

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
ANDA 091640

Name: Mesalamine Delayed-Release Tablets USP, 1.2g

Sponsor: Zydus Pharmaceuticals (USA) Inc.

Approval Date: June 12, 2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091640

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091640

APPROVAL LETTER



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 091640

ANDA APPROVAL

Zydus Pharmaceuticals (USA) Inc.
73 Route 31 North
Pennington, NJ 08534
Attention: Srinivas Gurram
Vice President and Head of Regulatory Affairs

Dear Sir:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 16, 2009, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Mesalamine Delayed-Release Tablets USP, 1.2 g.

Reference is also made to the complete response letter issued by this office on December 14, 2016, and to your amendment received on February 23, 2017.

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 Office of Bioequivalence has determined your Mesalamine Delayed-Release Tablets USP, 1.2 g, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Lialda Delayed-Release Tablets, 1.2 g, of Shire Development LLC (Shire). Your dissolution testing should be incorporated into the stability and quality control program using the FDA-recommended method and specification for your application (see enclosure).

The RLD upon which you have based your ANDA, Shire's Lialda Delayed-Release Tablets, 1.2 g, is subject to a period of patent protection. The following patent and expiration date is currently listed in the Agency's publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"):

U.S. Patent Number

Expiration Date

6,773,720 (the '720 patent)

June 8, 2020

Your ANDA contains a paragraph IV certification to the '720 patent under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that the patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Mesalamine Delayed-Release Tablets USP, 1.2 g, under this ANDA. You have notified the Agency that Zydus Pharmaceuticals (USA) Inc.

(Zydus) complied with the requirements of section 505(j)(2)(B) of the FD&C Act and that litigation was initiated within the statutory 45-day period against Zydus for infringement of the '720 patent in the United States District Court for the District of Delaware [Shire Development Inc., Shire Pharmaceutical Development Inc., Cosmo Technologies Limited, and Giuliani International Limited v. Cadila Healthcare Limited (d/b/a Zydus Cadila) and Zydus Pharmaceuticals (USA) Inc., Civil Action No. 1:10-cv-00581]. You have also notified the Agency that on September 16, 2016, the court entered a final judgment of non-infringement in Zydus' favor. You have further notified the Agency that the case was appealed to the United States Court of Appeals for the Federal Circuit and on May 9, 2017, the court affirmed the decision of the district court.

With respect to 180-day generic drug exclusivity, we note that Zydus was the first ANDA applicant for Mesalamine Delayed-Release Tablets USP, 1.2 g, to submit a substantially complete ANDA with a paragraph IV certification. Therefore, with this approval, Zydus may be eligible for 180 days of generic drug exclusivity for Mesalamine Delayed-Release Tablets USP, 1.2 g. This exclusivity, which is provided for under 505(j)(5)(B)(iv) of the FD&C Act, would begin to run from the date of the commercial marketing identified in section 505(j)(5)(B)(iv). The Agency notes that Zydus failed to obtain tentative approval of this ANDA within 30 months after the date of which the ANDA was filed. See section 505(j)(5)(D)(i)(IV) of the FD&C Act (forfeiture of exclusivity for failure to obtain tentative approval). The Agency is not, however, making a formal determination at this time of Zydus'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 Zydus begins commercial marketing of Mesalamine Delayed-Release Tablets USP, 1.2 g, or (b) at any time prior to the expiration of the '720 patent if Zydus has not begun commercial marketing. Please submit correspondence to this ANDA informing the Agency of the date commercial marketing begins.

Under section 506A of FD&C 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 and 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 FD&C Act.

REPORTING REQUIREMENTS

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

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling materials prior to publication or dissemination. Please note that these submissions are voluntary. To do so, submit, in triplicate, a cover letter requesting advisory comments, the

proposed materials in draft or mock-up form with annotated references, and the package insert (PI), Medication Guide, and patient PI (as applicable) to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

You must also submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

ANNUAL FACILITY FEES

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 1st 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.

CONTENT OF LABELING

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.

The Electronic Common Technical Document (eCTD) is CDER’s standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

Sincerely yours,

{See appended electronic signature page}

Heidi Lee, PharmD
Acting Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

ENCLOSURE:

DISSOLUTION

The “interim” dissolution specifications are as follows:

Method	Acid Stage A: 750 mL of 100 mM HCl (Acid Stage A) Buffer Stage B: 950 mL of Phosphate buffer, pH 6.4 (Buffer Stage B: A+ 200 mL 200 mM Na ₃ PO ₄) Buffer Stage C: 960 mL of Phosphate buffer, pH 7.2 (Buffer Stage C: B + 9 mL 2M NaOH adjusting pH with 2M NaOH or 2M HCl)
Apparatus	USP apparatus 2 (Paddle)
Speed	100 rpm
Specifications	Acid stage A: NMT (b)(4) 0% in 2 hours Buffer stage B: NMT (b)(4) 0% in 1 hour Buffer stage C: 1 hou NMT (b)(4) 0% 2 hours: (b)(4) 0% 6 hours: NLT (b)(4) 0%

The “interim” dissolution test(s) and tolerances should be finalized by submitting dissolution data for the first three production size batches. Data should be submitted as a Supplement – Changes Being Effected when there are no revisions to the “interim” specifications or when the final specifications are more stringent than the “interim” specifications. In all other instances, the information should be submitted in a Prior Approval Supplement.



Heidi
Lee

Digitally signed by Heidi Lee
Date: 6/05/2017 05:52:18PM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091640

LABELING



ZyGenerics

NDC 68382-362-64

ONCE DAILY

MESALAMINE

DELAYED-RELEASE

Tablets

1.2 g

Rx only

34 Tablets

Each delayed-release tablet contains 1.2 g of Mesalamine, USP

Usual Dosage: See package insert for complete prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Pharmacist: Dispense in a light, light-resistant container as defined in USP.

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Manufactured by:
Cadila Healthcare Ltd.
Ahmedabad, India

Distributed by:
Zydus Pharmaceuticals USA Inc.
Pennington, NJ 08534

Lot:

Exp:

Rev.: 05/11

85 x 40 mm



(b) (4)



ZyGenerics

NDC 68382-362-19

ONCE DAILY

MESALAMINE

DELAYED-RELEASE

Tablets

1.2 g

Rx only

120 Tablets

Each delayed-release tablet contains 1.2 g of Mesalamine, USP.

Usual Dosage: See package insert for complete prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Pharmacist: Dispense in a tight, light-resistant container as defined in USP.

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Manufactured by:
Cadila Healthcare Ltd.
Ahmedabad, India

Distributed by:
Zydus Pharmaceuticals USA Inc.
Pennington, NJ 08534

Lot:

Exp:

Rev.: 05/11

97 x 50.5 mm



(b) (4)



HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use mesalamine delayed-release tablets safely and effectively. See full prescribing information for mesalamine delayed-release tablets.

MESALAMINE Delayed-release Tablets, for oral use

Initial U.S. Approval: 1987

RECENT MAJOR CHANGES

Warnings and Precautions, Interference with Laboratory Tests (5.6), 08/2013

INDICATIONS AND USAGE

Mesalamine delayed-release tablets are locally acting 5-aminosalicylic acid (5-ASA) indicated for the induction of remission in adults with active, mild to moderate ulcerative colitis and for the maintenance of remission of ulcerative colitis. (1)

DOSAGE AND ADMINISTRATION

For induction of remission of active, mild to moderate ulcerative colitis, two to four 1.2 g tablets taken once daily with food. (1, 2) For maintenance of remission of ulcerative colitis, two 1.2 g tablets taken once daily with food. (1, 2)

DOSAGE FORMS AND STRENGTHS

Delayed-Release Tablets: 1.2 g (3)

CONTRAINDICATIONS

Patients with known hypersensitivity to salicylates or aminosaliclylates or to any of the ingredients of mesalamine delayed-release tablets. (4)

WARNINGS AND PRECAUTIONS

- Renal impairment may occur. Assess renal function at the beginning of treatment and periodically during treatment. (5.1)
- Mesalamine-induced acute intolerance syndrome has been reported. Observe patients closely for worsening of these symptoms while on treatment. (5.2)
- Use caution when treating patients who are hypersensitive to sulfasalazine. (5.3)
- Mesalamine-induced cardiac hypersensitivity reactions (myocarditis and pericarditis) have been reported. (5.3)

- Hepatic failure has been reported in patients with preexisting liver disease. Use caution when treating patients with liver disease. (5.4)
- Upper GI tract obstruction may delay onset of action. (5.5)
- Use of mesalamine may lead to spuriously elevated test results when measuring urinary normetanephrine by liquid chromatography with electrochemical detection. (5.6)

ADVERSE REACTIONS

- The most common adverse reactions (incidence $\geq 2\%$) are ulcerative colitis, headache, flatulence, liver function test abnormality, and abdominal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Zydus Pharmaceuticals USA Inc. at 1-877-993-8779 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Nephrotoxic agents including NSAIDs: renal reactions have been reported. (7.1)
- Azathioprine or 6-mercaptopurine: blood disorders have been reported. (7.2)

USE IN SPECIFIC POPULATIONS

- Renal impairment: Use mesalamine delayed-release tablets with caution in patients with a history of renal disease. (5.1, 7.1, 8.5, 13.2)
- Nursing Women: Caution should be exercised when administered to a nursing woman. (8.3)
- Geriatric Patients: Monitor blood cell counts in geriatric patients. (8.5)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

- INDICATIONS AND USAGE
- DOSAGE AND ADMINISTRATION
- DOSAGE FORMS AND STRENGTHS
- CONTRAINDICATIONS
- WARNINGS AND PRECAUTIONS
 - Renal Impairment
 - Mesalamine-Induced Acute Intolerance Syndrome

FULL PRESCRIBING INFORMATION

- INDICATIONS AND USAGE
Mesalamine delayed-release tablets are indicated for the induction of remission in patients with active, mild to moderate ulcerative colitis and for the maintenance of remission of ulcerative colitis.
- DOSAGE AND ADMINISTRATION
The recommended dosage for the induction of remission in adult patients with active, mild to moderate ulcerative colitis is two to four 1.2 g tablets taken once daily with a meal for a total daily dose of 2.4 g or 4.8 g. The recommended dosage for the maintenance of remission is two 1.2 g tablets taken once daily with a meal for a total daily dose of 2.4 g.
- DOSAGE FORMS AND STRENGTHS
Mesalamine Delayed-release Tablets, 1.2 g are pale red-brown, oval-shaped, biconvex, bevel film-coated tablets debossed with the "711" on one side and plain on other side.
- CONTRAINDICATIONS
Mesalamine delayed-release tablets are contraindicated in patients with known hypersensitivity to salicylates or aminosaliclylates or to any of the ingredients of mesalamine delayed-release tablets [see Warnings and Precautions (5.3), Description (11), Adverse Reactions (6.2)].
- WARNINGS AND PRECAUTIONS
 - Renal Impairment
Renal impairment, including minimal change nephropathy, acute and chronic interstitial nephritis, and, rarely, renal failure, has been reported in patients given products such as mesalamine delayed-release tablets that contain mesalamine or are converted to mesalamine. It is recommended that patients have an evaluation of renal function prior to initiation of mesalamine delayed-release tablets therapy and periodically while on therapy. Exercise caution when using mesalamine delayed-release tablets in patients with known renal dysfunction or a history of renal disease. In animal studies, the kidney was the principal organ for toxicity [see Drug Interactions (7.1) and Nonclinical Toxicology (13.2)].
 - Mesalamine-Induced Acute Intolerance Syndrome
Mesalamine has been associated with an acute intolerance syndrome that may be difficult to distinguish from an exacerbation of ulcerative colitis. Although the exact frequency of occurrence has not been determined, it has occurred in 3% of patients in controlled clinical trials of mesalamine or sulfasalazine. Symptoms include cramping, acute abdominal pain and bloody diarrhea, and sometimes fever, headache, and rash. Observe patients closely for worsening of these symptoms while on treatment. If acute intolerance syndrome is suspected, promptly discontinue treatment with mesalamine delayed-release tablets.
 - Hypersensitivity Reactions
Some patients who have experienced a hypersensitivity reaction to sulfasalazine may have a similar reaction to mesalamine delayed-release tablets or to other compounds that contain or are converted to mesalamine. Mesalamine-induced cardiac hypersensitivity reactions (myocarditis and pericarditis) have been reported with mesalamine delayed-release tablets and other mesalamine medications. Caution should be taken in prescribing this medicine to patients with conditions predisposing them to the development of myocarditis or pericarditis.
 - Hepatic Impairment
There have been reports of hepatic failure in patients with preexisting liver disease who have been administered mesalamine. Caution should be exercised when administering mesalamine delayed-release tablets to patients with liver disease.
 - Upper GI Tract Obstruction
Pyloric stenosis or other organic or functional obstruction in the upper gastrointestinal tract may cause prolonged gastric retention of mesalamine delayed-release tablets which would delay mesalamine release in the colon.
 - Interference with Laboratory Tests
Use of mesalamine may lead to spuriously elevated test results when measuring urinary normetanephrine by liquid chromatography with electrochemical detection because of the similarity in the chromatograms of normetanephrine and mesalamine's main metabolite, N-acetylamino salicylic acid (N-Ac-5-ASA). An alternative, selective assay for normetanephrine should be considered.

