Teva Pharmaceuticals USA. has submitted ANDA 91-028 for Omega-3 Acid Ethyl Esters Capsules, 1 gram. The ANDA contains a certification pursuant to 21 USC 355(j)(5)(B)(iv) stating that patent(s) for the reference listed drug will not be infringed by the manufacturing or sale of the proposed product. In order to accept an ANDA that contains the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study submitted by Teva Pharmaceuticals USA on November 10, 2008 for its Omega-3 Acid Ethyl Esters product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

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/s/

Eda Howard
12/10/2008 03:41:02 PM
APPLICATIONS EXA