- ADVERSE REACTIONS
The most serious adverse reactions seen in mesalamine delayed-release tablets clinical trials or with other products that contain or are metabolized to mesalamine are:
 - Renal impairment, including renal failure [See Warnings and Precautions (5.1)]
 - Mesalamine-induced acute intolerance syndrome [See Warnings and Precautions (5.2)]
 - Hypersensitivity reactions [See Warnings and Precautions (5.3)]
 - Hepatic impairment, including hepatic failure [See Warnings and Precautions (5.4)]
- 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. Mesalamine delayed-release tablets have been evaluated in 1368 ulcerative colitis patients in controlled and open-label trials.
Induction of Remission
In two 8 week placebo-controlled clinical trials involving 535 ulcerative colitis patients, 356 received 2.4 g/day or 4.8 g/day mesalamine delayed-release tablets and 179 received placebo. The most frequent adverse reaction leading to discontinuation from mesalamine delayed-release tablets therapy was exacerbation of ulcerative colitis (0.8%). Pancreatitis occurred in less than 1% of patients during clinical trials and resulted in discontinuation of therapy with mesalamine delayed-release tablets in patients experiencing this event.
Adverse reactions occurring in mesalamine delayed-release tablets or placebo groups at a frequency of at least 1% in two 8 week, doubleblind, placebo-controlled trials are listed in Table 1. The most common adverse reactions with mesalamine delayed-release tablets 2.4 g/day and 4.8 g/day were headache (5.6% and 3.4%, respectively) and flatulence (4% and 2.8%, respectively).

Table 1 Adverse Reactions in Two Eight-Week Placebo-Controlled Trials Experienced by at Least 1 % of the Mesalamine Delayed-release Tablets Group and at a Rate Greater than Placebo*			
Adverse Reaction	Mesalamine Delayed-release Tablets 2.4 g/day (n = 177)	Mesalamine Delayed-release Tablets 4.8 g/day (n = 179)	Placebo (n = 179)
Headache	10 (5.6%)	6 (3.4%)	1 (0.6%)
Flatulence	7 (4%)	5 (2.8%)	5 (2.8%)
Liver Function Test Abnormal	1 (0.6%)	4 (2.2%)	2 (1.1%)
Alopecia	0	2 (1.1%)	0
Pruritus	1 (0.6%)	2 (1.1%)	2 (1.1%)

* Adverse reactions for which the placebo rate equalled or exceeded the rate for at least one of the mesalamine delayed-release tablets treatment groups were abdominal pain, dizziness, dyspepsia, and nausea. The following adverse reactions, presented by body system, were reported infrequently (less than 1%) by mesalamine delayed-release tablets-treated ulcerative colitis patients in the two controlled trials.
Cardiac Disorder
Tachycardia
Vascular Disorders
Hypertension, hypotension
Skin and Subcutaneous Tissue Disorders
Acne, prurigo, rash, urticaria
Gastrointestinal Disorders
Abdominal distention, colitis, diarrhea, pancreatitis, rectal polyp, vomiting
Investigations
Decreased platelet count
Musculoskeletal and Connective Tissue Disorders
Arthralgia, back pain

- Hypersensitivity Reactions
- Hepatic Impairment
- Upper GI Tract Obstruction
- Interference with Laboratory Tests

ADVERSE REACTIONS

- Clinical Trials Experience
- Postmarketing Experience

DRUG INTERACTIONS

- Nephrotoxic Agents, Including Non-Steroidal Anti-Inflammatory Drugs
 - Azathioprine or 6-mercaptopurine
- USE IN SPECIFIC POPULATIONS**
- Pregnancy
 - Nursing Mothers
 - Pediatric Use
 - Geriatric Use

OVERDOSAGE

DESCRIPTION

CLINICAL PHARMACOLOGY

- Mechanism of Action
- Pharmacodynamics
- Pharmacokinetics

NONCLINICAL TOXICOLOGY

- Carcinogenesis, Mutagenesis, Impairment of Fertility
- Animal Toxicology and/or Pharmacology

CLINICAL STUDIES

- Active, Mild to Moderate Ulcerative Colitis
- Maintenance of Remission in Patients with Ulcerative Colitis

HOW SUPPLIED/STORAGE AND HANDLING

PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from Full Prescribing Information are not listed.

Nervous System Disorders
Somnolence, tremor
Respiratory, Thoracic and Mediastinal Disorders
Pharyngolaryngeal pain
General Disorders and Administrative Site Disorders
Asthenia, face edema, fatigue, pyrexia
Ear and Labyrinth Disorders
Ear pain
Maintenance of Remission of Ulcerative Colitis
The dose evaluated in three studies of mesalamine delayed-release tablets given for the maintenance of remission in patients with ulcerative colitis was 1.2 g twice daily or 2.4 g/once daily. One of these studies was a 6-month double-blind comparator study while two were 12-to 14-month open-label studies. The most common adverse reactions with mesalamine delayed-release tablets in the maintenance arms of long-term trials were colitis ulcerative (5.8%), headache (2.9%), liver function test abnormal (2.3%), and abdominal pain (2.2%). Of the 1082 subjects in the all maintenance studies pooled, 1.9% had severe adverse reactions. The most common severe adverse reactions were gastrointestinal disorders; these were mainly symptoms associated with ulcerative colitis.

Table 2
Adverse Reactions in Three Maintenance Trials Experienced by at Least 1% of the Mesalamine delayed-release tablets Group (maintenance phases of trials)

Adverse Reaction	All Mesalamine Delayed-release Tablets (n=1082)	
	n	%
Colitis ulcerative	63	(5.8%)
Headache	31	(2.9%)
Liver function test abnormal	25	(2.3%)
Abdominal pain	24	(2.2%)
Diarrhea	18	(1.7%)
Abdominal distension	14	(1.3%)
Abdominal pain upper	13	(1.2%)
Dyspepsia	13	(1.2%)
Back pain	13	(1.2%)
Rash	13	(1.2%)
Arthralgia	12	(1.1%)
Fatigue	11	(1.0%)
Hypertension	10	(1.0%)

The following adverse reactions, presented by body system, were reported infrequently (less than 1%) by mesalamine delayed-release tablets-treated ulcerative colitis patients in the three long-term maintenance trials (maintenance phases of these trials):
Cardiac Disorder
tachycardia
Skin and Subcutaneous Tissue Disorders
acne, alopecia, pruritis, urticaria
Gastrointestinal Disorders
colitis, flatulence, nausea, pancreatitis, rectal polyp, vomiting
Nervous System Disorders
dizziness
Respiratory, Thoracic and Mediastinal Disorder
pharyngolaryngeal pain
General Disorders and Administrative Site Disorders
asthenia, pyrexia
Ear and Labyrinth Disorders
ear pain

6.2 Postmarketing Experience

In addition to the adverse reactions reported above in clinical trials involving mesalamine delayed-release tablets, the adverse reactions listed below have been identified during post-approval use of mesalamine delayed-release tablets and other mesalamine-containing products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole

Lupus-like syndrome, drug fever

Cardiac Disorders

Pericarditis, pericardial effusion, myocarditis

Gastrointestinal

Pancreatitis, cholecystitis, gastritis, gastroenteritis, gastrointestinal bleeding, perforated peptic ulcer

Hepatic

Jaundice, cholestatic jaundice, hepatitis, liver necrosis, liver failure, Kawasaki-like syndrome including changes in liver enzymes

Hematologic

Agranulocytosis, aplastic anemia

Immune System Disorders

Anaphylactic reaction, angioedema, Stevens-Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS)

Musculoskeletal and Connective Tissue Disorders

myalgia

Neurological/Psychiatric

Peripheral neuropathy, Guillain-Barre syndrome, transverse myelitis

Renal Disorders

Interstitial nephritis

Respiratory, Thoracic and Mediastinal Disorders

Hypersensitivity pneumonitis (including interstitial pneumonitis, allergic alveolitis, eosinophilic pneumonitis)

Skin

Psoriasis, pyoderma gangrenosum, erythema nodosum

Urogenital

Reversible oligospermia

7 DRUG INTERACTIONS

No investigations of interaction between mesalamine delayed-release tablets and other drugs except for certain antibiotics have been performed [see Pharmacokinetics (12.3)]. However, the following drug-drug interactions have been reported for products containing mesalamine:

7.1 Nephrotoxic Agents, Including Non-Steroidal Anti-Inflammatory Drugs

The concurrent use of mesalamine with known nephrotoxic agents, including non-steroidal anti-inflammatory drugs (NSAIDs) may increase the risk of renal reactions.

7.2 Azathioprine or 6-mercaptopurine

The concurrent use of mesalamine with azathioprine or 6-mercaptopurine may increase the risk for blood disorders.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Reproduction studies with mesalamine have been performed in rats at doses up to 1000 mg/kg/day (1.8 times the maximum recommended human dose based on a body surface area comparison) and rabbits at doses up to 800 mg/kg/day (2.9 times the maximum recommended human dose based on a body surface area comparison) and have revealed no evidence of impaired fertility or harm to the fetus due to mesalamine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Mesalamine is known to cross the placental barrier.

8.3 Nursing Mothers

Low concentrations of mesalamine and higher concentrations of its N-acetyl metabolite have been detected in human breastmilk. The clinical significance of this has not been determined and there is limited experience of nursing women using mesalamine. Caution should be exercised if mesalamine delayed-release tablets are administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of mesalamine delayed-release tablets in pediatric patients have not been established.

8.5 Geriatric Use

Reports from uncontrolled clinical studies and postmarketing reporting systems suggested a higher incidence of blood dyscrasias, i.e., neutropenia and pancytopenia in patients who were 65 years or older who were taking mesalamine-containing products such as mesalamine delayed-release tablets. Caution should be taken to closely monitor blood cell counts during mesalamine therapy.

Clinical trials of mesalamine delayed-release tablets did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Systemic exposures are increased in elderly subjects [see Clinical Pharmacology (12.3)]. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concurrent disease or other drug therapy in elderly patients.

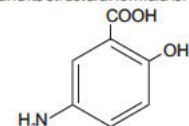
10 OVERDOSAGE

Mesalamine is an aminosalicylate, and symptoms of salicylate toxicity may include tinnitus, vertigo, headache, confusion, drowsiness, sweating, seizures, hyperventilation, dyspnea, vomiting, and diarrhea. Severe intoxication may lead to disruption of electrolyte balance and blood-pH, hyperthermia, dehydration, and end organ damage.

There is no specific known antidote for mesalamine overdose; however, conventional therapy for salicylate toxicity may be beneficial in the event of acute overdose. Fluid and electrolyte imbalance should be corrected by the administration of appropriate intravenous therapy. Adequate renal function should be maintained.

11 DESCRIPTION

Each mesalamine delayed-release tablet for oral administration contains 1.2 g 5-aminosalicylic acid (5-ASA; mesalamine), an anti-inflammatory agent. Mesalamine also has the chemical name 5-amino-2-hydroxybenzoic acid and its structural formula is:



Molecular formula: C₇H₇NO₄
Molecular weight: 153.14

Mesalamine, USP is a light tan to pink colored, needle-shaped crystals. Color may darken on exposure to air. It is odorless or may have a slight characteristic odor.

The tablet is coated with a pH dependent polymer film, which breaks down at or above pH 6.8, normally in the terminal ileum where mesalamine then begins to be released from the tablet core. The tablet core contains mesalamine with hydrophilic excipients and provides for extended release of mesalamine.

Each mesalamine delayed-release tablet intended for oral administration contains 1.2 g of mesalamine. In addition, each tablet contains the following inactive ingredients: carboxymethylcellulose sodium, colloidal silicon dioxide, hypromellose, iron oxide red, iron oxide yellow, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, triethyl citrate, talc and titanium dioxide.

USP Drug Release Test pending.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of mesalamine is not fully understood, but appears to have a topical anti-inflammatory effect on the colonic epithelial cells. Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase and lipoxygenase pathways, is increased in patients with chronic inflammatory bowel disease, and it is possible that mesalamine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin production in the colon.

Mesalamine has the potential to inhibit the activation of nuclear factor kappa B (NFκB) and consequently the production of key pro-inflammatory cytokines. It has been proposed that reduced expression of PPARγ nuclear receptors (γ-form of peroxisome proliferator-activated receptors) may

be implicated in ulcerative colitis. There is evidence that mesalamine produces pharmacodynamic effects through direct activation of PPARγ receptors in the colonic/rectal epithelium.

12.2 Pharmacodynamics

The pharmacodynamic actions of mesalamine occur in the colonic/rectal mucosae local to the delivery of drug from mesalamine delayed-release tablets into the lumen. There is information suggesting that severity of colonic inflammation in ulcerative colitis patients treated with mesalamine is inversely correlated with mucosal concentrations of mesalamine. Plasma concentrations representing systemically absorbed mesalamine are not believed to contribute extensively to efficacy.

12.3 Pharmacokinetics

Absorption

The total absorption of mesalamine from mesalamine delayed-release tablets 2.4 g or 4.8 g given once daily for 14 days to healthy volunteers was found to be approximately 21 to 22 % of the administered dose.

Gamma-scintigraphy studies have shown that a single dose of mesalamine delayed-release tablets 1.2 g (one tablet) passed intact through the upper gastrointestinal tract of fasted healthy volunteers. Scintigraphic images showed a trail of radio-labeled tracer in the colon, suggesting that mesalamine had distributed through this region of the gastrointestinal tract.

In a single dose study, mesalamine delayed-release tablets 1.2 g, 2.4 g and 4.8 g were administered in the fasted state to healthy subjects. Plasma concentrations of mesalamine were detectable after 2 hours and reached a maximum by 9 to 12 hours on average for the doses studied. The pharmacokinetic parameters are highly variable among subjects (Table 3). Mesalamine systemic exposure in terms of area under the plasma concentration-time curve (AUC) was slightly more than dose proportional between 1.2 g and 4.8 g mesalamine delayed-release tablets. Maximum plasma concentrations (C_{max}) of mesalamine increased approximately dose proportionately between 1.2 g and 2.4 g and sub-proportionately between 2.4 g and 4.8 g mesalamine delayed-release tablets, with the dose normalized value at 4.8 g representing, on average, 74 % of that at 2.4 g based on geometric means.

Table 3 Mean (SD) PK Parameters for Mesalamine Following Single Dose Administration of Mesalamine Delayed-release Tablets Under Fasting Conditions			
Parameter of Mesalamine	Mesalamine Delayed-release Tablets 1.2 g (N=47)	Mesalamine Delayed-release Tablets 2.4 g (N=48)	Mesalamine Delayed-release Tablets 4.8 g (N=48)
AUC ₀₋₁₂ (ng.h/mL)	9039 ^a (5054)	20538 (12980)	41434 (26640)
AUC _{0-∞} (ng.h/mL)	9578 (5214)	21084 (13185)	44775 ^a (30302)
C _{max} (ng/mL)	857 (638)	1595 (1484)	2154 (1140)
T _{max} (h)	9 ^a (4 to 32.1)	12 (4 to 34.1)	12 (4 to 34)
T _{1/2} (h)	2 ^a (0 to 8)	2 (1 to 4)	2 (1 to 4)
T _{1/2} (h) (Terminal Phase)	8.56 (6.38)	7.05 ^a (5.54)	7.25 ^a (6.32)

^aArithmetic mean of parameter values are presented except for T_{max} and T_{1/2}.

Median (min, max): N=43, N=27, N=33, N=36, N=46

Administration of a single dose of mesalamine delayed-release tablets 4.8 g with a high fat meal resulted in further delay in absorption, and plasma concentrations of mesalamine were detectable 4 hours following dosing. However, a high fat meal increased systemic exposure of mesalamine (mean C_{max} ↑ 91 %; mean AUC: ↑ 16 %) compared to results in the fasted state. Mesalamine delayed-release tablets were administered with food in the controlled clinical trials that supported its approval.

In a single and multiple dose pharmacokinetic study of mesalamine delayed-release tablets, 2.4 g or 4.8 g was administered once daily with standard meals to 28 healthy volunteers per dose group. Plasma concentrations of mesalamine were detectable after 4 hours and were maximal by 8 hours after the single dose. Steady state was achieved generally by 2 days after dosing. Mean AUC at steady state was only modestly greater (1.1- to 1.4-fold) than predictable from single dose pharmacokinetics.

In a single dose pharmacokinetic study of mesalamine delayed-release tablets, 4.8 g was administered in the fasted state to 71 healthy male and female volunteers (28 young (18 to 35 yrs); 28 elderly (65 to 75 yrs); 15 elderly (> 75 yrs)). Increased age resulted in increased systemic exposure (approximately 2-fold in C_{max}), to mesalamine and its metabolite N-acetyl-5-aminosalicylic acid. Increased age resulted in a slower apparent elimination of mesalamine, though there was high between-subject variability. Systemic exposures in individual subjects were inversely correlated with renal function as assessed by estimated creatinine clearance.

Table 4 Mean (SD) PK Parameters for Mesalamine Following Single Dose Administration of Mesalamine Delayed-release Tablets 4.8 g under Fasting Conditions to Young and Elderly Subjects			
Parameter of 5-ASA	Young Subjects (18 to 35 yrs) (N=28)	Elderly Subjects (65 to 75 yrs) (N=28)	Elderly Subjects (> 75 yrs) (N=15)
AUC ₀₋₁₂ (ng.h/mL)	51570 (23870)	73001 (42608)	65820 (25283)
AUC _{0-∞} (ng.h/mL)	58057 ^a (22429)	89612 ^a (40596)	63067 ^a (22531)
C _{max} (ng/mL)	2243 (1410)	4999 (4381)	4832 (4383)
t _{max} ^a (h)	22 (5.98 to 48)	12.5 (4 to 36)	16 (4 to 26)
t _{1/2} ^a (h)	2 (1 to 6)	2 (1 to 4)	2 (2 to 4)
t _{1/2} (h), terminal phase	5.68 ^a (2.83)	9.68 ^a (7.47)	8.67 ^a (5.84)
Renal clearance (L/h)	2.05 (1.33)	2.04 (1.16)	2.13 (1.20)

Arithmetic mean (SD) data are presented, N = Number of subjects * Median (min - max). N=15, N=16, N=13

Distribution

Mesalamine is approximately 43% bound to plasma proteins at the concentration of 2.5 mcg/mL.

Metabolism

The only major metabolite of mesalamine (5-aminosalicylic acid) is N-acetyl-5-aminosalicylic acid. Its formation is brought about by N-acetyltransferase (NAT) activity in the liver and intestinal mucosa cells, principally by NAT-1.

Elimination

Elimination of mesalamine is mainly via the renal route following metabolism to N-acetyl-5-aminosalicylic acid (acetylation). However, there is also limited excretion of the parent drug in urine. Of the approximately 21 to 22% of the dose absorbed, less than 8% of the dose was excreted unchanged in the urine after 24 hours, compared with greater than 13% for N-acetyl-5-aminosalicylic acid. The apparent terminal half-lives for mesalamine and its major metabolite after administration of mesalamine delayed-release tablets 2.4 g and 4.8 g were, on average, 7 to 9 hours and 8 to 12 hours, respectively.

Drug Interactions

The potential effect of mesalamine (4.8 g given once daily) on the pharmacokinetics of four commonly used antibiotics were evaluated in healthy subjects. The four antibiotics studied and their dosing regimens were as follows: amoxicillin (single 500 mg dose), ciprofloxacin XR (single 500 mg dose), metronidazole (750 mg twice daily for 3.5 days), and sulfamethoxazole/trimethoprim (800 mg/160 mg twice daily for 3.5 days). Coadministration of mesalamine did not result in clinically significant changes in the pharmacokinetics of any of the four antibiotics. The change in C_{max} and AUC of amoxicillin, ciprofloxacin and metronidazole when they were coadministered with mesalamine were all ≤ 3%. There was an increase of 12% in C_{max} and an increase of 15% in AUC of sulfamethoxazole when sulfamethoxazole/trimethoprim was coadministered with mesalamine [see Drug Interactions (7)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a 104 week dietary carcinogenicity study in CD-1 mice, mesalamine at doses up to 2500 mg/kg/day was not tumorigenic. This dose is 2.2 times the maximum recommended human dose (based on a body surface area comparison) of mesalamine delayed-release tablets. Furthermore, in a 104 week dietary carcinogenicity study in Wistar rats, mesalamine up to a dose of 800 mg/kg/day was not tumorigenic. This dose is 1.4 times the recommended human dose (based on a body surface area comparison) of mesalamine delayed-release tablets.

Mutagenesis

No evidence of mutagenicity was observed in an *in vitro* Ames test or an *in vivo* mouse micronucleus test.

Impairment of Fertility

No effects on fertility or reproductive performance were observed in male or female rats at oral doses of mesalamine up to 400 mg/kg/day (0.7 times the maximum recommended human dose based on a body surface area comparison).

13.2 Animal Toxicology and/or Pharmacology

In animal studies with mesalamine, a 13 week oral toxicity study in mice and 13 week and 52 week oral toxicity studies in rats and cynomolgus monkeys have shown the kidney to be the major target organ of mesalamine toxicity. Oral daily doses of 2400 mg/kg in mice and 1150 mg/kg in rats produced renal lesions including granular and hyaline casts, tubular degeneration, tubular dilation, renal infarct, papillary necrosis, tubular necrosis, and interstitial nephritis. In cynomolgus monkeys, oral daily doses of 250 mg/kg or higher produced nephrosis, papillary edema, and interstitial fibrosis.

14 CLINICAL STUDIES

14.1 Active, Mild to Moderate Ulcerative Colitis

Two similarly designed, randomized, double-blind, placebo-controlled trials were conducted in 517 adult patients with active, mild to moderate ulcerative colitis. The study population was primarily Caucasian (80%), had a mean age of 42 years (6% age 65 years or older), and was approximately 50% male. Both studies used mesalamine delayed-release tablets doses of 2.4 g/day and 4.8 g/day administered once daily for 8 weeks except for the 2.4 g/day group in Study 1, which was given in two divided doses (1.2 g twice daily). The primary efficacy end-point in both trials was to compare the percentage of patients in remission after 8 weeks of treatment for the mesalamine delayed-release tablets treatment groups versus placebo. Remission was defined as an Ulcerative Colitis Disease Activity Index (UC-DAI) of ≤ 1, with scores of zero for rectal bleeding and for stool frequency, and a sigmoidoscopy score reduction of 1 point or more from baseline.

In both studies, the mesalamine delayed-release tablets doses of 2.4 g/day and 4.8 g/day demonstrated superiority over placebo in the primary efficacy endpoint (Table 5). Both mesalamine delayed-release tablets doses also provided consistent benefit in secondary efficacy parameters, including clinical improvement, treatment failure, clinical remission, and sigmoidoscopic improvement. Mesalamine delayed-release tablets 2.4 g/day and 4.8 g/day had similar efficacy profiles.

Table 5 Patients in Remission at Week 8		
Dose	Study 1 (n=262) n/N (%)	Study 2 (n=255) n/N (%)
Mesalamine Delayed-release Tablets 2.4 g/day	30/88 (34.1)	34/84 (40.5)
Mesalamine Delayed-release Tablets 4.8 g/day	26/89 (29.2)	35/85 (41.2)
Placebo	11/85 (12.9)	19/86 (22.1)

14.2 Maintenance of Remission in Patients with Ulcerative Colitis

A multicenter, randomized, double-blind, active comparator study was conducted in a total of 826 adult patients in remission from ulcerative colitis. The study population had a mean age of 45 years (8% age 65 years or older), were 52% male, and were primarily Caucasian (64%). Maintenance of remission was assessed using a modified Ulcerative Colitis Disease Activity Index (UC-DAI). For this trial, maintenance of remission was based on maintaining endoscopic remission defined as a modified UC-DAI endoscopy subscore of ≤ 1. An endoscopy subscore of 0 represented normal mucosal appearance with intact vascular pattern and no friability or granulation. For this trial the endoscopy score definition of 1 (mild disease) was modified such that it could include erythema, decreased vascular pattern, and minimal granularity; however, it could not include friability. Subjects were randomized in a 1:1 ratio to receive either mesalamine delayed-release tablets 2.4 g/day administered once daily or mesalamine delayed-release tablets 1.8 g/day administered as 0.8 g twice daily. The proportion of patients who maintained remission at Month 6 in this study using mesalamine delayed-release tablets 2.4 g once daily (83.7%) was similar to that seen using the comparator (mesalamine delayed-release tablets 1.8 g/day (81.5%).

16 HOW SUPPLIED/STORAGE AND HANDLING

Mesalamine Delayed-release Tablets, 1.2 g are pale red-brown, oval-shaped, biconvex, bevel film-coated tablets debossed with the '711' on one side and plain on other side and are supplied as follows: NDC 68382-711-64 in bottles of 34 tablets
NDC 68382-711-19 in bottles of 120 tablets

Storage

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container.

17 PATIENT COUNSELING INFORMATION

- Instruct patients not to take mesalamine delayed-release tablets if they have hypersensitivity to salicylates (e.g., aspirin) or other mesalamines.
- Inform patients to let their physicians know all medications they are taking and if they:
 - are allergic to sulfasalazine, salicylates or mesalamine;
 - are taking non-steroidal anti-inflammatory drugs (NSAIDs) or other nephrotoxic agents;
 - are taking azathioprine, or 6-mercaptopurine;
 - experience cramping, abdominal pain, bloody diarrhea, fever, headache or rash;
 - have a history of myocarditis or pericarditis;
 - have kidney or liver disease;
 - have a history of stomach blockage;
 - are pregnant, intend to become pregnant or are breastfeeding.
- Patients should be instructed to swallow mesalamine delayed-release tablets whole, taking care not to break the outer coating.

This product's label may have been updated. For current full prescribing information, please visit www.zyudusa.com

Manufactured by:
Cadila Healthcare Ltd.
Ahmedabad, India

Distributed by:
Zydus Pharmaceuticals USA Inc.
Pennington, NJ 08534

Rev: 10/14

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091640

LABELING REVIEWS

(APPROVAL SUMMARY)

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	2/2/2015
ANDA Number(s)	091640
Review Cycle Number	5th
Applicant Name	Zydus Pharmaceuticals (USA) Inc.
Established Name & Strength(s)	Mesalamine Delayed-release Tablets USP, 1.2 g
Proposed Proprietary Name	None
Submission Received Date	12/6/2014
Labeling Reviewer	Chan Park
Labeling Team Leader	Lisa Kwok
Review Conclusion ☐ ACCEPTABLE – No Comments. ☒ ACCEPTABLE – Include Post Approval Comments ☐ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant. *Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.	

1.1 **POST APPROVAL REVISIONS**

These comments will NOT be sent to the applicants at this time.

These comments will be addressed post approval (in the next supplement review).

INSERT; a.

(b) (4)

b. 8.1 Pregnancy: Pregnancy Category B

(b) (4)

(b) (4)

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment. Include the previous review(s) finalized date(s). 1/28/2014.

Reviewer Comments: None (APPROVAL SUMMARY)

This amendment is submitted for revision to the insert labeling per the updated RLD labeling.

2.1 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s).

Reviewer Comments:

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

From: Park, Chan H

Sent: Wednesday, July 11, 2012 2:08 PM To: Majumder, Quamrul

Cc: Park, Chan H

Subject: ANDA 091640 (Mesalamine D-R Tablets)

Hi Quamrul,

I note that the description section of the sponsor's proposed labeling is different from that of the RLD, Lialda Tablets, in terms of the delayed-release mechanism. I am not sure it may or may not be an issue, so I would like to run it by you. Thanks,

Chan

RLD - The tablet is coated with a pH dependent polymer film, which breaks down at or above pH 6.8, normally in the terminal ileum where mesalamine then begins to be released from the tablet core.

The tablet core contains mesalamine with hydrophilic and lipophilic excipients and provides for extended release of mesalamine.

ANDA –

(b) (4)

(b) (4)

From: Park, Chan H
Sent: Wednesday, July 11, 2012 2:50 PM
To: Majumder, Quamrul
Cc: Park, Chan H
Subject: FW: ANDA 091640 (Mesalamine D-R Tab lets)

Hi Quamrul,

I have additional comments on this application. The sponsor revised the imprint of the tablet from (b) (4) to "711". (b) (4)

Chan

From: Majumder, Quamrul
Sent: Wednesday, July 11, 2012 3:45 PM
To: Park, Chan H
Cc: Rajagopalan, Radhika
Subject: RE: ANDA 091640 (Mesalamine D-R Tab lets)

Hi Chan

The sponsor revised the imprint of the tablet from (b) (4) to "711". (b) (4)
(b) (4) 7 and 1 . Hence 711 (b) (4)

Due to formulation variation labeling information are changed. In both formulations, drug is released in pH above 6.8 . If bio equivalence (this drug is not systemically absorbed ...hence bio equivalency demonstration is a problem) is not an issue, then this labeling difference should not be a concern.

Thanks again for your observation and bringing the issues to chemistry review's attention.

- Quamrul

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in SharePoint Repository files? If Yes, please explain. NO

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check all that apply)

☒ MOST RECENTLY APPROVED REFERENCE LISTED DRUG NDA# or ANDA#/Supplement (S-000 if original): NDA 022000/S-013 Supplement Approval Date: 10/16/2014 Proprietary Name: Lialda® delayed-release tablets Established Name: Mesalamine delayed-release tablets Description of Supplement: Addition of angioedema to the Post-marketing Experience section of the package insert.
☐ BPCA or PREA TEMPLATE (Describe): No
☐ OTHER (Describe): No

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under [21 CFR 314.94\(a\)\(8\)](#)? **YES**

Are the specific requirements for format met under [21 CFR 201.57\(new\)](#) or [201.80\(old\)](#)? **YES**

Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments:

None

3.3 MODEL CONTAINER LABELS

Model labels and carton labeling. [Insert or paste images below]

ONCE-DAILY NDC 54092-476-12

Lialda®
(mesalamine)
delayed release
tablets
1.2 g per tablet

Rx Only 120 Tablets

Shire

KEEP THIS AND ALL MEDICATION
OUT OF THE REACH OF CHILDREN.

Each tablet contains: mesalamine 1.2 g

Pharmacist: Dispense in tight, light-resistant container
as defined in USP. Store at room temperature
15°C to 25°C (59°F to 77°F); excursions permitted to
30°C (86°F). See USP Controlled Room Temperature.
SEE PACKAGE INSERT FOR DOSAGE INFORMATION.

1612v2 113173 Rev. 09/13

Manufactured for Shire US Inc.
725 Chesterbrook Blvd., Wayne, PA 19087, USA
© 2013 Shire US Inc.
By license of Nogra Pharma Limited, Dublin, Ireland
Product of Germany

DailyMeds (Rev. 6/2014)

3.4 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results				
	Date Searched	Monograph? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP	2/3/2015	YES	Mesalamine delayed-release tablets	Preserve in tight containers
PF	NA	NA to enter text.	NA to enter text.	NA to enter text.

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 2/3/2015

Table 3 provides Orange Book patents for the Model Labeling and ANDA patent certifications.

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
6773720	6/8/2020	NA to enter text.	NA to enter text.	IV	12/16/2009	NONE

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

None

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
NA	NA to enter text.	NA to enter text.	NA to enter text.	NA to enter text.	NA to enter text.

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments: None

NA to enter text.

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the DESCRIPTION section, HOW SUPPLIED section and manufacturing statements of the Prescribing Information when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section? **NO**

Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED? **NO**

Are there changes to the manufacturing statements? **NO**

If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section		
Previous Labeling Review	Currently Proposed	Assessment

Table 6: Comparison of HOW SUPPLIED Section		
Previously Labeling Review	Currently Proposed	Assessment

Table 7: Manufactured by statement		
Previously Labeling Review	Currently Proposed	Assessment

5. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments:

See the information under section 2.1 above.

6. COMMENTS FOR OTHER REVIEW DISCIPLINES

During the course of this review, was clarification sought on issues to determine if a label or labeling revision is necessary? **NO**

Reviewer Assessment:

Does the response(s) received require a label and/or labeling revision? **NA**

Reviewer Comments:

None

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for each material analyzed in this review.

For each row, if you enter “NA” under the second column, you do NOT need to enter “NA” for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	Packaging Sizes	Submission Date	Recommendation
Container	Final	34s and 120s	5/19/2011	AC
Blister	Choose an item.	NA to enter text.	NA to enter text.	NA to enter text.
Carton	Choose an item.	NA to enter text.	NA to enter text.	NA to enter text.
(Other – specify)	Choose an item.	NA to enter text.	NA to enter text.	NA to enter text.
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	Revision Date and/or Code	Submission Date	Recommendation
Prescribing Information	Final	10/2014	12/6/2014	AC
Medication Guide	Choose an item.	NA to enter text.	NA to enter text.	NA to enter text.
Patient Information	Choose an item.	NA to enter text.	NA to enter text.	NA to enter text.
SPL Data Elements		10/2014	NA to enter text.	AC

8. SPECIAL CONSIDERATION

a. This the **FIRST generic** application.

b. USP Issue

It appears that the dissolution test for the sponsor’s drug product does not meet the dissolution specification appearing in the USP monograph for this drug product. The sponsor decided not to use the designation “USP” in association with their drug product for this reason. The sponsor added “USP Drug Release Test Pending” to the DESCRIPTION section as requested.

(APPROVAL SUMMARY)

Office of Generic Drugs

REVIEW OF PROFESSIONAL LABELING (4th Cycle)

ANDA Number: 091640

Date of Submission: January 8, 2014

Applicant: Zydus Pharmaceuticals (USA) Inc.

Established Name and Strength: Mesalamine Delayed-release Tablets USP, 1.2 g

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 or Tentative 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 January 8, 2014.

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

EMS required? No (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

REVIEW SUMMARY

	FPL	Submission Date	Recommendation
Container – 34s and 120s	yes	May 19, 2011	AC for AP
Package Insert	yes	January 8, 2014	AC for AP
SPL- DLDE	N/A	January 8, 2014	AC for AP

REVISIONS NEEDED POST APPROVAL? No

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

From: Park, Chan H
Sent: Wednesday, July 11, 2012 2:08 PM
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Cc: Park, Chan H
Subject: ANDA 091640 (Mesalamine D-R Tab lets)

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ANDA –

(b) (4)

(b) (4)

From: Park, Chan H
Sent: Wednesday, July 11, 2012 2:50 PM
To: Majumder, Quamrul
Cc: Park, Chan H
Subject: FW: ANDA 091640 (Mesalamine D-R Tab lets)

Hi Quamrul,

I have additional comments on this application. The sponsor revised the imprint of the tablet from (b) (4) to "711". (b) (4)
Chan

From: Majumder, Quamrul
Sent: Wednesday, July 11, 2012 3:45 PM
To: Park, Chan H
Cc: Rajagopalan, Radhika
Subject: RE: ANDA 091640 (Mesalamine D-R Tab lets)

Hi Chan

The sponsor revised the imprint of the tablet from (b) (4) to "711" . (b) (4)
(b) (4) 7 and 1 . Hence 711 (b) (4)

Due to formulation variation labeling information are changed. In both formulations, drug is released in pH above 6.8 . If bio equivalence (this drug is not systemically absorbed ...hence bio equivalency demonstration is a problem) is not an issue, then this labeling difference should not be a concern.

Thanks again for your observation and bringing the issues to chemistry review's attention.

- Quamrul

FOR THE RECORD: (Portion of the review is from the previous review done by Sarah Park)

1. MODEL LABELING – Lialda Delayed-Release Tablets, 1.2 g, NDA 022000/S-011, approved December 16, 2013.

NOTE: This is the **first generic** for this drug product.



2. USP 36 Drug Product Monograph (1/13/2014):

Reference ID: A40322
Packaging and storage – Preserve in tight containers

PF 37: No new information for the drug product.

***It appears that the dissolution test for the sponsor's drug product does not meet the dissolution specification appearing in the USP monograph for this drug product. The sponsor decided not to use the designation "USP" in association with their drug product for this reason. The sponsor added "USP Drug Release Test Pending" to the DESCRIPTION section as requested.

3. PATENTS AND EXCLUSIVITIES Patent Data (1/13/2014)

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Patent Certification	Labeling Impact
N022000	001	6773720	Jun 8, 2020	IV	none

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration	Labeling Impact
N022000	001	I - 640	Jul 14, 2014	Carve-out

Code Definition

I - 640 MAINTENANCE OF REMISSION OF ULCERATIVE COLITIS

The sponsor submitted the exclusivity statement regarding I-640 on 9/24/2011 stating that they will not seek approval for the protected information until after the expiry of this exclusivity.

4. INACTIVE INGREDIENTS:

The listing of inactive ingredients in the DESCRIPTION section of the package insert is consistent with the listing of inactive ingredients found in the statement of components and composition.

Each mesalamine delayed-release tablet intended for oral administration contains 1.2 g of mesalamine. In addition, each tablet contains the following inactive ingredients: carboxymethylcellulose sodium, colloidal silicon dioxide, hypromellose, iron oxide red, iron oxide yellow, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, triethyl citrate, talc and titanium dioxide.

(b) (4)

The tablets contain red and yellow iron oxides. According to 21 CFR 73.1200©, the total daily amount of elemental iron for an adult patient taking the maximum recommended daily dose should not exceed 5 mg. The firm provided the following calculation:

Hence the amount of elemental iron that would be ingested daily while consuming of Mesalamine Delayed-release Tablets, 1.2 g does not exceed 5 mg (calculated as elemental iron) [21 CFR 73.1200 (c)].

5. MANUFACTURING FACILITY

Cadila Healthcare Limited
(b) (4) India

(b) (4)

Ahmedabad –

6. PRODUCT DESCRIPTION:

RLD: “red-brown ellipsoidal film coated tablets containing 1.2 g mesalamine, and debossed on one side imprinted with S476”

Refer ANDA:

(b) (4)

Drug Product Specifications:

(b) (4)

7. CONTAINER/CLOSURE SYSTEM: Container: HDPE bottles
Closure: CRC for bottles of 34 and 120,

8. PRODUCT LINE: RLD: Bottles of 120
ANDA: Bottles of 34, 120

(b) (4)

9. STORAGE CONDITIONS:

RLD: "Store at room temperature 15°C - 25°C (59°F - 77°F); excursions permitted to 30°C (86°F) See USP Controlled Room Temperature"

ANDA: "Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]."

Stability: Accelerated stability (40°C ± 2°C / 75% ±5% RH) at 0, 1, 2, and 3 months;
Intermediate stability (30°C ± 2°C / 65% ±5% RH) at 0, 3, 6, 9, and 12 months; and at room temperature stability (25°C ± 2°C / 60% ±5% RH) at 0, 3, 6, 9, and 12 months

10. DISPENSING RECOMMENDATIONS:

RLD: "Pharmacist: Dispense in tight, light-resistant container as defined in USP."

ANDA: "Pharmacist: Dispense in a tight, light-resistant container as defined in USP."

11. MEDWATCH (checked 1/13/2014) – The following safety information has been included in the Lialda® Tablets already.

Pentasa (mesalamine) Controlled-Release Capsules

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

December 2013

ADVERSE REACTIONS

Post marketing Experience

•

(b) (4)

July 2013

WARNINGS AND PRECAUTIONS

Interference with Laboratory Tests

- Use of mesalamine may lead to spuriously elevated test results when measuring urinary normetanephrine by liquid chromatography with electrochemical detection, because of the similarity in the chromatograms of normetanephrine and mesalamine's main metabolite,

Nacetylaminosalicylic acid (N-Ac-5-ASA). An alternative, selective assay for normetanephrine should be considered.

Date of Review: January 13, 2014.

Primary Reviewer: Chan Park

Team Leader: Koung Lee



ZyGenerics

NDC 68382-362-64

ONCE DAILY

MESALAMINE

DELAYED-RELEASE

Tablets

1.2 g

Rx only

34 Tablets

Lot:

Exp:

Rev.: 05/11

Each delayed-release tablet contains 1.2 g of Mesalamine, USP

Usual Dosage: See package insert for complete prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Pharmacist: Dispense in a light, light-resistant container as defined in USP.

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Manufactured by:
Cadila Healthcare Ltd.
Ahmedabad, India

Distributed by:
Zydus Pharmaceuticals USA Inc.
Pennington, NJ 08534

85 x 40 mm



(b) (4)



(b) (4)

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

/s/

CHAN H PARK
01/28/2014

KOUNG U LEE
01/28/2014

**(APPROVAL SUMMARY)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 091640

Applicant's Name: Zydus Pharmaceuticals (USA) Inc.

Submission Date: August 18, 2012 (Amendment)

Established Name: Mesalamine Delayed-release Tablets USP, 1.2 g

**REMS Check Boxes
RISK EVALUATION AND MITIGATION STRATEGY**

REMS required? No

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

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

	FPL	Submission Date	Recommendation
Container – 34s and 120s	yes	May 19, 2011	AC for AP
Package Insert	yes	August 18, 2012	AC for AP
SPL- DLDE	N/A	August 18, 2012	AC for AP

NOTES/QUESTIONS TO THE CHEMIST:

From: Park, Chan H
Sent: Wednesday, July 11, 2012 2:08 PM
To: Majumder, Quamrul
Cc: Park, Chan H
Subject: ANDA 091640 (Mesalamine D-R Tab lets)

Hi Quamrul,

I note that the description section of the sponsor's proposed labeling is different from that of the RLD, Lialda Tablets, in terms of the delayed-release mechanism. I am not sure it may or may not be an issue, so I would like to run it by you. Thanks,

Chan

RLD - The tablet is coated with a pH dependent polymer film, which breaks down at or above pH 6.8, normally in the terminal ileum where mesalamine then begins to be released from the tablet core. The tablet core contains mesalamine with hydrophilic and lipophilic excipients and provides for extended release of mesalamine.

ANDA –

(b) (4)

(b) (4)

From: Park, Chan H
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I have additional comments on this application. The sponsor revised the imprint of the tablet from (b) (4) to "711". (b) (4)

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From: Majumder, Quamrul
Sent: Wednesday, July 11, 2012 3:45 PM
To: Park, Chan H
Cc: Rajagopalan, Radhika
Subject: RE: ANDA 091640 (Mesalamine D-R Tab lets)

Hi Chan

The sponsor revised the imprint of the tablet from (b) (4) to "711". (b) (4)
edges than 7 and 1. Hence 711 (b) (4)

Due to formulation variation labeling information are changed. In both formulations, drug is released in pH above 6.8. If bio equivalence (this drug is not systemically absorbed ...hence bio equivalency demonstration is a problem) is not an issue, then this labeling difference should not be a concern.

Thanks again for your observation and bringing the issues to chemistry review's attention.

- Quamrul

FOR THE RECORD: (Portion of the review is from the previous review done by Sarah Park)

1. MODEL LABELING – Lialda Delayed-Release Tablets, 1.2 g, NDA 022000/S-005, approved July 14, 2011. It is still current as pf the 9/14/2012.

NOTE: This is the **first generic** for this drug product.



2. USP 35 Drug Product Monograph (9/14/2012): Packaging and storage – Preserve in tight containers
PF 37: No new information for the drug product.

*****It appears that the dissolution test for the sponsor's drug product does not meet the dissolution specification appearing in the USP monograph for this drug product. The sponsor decided not to use the designation "USP" in association with their drug product for this reason. The sponsor added "USP Drug Release Test Pending" to the DESCRIPTION section as requested.**

3. PATENTS AND EXCLUSIVITIES Patent Data (9/14/2012)

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Patent Certification	Labeling Impact
N022000	001	6773720	Jun 8, 2020	IV	none

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration	Labeling Impact
N022000	001	I- 640	Jul 14, 2014	Carve-out

Code Definition

I - 640 MAINTENANCE OF REMISSION OF ULCERATIVE COLITIS

The sponsor submitted the exclusivity statement regarding I-640 on 9/24/2011 stating that they will not seek approval for the protected information until after the expiry of this exclusivity.

4. INACTIVE INGREDIENTS:

The listing of inactive ingredients in the DESCRIPTION section of the package insert is consistent with the listing of inactive ingredients found in the statement of components and composition.

Each mesalamine delayed-release tablet intended for oral administration contains 1.2 g of mesalamine. In addition, each tablet contains the following inactive ingredients: carboxymethylcellulose sodium, colloidal silicon dioxide, hypromellose, iron oxide red, iron oxide yellow, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, triethyl citrate, talc and titanium dioxide.

(b) (4)

The tablets contain red and yellow iron oxides. According to 21 CFR 73.1200©, the total daily amount of elemental iron for an adult patient taking the maximum recommended daily dose should not exceed 5 mg. The firm provided the following calculation:

(b) (4)

5. MANUFACTURING FACILITY

Cadila Healthcare Limited
(b) (4) India

(b) (4)

Ahmedabad

(b) (4)

6. PRODUCT DESCRIPTION:

RLD: "red-brown ellipsoidal film coated tablets containing 1.2 g mesalamine, and debossed on one side imprinted with S476"

ANDA:

(b) (4)

Drug Product Specifications:

(b) (4)

7. CONTAINER/CLOSURE SYSTEM: Container: HDPE bottles

Closure: CRB for bottles of 34 and 120,
Reference ID: A789839

8. PRODUCT LINE: RLD: Bottles of 120
ANDA: Bottles of 34, 120

(b) (4)

9. STORAGE CONDITIONS:

RLD: "Store at room temperature 15°C - 25°C (59°F - 77°F); excursions permitted to 30°C (86°F) See USP Controlled Room Temperature"

ANDA: "Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]."

Stability: Accelerated stability (40°C ± 2°C / 75% ±5% RH) at 0, 1, 2, and 3 months; Intermediate stability (30°C ± 2°C / 65% ±5% RH) at 0, 3, 6, 9, and 12 months; and at room temperature stability (25°C ± 2°C / 60% ±5% RH) at 0, 3, 6, 9, and 12 months

10. DISPENSING RECOMMENDATIONS:

RLD: "Pharmacist: Dispense in tight, light-resistant container as defined in USP."

ANDA: "Pharmacist: Dispense in a tight, light-resistant container as defined in USP."

11. MEDWATCH (checked 9/14/2012) No new alerts or labeling changes.

12. REMS (checked 9/14/2012) None

Date of Review: September 14, 2012

Primary Reviewer: Chan Park

Team Leader: Koung Lee



ZyGenerics

NDC 68382-362-64

ONCE DAILY

MESALAMINE

DELAYED-RELEASE

Tablets

1.2 g

Rx only

34 Tablets

Each delayed-release tablet contains 1.2 g of Mesalamine, USP

Usual Dosage: See package insert for complete prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Pharmacist: Dispense in a light, light-resistant container as defined in USP.

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Manufactured by:
Cadila Healthcare Ltd.
Ahmedabad, India

Distributed by:
Zydus Pharmaceuticals USA Inc.
Pennington, NJ 08534

Lot:

Exp:

Rev.: 05/11

85 x 40 mm





ZyGenerics

NDC 68382-362-19

ONCE DAILY

MESALAMINE

DELAYED-RELEASE

Tablets

1.2 g

Rx only

120 Tablets

Lot:

Exp:

Rev.: 05/11

Each delayed-release tablet contains 1.2 g of Mesalamine, USP

Usual Dosage: See package insert for complete prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Pharmacist: Dispense in a tight, light-resistant container as defined in USP.

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Manufactured by:
Cadila Healthcare Ltd.
Ahmedabad, India

Distributed by:
Zydus Pharmaceuticals USA Inc.
Pennington, NJ 08534

97 x 50.5 mm



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

/s/

CHAN H PARK
09/18/2012

KOUNG U LEE
09/19/2012

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

ANDA Number: 091640

Applicant's Name: Zydus Pharmaceuticals (USA) Inc.

Submission Date: May 11, 2011, September 29, 2011 and June 27, 2012 (Amendments)

Established Name: Mesalamine Delayed-release Tablets USP, 1.2 g

Labeling Deficiencies:

1. GENERAL COMMENT

We acknowledge that you revised the NDC numbers on the labeling to reflect the revised imprinting of your drug product from (b) (4) to "711". Please submit the CMC information associated with the revised imprint of your drug product and/or comment.

2. CONTAINER – 34s and 120s

3. (b) (4)

4. (b) (4)

5. INSERT

a. GENERAL

We note that you replaced "LIALDA" with (b) (4) "mesalamine delayed-release tablets" (b) (4)

b. HIGHLIGHTS OF PRESCRIBING INFORMATION - DOSAGE AND ADMINISTRATION:

Revise to read "For induction of remission of active, mild to moderate ulcerative colitis, two to four 1.2 g tablets taken once daily with food (1, 2)".

c. FULL PRESCRIPTION INFORMATION - 11 DESCRIPTION:

- i. We note that you revised this section from your original proposal regarding the mechanism on the delayed-release of your drug product. Please justify/explain this revision.
- ii. According to your labeling amendment dated May 11, 2011, it appears that your drug product does not meet the dissolution specification appearing in the USP monograph for your drug product. Please include the following statement at the end of this section until it meets the USP dissolution specification:

Revise the labeling as described above and submit final printed labeling electronically. Please provide the labeling in the Structured Product Labeling (SPL) as well as pdf. format.

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, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug's 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

NOTES/QUESTIONS TO THE CHEMIST:

From: Park, Chan H
Sent: Wednesday, July 11, 2012 2:08 PM
To: Majumder, Quamrul
Cc: Park, Chan H
Subject: ANDA 091640 (Mesalamine D-R Tab lets)

Hi Quamrul,

I note that the description section of the sponsor's proposed labeling is different from that of the RLD, Lialda Tablets, in terms of the delayed-release mechanism. I am not sure it may or may not be an issue, so I would like to run it by you. Thanks,

Chan

RLD - The tablet is coated with a pH dependent polymer film, which breaks down at or above pH 6.8, normally in the terminal ileum where mesalamine then begins to be released from the tablet core. The tablet core contains mesalamine with hydrophilic and lipophilic excipients and provides for extended release of mesalamine.

ANDA -

(b) (4)

(b) (4)

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Sent: Wednesday, July 11, 2012 2:50 PM
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(b) (4)

to

Reference [

(b) (4)

Chan

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Sent: Wednesday, July 11, 2012 3:45 PM
To: Park, Chan H
Cc: Rajagopalan, Radhika
Subject: RE: ANDA 091640 (Mesalamine D-R Tab lets)

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(b) (4)
The sponsor revised the imprint of the tablet from (b) (4) to "711" . (b) (4)
7 and 1 . Hence 711 (b) (4)

Due to formulation variation labeling information are changed. In both formulations, drug is released in pH above 6.8 . If bio equivalence (this drug is not systemically absorbed ...hence bio equivalency demonstration is a problem) is not an issue, then this labeling difference should not be a concern.

Thanks again for your observation and bringing the issues to chemistry review's attention.

- Quamrul

FOR THE RECORD: (Portion of the review is from the previous review done by Sara

1. MODEL LABELING – Lialda Delayed-Release Tablets, 1.2 g, NDA 022000/S-005, approved July 14, 2011

NOTE: This is the **first generic** for this drug product.

2. USP 33 Drug Product Monograph (7/11/2012): Packaging and storage – Preserve in tight containers
PF 36: No new information for the drug product.

***It appears that the dissolution test for the sponsor's drug product does not meet the dissolution specification appearing in the USP monograph for this drug product. The sponsor decided not to use the designation "USP" in association with their drug product for this reason. See comment 5(c)(ii) above.

3. PATENTS AND EXCLUSIVITIES Patent Data (7/11/2012)

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Patent Certification	Labeling Impact
N022000	001	6773720	Jun 8, 2020		none

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration	Labeling Impact
N022000	001	I - 640	Jul 14, 2014	Carve-out

Code Definition

I - 640 MAINTENANCE OF REMISSION OF ULCERATIVE COLITIS

The sponsor submitted the exclusivity statement regarding I-640 on 9/24/2011 stating that they will not seek approval for the protected information until after the expiry of this exclusivity.

4. INACTIVE INGREDIENTS:

Reference ID: A159693
The listing of inactive ingredients in the DESCRIPTION section of the package insert is consistent with the listing of inactive ingredients found in the statement of components and composition.

Each mesalamine delayed-release tablet intended for oral administration contains 1.2 g of mesalamine. In addition, each tablet contains the following inactive ingredients: carboxymethylcellulose sodium, colloidal silicon dioxide, hypromellose, iron oxide red, iron oxide yellow, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, triethyl citrate, talc and titanium dioxide.

(b) (4)

The tablets contain red and yellow iron oxides. According to 21 CFR 73.1200, the total daily amount of elemental iron for an adult patient taking the maximum recommended daily dose should not exceed 5 mg. The firm provided the following calculation:

(b) (4)

5. MANUFACTURING FACILITY

Cadila Healthcare Limited

(b) (4)

Ahmedabad

(b) (4)

(b) (4) India

6. PRODUCT DESCRIPTION:

RLD: "red-brown ellipsoidal film coated tablets containing 1.2 g mesalamine, and debossed on one side imprinted with S476"

ANDA:

(b) (4)

Drug Product Specifications:

(b) (4)

7. CONTAINER/CLOSURE SYSTEM: Container: HDPE bottles

Closure: CRC for bottles of 34 and 120,

(b) (4)

8. PRODUCT LINE: RLD: Bottles of 120

ANDA: Bottles of 34, 120

(b) (4)

9. STORAGE CONDITIONS:

RLD: "Store at room temperature 15°C - 25°C (59°F - 77°F); excursions permitted to 30°C (86°F) See USP Controlled Room Temperature"

ANDA: "Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]."

Stability: Accelerated stability (40°C ± 2°C / 75% ±5% RH) at 0, 1, 2, and 3 months; Intermediate stability (30°C ± 2°C / 65% ±5% RH) at 0, 3, 6, 9, and 12 months; and at room temperature stability (25°C ± 2°C / 60% ±5% RH) at 0, 3, 6, 9, and 12 months

10. DISPENSING RECOMMENDATIONS:

RLD: "Pharmacist: Dispense in tight, light-resistant container as defined in USP."

ANDA: "Pharmacist: Dispense in a tight, light-resistant container as defined in USP."

11. MEDWATCH (checked 7/11/2012) No new alerts or labeling changes.

12. REMS (checked 7/11/2011) None

Date of Review: July 11, 2012

Primary Reviewer: Chan Park

Team Leader: Koung Lee

The image shows the packaging information for Lialda (mesalamine) delayed release tablets. The central text reads "ONCE-DAILY Lialda (mesalamine) delayed release tablets 1.2g 120 Tablets". Above this, the NDC number "NDC 54092-476-12" is printed. To the left, there is a barcode with the number "54092147612" and a small "3" above it. Below the barcode, it says "Manufactured for Shire US Inc. 725 Chesterbrook Blvd., Wayne, PA 19087, USA © 2007 Shire US Inc. By license of Giuliani S.p.A., Milan, Italy Made in Italy". To the right of the central text, there is a warning: "KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN. Each tablet contains: mesalamine 1.2g". Below the warning, it says "Pharmacist: Dispense in tight, light-resistant container as defined in USP. Store at room temperature 15°C to 25°C (59°F to 77°F); excursions permitted to 30°C (86°F). See USP Controlled Room Temperature. SEE PACKAGE INSERT FOR DOSAGE INFORMATION." At the bottom right, there is a lot and expiration date section: "LOT: 107306 EXP: 476 1201 002A Rev. 01/07". A small "Rx only" label is at the bottom left, and the "Shire" logo is at the bottom right.

NDC 54092-476-12

ONCE-DAILY

LialdaTM

(mesalamine)

delayed release tablets

1.2g 120 Tablets

Rx only Shire

3
54092147612
1

Manufactured for Shire US Inc.
725 Chesterbrook Blvd., Wayne, PA 19087, USA
© 2007 Shire US Inc.
By license of Giuliani S.p.A., Milan, Italy
Made in Italy

**KEEP THIS AND ALL MEDICATION
OUT OF THE REACH OF CHILDREN.**

Each tablet contains: mesalamine 1.2g

Pharmacist: Dispense in tight, light-resistant container
as defined in USP. Store at room temperature
15°C to 25°C (59°F to 77°F); excursions permitted to
30°C (86°F). See USP Controlled Room Temperature.
SEE PACKAGE INSERT FOR DOSAGE INFORMATION.

LOT: 107306
EXP: 476 1201 002A
Rev. 01/07

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

/s/

CHAN H PARK
07/13/2012

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

ANDA Number: 091640

Date of Submission: December 12, 2009 (Original)

Applicant's Name: Zydus Pharmaceuticals (USA) Inc.

Established Name: Mesalamine Delayed-release Tablets USP, 1.2 g

Labeling Deficiencies:

1. GENERAL COMMENT

This drug product is subject of a USP monograph. Please revise your labels and labeling accordingly.

2. INSERT

Please revise your insert labeling to be in accordance with the labeling for Lialda Delayed-Release Tablets, 1.2 g, NDA 022000/S-003, approved September 22, 2010.

Revise your labels and labeling, as instructed above, and submit final printed 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, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug's 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

NOTES/QUESTIONS TO THE CHEMIST: None

FOR THE RECORD:

1. MODEL LABELING – Lialda Delayed-Release Tablets, 1.2 g, NDA 022000/S-003, approved September 22, 2010

NOTE: This is the first generic for this drug product.

2. USP 33 Drug Product Monograph: Packaging and storage – Preserve in tight containers
PF 36: No new information for the drug product.

3. PATENTS AND EXCLUSIVITIES

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Certification	Labeling Impact	Use Code
022000	001	6773720	Jun 8, 2020	IV	None	

Exclusivity Data

There is no unexpired exclusivity for this product. (NP Exclusivity expired on 1/16/2010)

4. INACTIVE INGREDIENTS:

The listing of inactive ingredients in the DESCRIPTION section of the package insert is consistent with the listing of inactive ingredients found in the statement of components and composition.

The tablets contain red and yellow iron oxides. According to 21 CFR 73.1200, the total daily amount of elemental iron for an adult patient taking the maximum recommended daily dose should not exceed 5 mg. The firm provided the following calculation:



5. MANUFACTURING FACILITY

Cadila Healthcare Limited

(b) (4)

Ahmedabad

(b) (4)

(b) (4) India

6. PRODUCT DESCRIPTION:

RLD: "red-brown ellipsoidal film coated tablets containing 1.2 g mesalamine, and debossed on one side imprinted with S476"

ANDA: (b) (4)

Drug Product Specifications:

(b) (4)

The tablet debossing(s) have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95).

7. CONTAINER/CLOSURE SYSTEM:

Container: HDPE bottles

Closure: CRC for bottles of 34 and 120, (b) (4)

8. PRODUCT LINE:

RLD: Bottles of 120

ANDA: Bottles of 34, 120 (b) (4)

9. STORAGE CONDITIONS:

RLD: "Store at room temperature 15°C - 25°C (59°F - 77°F); excursions permitted to 30°C (86°F) See USP Controlled Room Temperature"

ANDA: "Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]."

Stability: Accelerated stability (40°C ± 2°C / 75% ± 5% RH) at 0, 1, 2, and 3 months; Intermediate stability (30°C ± 2°C / 65% ± 5% RH) at 0, 3, 6, 9, and 12 months; and at room temperature stability (25°C ± 2°C / 60% ± 5% RH) at 0, 3, 6, 9, and 12 months

10. DISPENSING RECOMMENDATIONS:

RLD: "Pharmacist: Dispense in tight, light-resistant container as defined in USP."

ANDA: "Pharmacist: Dispense in a tight, light-resistant container as defined in USP."

11. SPL DATA ELEMENTS:

Satisfactory

12. MEDWATCH (checked 04/27/2011)

No new alerts or labeling changes.

13. REMS (checked 04/27/2011)

None

Date of Review: April 27, 2011

Primary Reviewer: Sarah Park

Team Leader: Koungh Lee

Review 01 – NA1

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

/s/

SOOJUNG S PARK
04/28/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091640

CHEMISTRY REVIEWS

CHECKLIST FOR THE CHEMISTRY REVIEW:**ANDA 091640 Mesalamine Delayed-release Tablets, 1.2 g****Camille Smith, RBPM**

Function	Performed By (Initial and Date)	Check appropriate box
Is this package for new strength PAS?	RBPM	☐ Yes ☒ No
DMF adequate? REV (NAI) 8-18-16	RBPM	☒ Yes ☐ No *(see comments)
Any outstanding consults?	RBPM	☐ Yes *(see comments) ☒ No
Final recommended dissolution method/specification acknowledged by Firm?	Lead Chemist	☒ Yes ☐ No ☐ N/A
Are all facility inspections acceptable?	RBPM	☒ Yes ☐ No
Is microbiology recommendation adequate for sterile products?	RBPM	☐ Yes ☐ No ☒ N/A
Are there comparability protocols provided? If yes, how many?	Lead Chemist	☐ Yes How many: _____ ☒ No
If USP monograph exists, do the specifications conform to the current USP?	Lead Chemist	☐ Yes ☒ No *(see comments) ☐ N/A
Is the final review uploaded into the current IT platform?	RBPM	☒ Yes ☐ No
5.26.2017		
Dissolution test method used by the firm is the one recommended by the FDA DBE. Assy, and content uniformity comply with the USP. Impurities are tighter than the USP monograph.		
Division	Name	Date
DMRP, Branch 1	Radhika Rajagopalan	5.26.2017



Camille
Smith

Digitally signed by Camille Smith
Date: 5/26/2017 06:41:11AM
GUID: 56268f11002393c2a965ba586399e57f



Radhika
Rajagopalan

Digitally signed by Radhika Rajagopalan
Date: 5/26/2017 08:56:14AM
GUID: 508da70d00028fa6fd86f839d98b6619



**Q1 ANDA Amendment
QUALITY ASSESSMENT**



Recommendation:

ANDA:



Approval



Information Request – Minor

(_____ days for applicant to response)



Complete Response - Minor



Complete Response – Major

ANDA 091640

Amendment Review

Drug Name/Dosage Form	Mesalamine Delayed-release Tablets
Strength	1.2 g
Reviewer(s)	Quamrul Majumder
Applicant	Zydus Pharmaceuticals, Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE
AMENDMENT (SD#34)	2/23//2017

2.3.S DRUG SUBSTANCE

S.1 No Change

S.2 :

Reviewer's Assessment: Acceptable.

(b) (4)

S.3 No Change

S.4

Summary of Applicant's Amendment:

The applicant informed the Agency that they have revised the drug substance specification and standard testing procedure to include an Identification Test by (b) (4) to be in-line with the current USP monograph.

The revised drug substance specification and standard testing procedure are provided in Module 3.2.S.4.1 and Module 3.2.S.4.2, respectively.

(b) (4)

S.5 No Change

S.6 No Change

S.7 No Change

2.3.P DRUG PRODUCT

P.1 No Change

P.2 No Change

P.3 No Change

P.4 No Change

P.5 No Change

P.6 No Change – Firm acknowledged the dissolution procedure for release and stability once again as pasted below:

DISSOLUTION

We acknowledge that you will conduct the dissolution testing of your test product using the following FDA-recommended dissolution method and specification:

Method	Acid Stage A: 750 mL of 100 mM HCl (Acid Stage A) Buffer Stage B: 950 mL of Phosphate buffer, pH 6.4 (Buffer Stage B: A+ 200 mL 200 mM Na ₃ PO ₄) Buffer Stage C: 960 mL of Phosphate buffer, pH 7.2 (Buffer Stage C: B + 9 mL 2M NaOH adjusting pH with 2M NaOH or 2M HCl)
Apparatus	USP apparatus 2 (Paddle)
Speed	100 rpm
Specifications	Acid stage A: NMT (b)(4)% in 2 hours Buffer stage B: NMT (b)(4)% in 1 hour Buffer stage C: 1 hour: NMT (b)(4)% 2 hours: (b)(4)% 6 hours: NLT (b)(4)%

P.7 No Change

P.8 No Change

Labeling & Package CMC Related Concerns: None.

Final labelling review is acceptable on 2/3/15.

Overall Reviewer's Assessment and Signature:

The ANDA is approvable from CMC perspective.

Quamrul Majumder, OPF/DIV I/Branch II, 5/17/2017

Secondary Review Comments and Concurrence: Concur

Radhika. Rajagopalan , OLDP 5/19/2017

List of Deficiencies To Be Communicated by Information Request or Complete Response: NA

Review# 6- Acceptable

ANDA 91640

**Mesalamine Delayed Release Tablets, USP
1200 mg**

Zydus Pharmaceutical, Inc.

**Quamrul Majumder, Ph.D.
Chemistry Division II**

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5. PREVIOUS DOCUMENTS:	2
6. SUBMISSION(S) BEING REVIEWED:	2
7. NAME & ADDRESS OF APPLICANT:	2
8. DRUG PRODUCT NAME/CODE/TYPE:	3
9. LEGAL BASIS FOR SUBMISSION:	3
10. PHARMACOL. CATEGORY:	3
11. DOSAGE FORM:	3
Delayed Release Tablet	3
12. STRENGTH/POTENCY:	3
13. ROUTE OF ADMINISTRATION: Oral	3
14. Rx/OTC DISPENSED: X Rx ___ OTC	3
15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):	3
15b. NANO TECHNOLOGY	3
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:	3
17. RELATED/SUPPORTING DOCUMENTS:	4
18. STATUS	5
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A	APPENDICES	100
A.1	Facilities and Equipment (biotech only)	100
A.2	Adventitious Agents Safety Evaluation NA	100
A.3	Novel Excipients No	100
R	REGIONAL INFORMATION	100
R.1	Executed Batch Records	100
R.2	Comparability Protocols	102
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Chemistry Review Data Sheet

1. ANDA #: 91640
2. REVIEW #: 6
3. REVIEW DATE: 6/25/2014
4. REVIEWER: Quamrul Majumder
5. PREVIOUS DOCUMENTS:

<u>Previous Document(s)</u>	<u>Document Date</u>
Original Application	12/12/2009
Quality/Response To Information Request	02/11/2010
Quality/Response To Information Request	05/20/2010
Quality/Response To Information Request	07/17/2012
Quality/Response To Information Request	06/20/2012
Quality/Response To Information Request	10/23/2012
Quality/Response To Information Request	10/23/2013
Quality/Response To Information Request	02/07/2014

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Quality/Response To Information Request	05/25/2014

7. NAME & ADDRESS OF APPLICANT:

Name: Zydus Pharmaceuticals, Inc.
Address: 210 Carnegie Center, Suite 103 • First Floor,
Princeton, NJ 08540
Representative: G. Srinivas
Telephone: 609-275-5125
Fax: 609-275-3711
Email: gsrinivas@zydususa.com

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name:

Non-Proprietary Name (USAN): Mesalamine Delayed Release Tablets

9. LEGAL BASIS FOR SUBMISSION:

This Abbreviated New Drug Application (ANDA) is based upon the reference listed drug (RLD) LIALDA®, NDA No. 22000, manufactured by Shire US Inc.. The firm has filed Paragraph IV certification for U.S. Patent Nos. 6,773,720 (exp. June 8, 2020). They have also indicated that according to the Orange Book, there is no unexpired exclusivity for the product.

10. PHARMACOL. CATEGORY:

Indicated for mild to moderate ulcerative colitis.

11. DOSAGE FORM:

Delayed Release Tablet

12. STRENGTH/POTENCY:

1200 mg

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. NANO TECHNOLOGY** NANO product – Form Completed X Not a NANO product**16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

Please see drug substance section

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CO DE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	11/28/2012*	By QMAjunder
	III				NA	(b) (4)	
	III				NA		
	III				NA		
	III				NA		

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)

*As of 6/25/2014 no AR update. LOAs only received.

B. Other Documents:



CHEMISTRY REVIEW



Chemistry Review Data Sheet

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA		

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Pending	3/4/14	
Methods Validation Samples	NA Yes received for visual evaluation		Q. Majumdar
Labeling	Acceptable	09/19/2012	C. Park
Bioequivalence	Dissolution, studies- acceptable	07/16/2014	Z. Zhao
EA	Categorical Exclusion requested 21 CFR 25.31(a)		
Radiopharmaceutical	NA		

19. ORDER OF REVIEW

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

20. EES INFORMATION

Drug Substance			
Function	Site Information	FEI/CF N#	Status
[i.e. manufacturer, contract lab, etc.]	[Location, address, etc.]		
(b) (4)	(b) (4)	(b) (4)	Pending
Drug Product			
Function	Site Information	FEI/CF N#	Status
[i.e. manufacturer, contract lab, etc.]	[Location, address, etc.]		
(b) (4)	Cadila Healthcare Limited (b) (4) (b) (4) Ahmedabad (b) (4) India	FEI Number: 3002984 011	Acceptable

Chemistry Review for ANDA 91640

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable from CMC perspective.

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

NA

II. Summary of Chemistry Assessments

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

(b) (4)



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

(b) (4)



Executive Summary Section

=

(b) (4)

The usual dosage in adults is once daily with meal for a total daily dose of 2.4g or 4.8g. Treatment duration in controlled clinical trials was up to 8 weeks.

	<u>IT</u>	<u>QT</u>
DS	0.05%	0.05%
DP	0.10%	0.15%

C. Basis for Approvability or Not-Approval Recommendation

CMC has no further questions at this point and CMC is acceptable. Bio has no further dissolution related deficiencies.

Chemistry Assessment

QUALITY OVERALL SUMMARY

2.3 Introduction to the Quality Overall Summary

Proprietary Name of Drug Product	:	Not Applicable
Non-Proprietary Name of Drug Product	:	Mesalamine Delayed-release Tablets
Non-Proprietary Name of Drug Substance	:	Mesalamine, USP
Company Name	:	Zydus Pharmaceuticals USA Inc. (A subsidiary of Cadila Healthcare Ltd.)
Dosage Form	:	Delayed Release Tablets
Strength	:	1.2 g
Route of Administration	:	Oral
Proposed Indication(s)	:	(b) (4)

2.3.S DRUG SUBSTANCE

2.3.S.1 General Information

What are the nomenclature, molecular structure, molecular formula, and molecular weight?

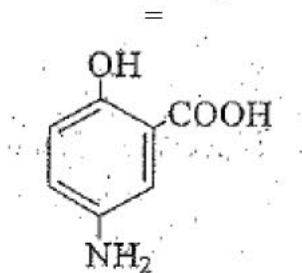
Chemical Name: : 5-amino-2-hydroxybenzoic acid
5-amino-salicylic acid

CAS Number : [89-57-6]

USAN : Mesalamine

Molecular Structure :

Executive Summary Section

**Figure 1: Molecular Structure**

Molecular Formula : $C_7H_7NO_3$

Molecular Weight : 153.14

What are the physicochemical properties including physical description, pKa, polymorphism, aqueous solubility (as function of pH), hygroscopicity, melting points, and partition coefficient?

Physical Description: Light tan to pink colored, needle-shaped crystals.

(b) (4)

ADMINISTRATIVE**A. Reviewer's Signature**

Quamrul Majumder

B. Endorsement Block

Chemist Name/Date: Q Majumder /6/25/2014

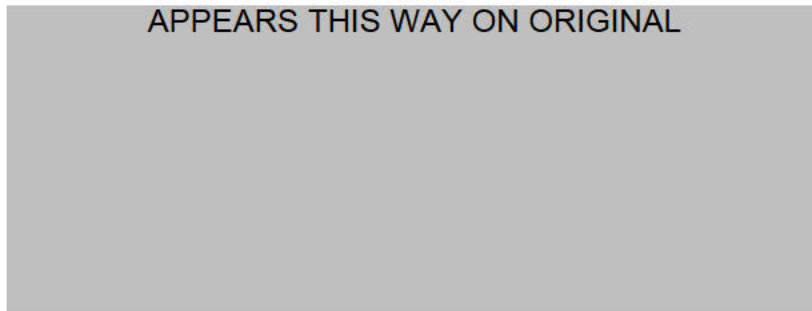
Chemistry Team Leader Name/Date: R. Rajagopalan/ 7/22/14 (after
7/16/14 Bio review was completed)

Project Manager Name/Date: F Nice/7/24/14

Division Name/Date: /G. Smith/P.Capella for G. Smith/24-Jul-2014

TYPE OF LETTER: None

APPEARS THIS WAY ON ORIGINAL



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/s/

QUAMRUL MAJUMDER
07/24/2014

FRANK J NICE
07/24/2014

RADHIKA RAJAGOPALAN
07/24/2014

PETER CAPELLA on behalf of GLEN J SMITH
07/28/2014

Review# 5- Minor

ANDA 91640

**Mesalamine Delayed Release Tablets, USP
1200 mg**

Zydus Pharmaceutical, Inc.

**Quamrul Majumder, Ph.D.
Chemistry Division II**

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4. REVIEWER: Quamrul Majumder	2
5. PREVIOUS DOCUMENTS:	2
6. SUBMISSION(S) BEING REVIEWED:	2
7. NAME & ADDRESS OF APPLICANT:	2
8. DRUG PRODUCT NAME/CODE/TYPE:	3
9. LEGAL BASIS FOR SUBMISSION:	3
10. PHARMACOL. CATEGORY:	3
11. DOSAGE FORM:	3
Delayed Release Tablet	3
12. STRENGTH/POTENCY:	3
13. ROUTE OF ADMINISTRATION: Oral	3
14. Rx/OTC DISPENSED: X Rx ___ OTC	3
15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):	3
15b. NANO TECHNOLOGY	3
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:	3
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A.3	Novel Excipients No	99
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R.2	Comparability Protocols	101
R.3	Methods Validation Package	101
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Chemistry Review Data Sheet

1. ANDA #: 91640
2. REVIEW #: 5
3. REVIEW DATE: 11/27/2013 and 3/5/2014 (after ECD)
4. REVIEWER: Quamrul Majumder

5. PREVIOUS DOCUMENTS:

<u>Previous Document(s)</u>	<u>Document Date</u>
Original Application	12/12/2009
Quality/Response To Information Request	02/11/2010
Quality/Response To Information Request	05/20/2010
Quality/Response To Information Request	07/17/2012
Quality/Response To Information Request	06/20/2012
Quality/Response To Information Request	10/23/2012

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Quality/Response To Information Request	10/23/2013
Quality/Response To Information Request	02/07/2014

7. NAME & ADDRESS OF APPLICANT:

Name: Zydus Pharmaceuticals, Inc.
Address: 210 Carnegie Center, Suite 103 • First Floor,
Princeton, NJ 08540
Representative: G. Srinivas
Telephone: 609-275-5125
Fax: 609-275-3711
Email: gsrinivas@zydususa.com

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name:

Non-Proprietary Name (USAN): Mesalamine Delayed Release Tablets

9. LEGAL BASIS FOR SUBMISSION:

This Abbreviated New Drug Application (ANDA) is based upon the reference listed drug (RLD) LIALDA®, NDA No. 22000, manufactured by Shire US Inc.. The firm has filed Paragraph IV certification for U.S. Patent Nos. 6,773,720 (exp. June 8, 2020). They have also indicated that according to the Orange Book, there is no unexpired exclusivity for the product.

10. PHARMACOL. CATEGORY:

Indicated for mild to moderate ulcerative colitis.

11. DOSAGE FORM:

Delayed Release Tablet

12. STRENGTH/POTENCY:

1200 mg

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. NANO TECHNOLOGY** NANO product – Form Completed X Not a NANO product**16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

Please see drug substance section

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CO DE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	11/28/2012*	By QMAjunder
	III				NA	(b) (4)	
	III				NA		
	III				NA		
	III				NA		

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)

*As of 1/27/2013 no AR update. LOAs only received.

B. Other Documents:

Chemistry Review Data Sheet

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA		

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Pending	3/4/14	Nice, FJ
Methods Validation Samples	NA Yes received for visual evaluation		Q. Majumdar
Labeling	Acceptable	09/19/2012	C. Park
Bioequivalence	Inadequate	03/01/2014	ZHAO, ZHUOJUN
EA	Categorical Exclusion requested 21 CFR 25.31(a)		
Radiopharmaceutical	NA		

19. ORDER OF REVIEW

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

20. EES INFORMATION

Drug Substance			
Function	Site Information	FEI/CF N#	Status
<i>[i.e. manufacturer, contract lab, etc.]</i>	<i>[Location, address, etc.]</i>		
(b) (4)	(b) (4)		
Drug Product			
Function	Site Information	FEI/CF N#	Status
<i>[i.e. manufacturer, contract lab, etc.]</i>	<i>[Location, address, etc.]</i>		
(b) (4)	Cadila Healthcare Limited (b) (4) Ahmedabad India	FEI Number: 3002984 011	

Chemistry Review for ANDA 91640

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable from CMC perspective.

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

NA

II. Summary of Chemistry Assessments

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

(b) (4)



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

(b) (4)



Executive Summary Section

(b) (4)

The usual dosage in adults is once daily with meal for a total daily dose of 2.4g or 4.8g. Treatment duration in controlled clinical trials was up to 8 weeks.

	<u>IT</u>	<u>QT</u>
DS	0.05%	0.05%
DP	0.10%	0.15%

C. Basis for Approvability or Not-Approval Recommendation

CMC has no further questions at this point. Bio has dissolution related deficiencies which will result in dissolution method updates. Review team notes that if Bio is not satisfactory, that may result in additional CMC questions.

Chemistry Assessment

QUALITY OVERALL SUMMARY

2.3 Introduction to the Quality Overall Summary

Proprietary Name of Drug Product	:	Not Applicable
Non-Proprietary Name of Drug Product	:	Mesalamine Delayed-release Tablets
Non-Proprietary Name of Drug Substance	:	Mesalamine, USP
Company Name	:	Zydus Pharmaceuticals USA Inc. (A subsidiary of Cadila Healthcare Ltd.)
Dosage Form	:	Delayed Release Tablets
Strength	:	1.2 g
Route of Administration	:	Oral
Proposed Indication(s)	:	(b) (4)

2.3.S DRUG SUBSTANCE

2.3.S.1 General Information

What are the nomenclature, molecular structure, molecular formula, and molecular weight?

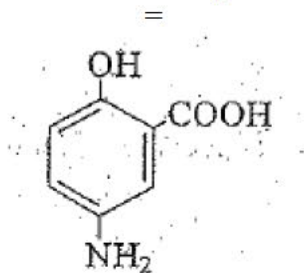
Chemical Name: : 5-amino-2-hydroxybenzoic acid
5-amino-salicylic acid

CAS Number : [89-57-6]

USAN : Mesalamine

Molecular Structure :

Executive Summary Section

**Figure 1: Molecular Structure**

Molecular Formula : $C_7H_7NO_3$

Molecular Weight : 153.14

What are the physicochemical properties including physical description, pKa, polymorphism, aqueous solubility (as function of pH), hygroscopicity, melting points, and partition coefficient?

(b) (4)

ADMINISTRATIVE**A. Reviewer's Signature**

Quamrul Majumder

B. Endorsement Block

Chemist Name/Date: Q Majumder 2/3/2014 and 3/5/2014 (after ECD)

Chemistry Team Leader Name/Date: R. Rajagopalan/2/1/2014; 3/6/2014
(after ECD)

Project Manager Name/Date: F Nice/4/20/14

Division Name/Date: /G. Smith/2/1/2014; 3/19/2014

TYPE OF LETTER: Minor

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

/s/

QUAMRUL MAJUMDER
03/20/2014

FRANK J NICE
03/20/2014

RADHIKA RAJAGOPALAN
03/20/2014

PETER CAPELLA on behalf of SUSAN M ROSENCRANCE
03/21/2014

ANDA 91640

**Mesalamine Delayed Release Tablets, USP
1200 mg**

Zydus Pharmaceutical , Inc.

**Quamrul Majumder, Ph.D.
Chemistry Division II**

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Chemistry Review Data Sheet

1. ANDA #: 91640
2. REVIEW #: 4
3. REVIEW DATE: 11/13/2012
4. REVIEWER: Quamrul Majumder
5. PREVIOUS DOCUMENTS:

<u>Previous Document(s)</u>	<u>Document Date</u>
Original Application	12/12/2009
Quality/Response To Information Request	02/11/2010
Quality/Response To Information Request	05/20/2010
Quality/Response To Information Request	07/17/2012
Quality/Response To Information Request	06/20/2012

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Application	12/12/2009
Quality/Response To Information Request	10/23/2012

7. NAME & ADDRESS OF APPLICANT:

Name: Zydus Pharmaceuticals, Inc.
Address: 210 Carnegie Center, Suite 103 • First Floor,
Princeton, NJ 08540
Representative: G. Srinivas
Telephone: 609-275-5125
Fax: 609-275-3711
Email: gsrinivas@zydususa.com

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name:

Non-Proprietary Name (USAN): Mesalamine Delayed Release Tablets

9. LEGAL BASIS FOR SUBMISSION:

This Abbreviated New Drug Application (ANDA) is based upon the reference listed drug (RLD) LIALDA®, NDA No. 22000, manufactured by Shire US Inc.. The firm has filed Paragraph IV certification for U.S. Patent Nos. 6,773,720 (exp. June 8, 2020). They have also indicated that according to the Orange Book, there is no unexpired exclusivity for the product.

10. PHARMACOL. CATEGORY:

Indicated for mild to moderate ulcerative colitis.

11. DOSAGE FORM:

Delayed Release Tablet

12. STRENGTH/POTENCY:

1200 mg

13. ROUTE OF ADMINISTRATION: Oral**14. Rx/OTC DISPENSED:** ☒ **Rx** ☐ **OTC****15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**☐ SPOTS product – Form Completed☒ Not a SPOTS product**15b. NANO TECHNOLOGY**☐ NANO product – Form Completed☒ Not a NANO product**16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

Please see drug substance section

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CO DE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	11/28/2012	By QMAjumper
	III				NA	(b) (4)	
	III				NA		
	III				NA		
	III				NA		
	III				NA		

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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA		

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Acceptable	7/17/12; Reevaluation Date: 9/24/13	Nice, FJ
Methods Validation Samples	NA Yes received for visual evaluation		Q. Majumdar
Labeling	Acceptable	09/19/2012	C. Park
Bioequivalence	Incomplete (Dissolution only) Bioequivalence is pending PK studies requested along with more dissolution data	02/23/2012	ZHAO, ZHUOJUN Additional studies (PK) are requested; f2 dissolution calculation also requested. Pending
EA	Categorical Exclusion requested 21 CFR 25.31(a)		
Radiopharmaceutical	NA		

19. ORDER OF REVIEW

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

Chemistry Review for ANDA 91640

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable for CMC deficiency.

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

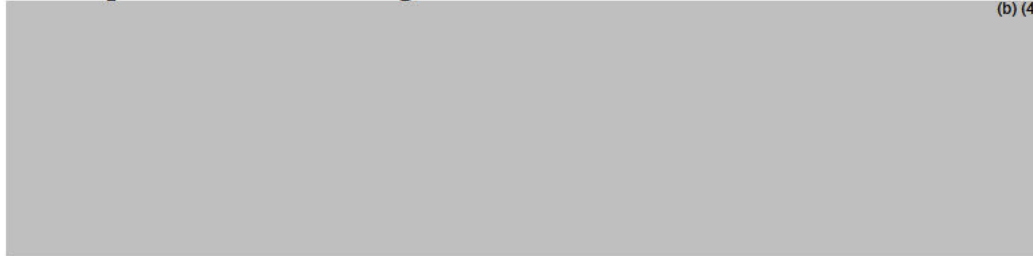
NA

II. Summary of Chemistry Assessments

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



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



Executive Summary Section

=

(b) (4)

The usual dosage in adults is once daily with meal for a total daily dose of 2.4g or 4.8g. Treatment duration in controlled clinical trials was up to 8 weeks.

	<u>IT</u>	<u>QT</u>
DS	0.05%	0.05%
DP	0.10%	0.15%

C. Basis for Approvability or Not-Approval Recommendation

The application is not recommended for approval. Minor CMC deficiency is recommended.

Chemistry Assessment**QUALITY OVERALL SUMMARY****2.3 Introduction to the Quality Overall Summary**

Proprietary Name of Drug Product	: Not Applicable
Non-Proprietary Name of Drug Product	: Mesalamine Delayed-release Tablets
Non-Proprietary Name of Drug Substance	: Mesalamine, USP
Company Name	: Zydus Pharmaceuticals USA Inc. (A subsidiary of Cadila Healthcare Ltd.)
Dosage Form	: Delayed Release Tablets
Strength	: 1.2 g
Route of Administration	: Oral
Proposed Indication(s)	: (b) (4)

2.3.S DRUG SUBSTANCE

Executive Summary Section

=

2.3.S.1 General Information

What are the nomenclature, molecular structure, molecular formula, and molecular weight?

Chemical Name: : 5-amino-2-hydroxybenzoic acid
5-amino-salicylic acid

CAS Number : [89-57-6]

USAN Mesalamine

Molecular Structure :

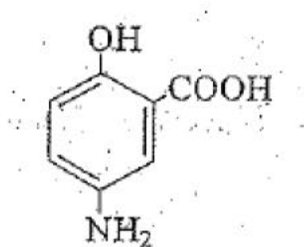


Figure 1: Molecular Structure

Molecular Formula : $C_7H_7NO_3$

Molecular Weight : 153.14

What are the physicochemical properties including physical description, pKa, polymorphism, aqueous solubility (as function of pH), hygroscopicity, melting points, and partition coefficient?

Physical Description: Light tan to pink colored, needle-shaped crystals.

(b) (4)

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/s/

QUAMRUL MAJUMDER
02/19/2013

FRANK J NICE
02/19/2013

RADHIKA RAJAGOPALAN
02/19/2013

SUSAN M ROSENCRANCE
02/26/2013

ANDA 91640

**Mesalamine Delayed Release Tablets, USP
1200 mg**

Zydus Pharmaceutical , Inc.

**Quamrul Majumder, Ph.D.
Chemistry Division II**

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10. PHARMACOL. CATEGORY:.....	3
11. DOSAGE FORM:.....	3
Delayed Release Tablet.....	3
12. STRENGTH/POTENCY:	3
13. ROUTE OF ADMINISTRATION: Oral	3
14. Rx/OTC DISPENSED: X Rx ___ OTC	3
15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM) : Error!	
Bookmark not defined.	
15b. NANOTECHNOLOGY PRODUCT TRACKING: ... Error! Bookmark not	
defined.	
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:	3
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A.3	Novel Excipients No	96
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R.3	Methods Validation Package	97
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Figure 1:	Molecular Structure	10
Figure 2	List of Impurities	13

Chemistry Review Data Sheet

1. ANDA #: 91640
2. REVIEW #: 3
3. REVIEW DATE: 7/5/2012; 8/14/2012
4. REVIEWER: Quamrul Majumder
5. PREVIOUS DOCUMENTS:

<u>Previous Document(s)</u>	<u>Document Date</u>
Original Application	12/12/2009
Quality/Response To Information Request	02/11/2010
Quality/Response To Information Request	05/20/2010

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Quality/Response To Information Request	07/17/2012
Quality/Response To Information Request	06/20/2012

7. NAME & ADDRESS OF APPLICANT:

Name: Zydus Pharmaceuticals, Inc.
Address: 210 Carnegie Center, Suite 103 • First Floor,
Princeton, NJ 08540
Representative: G. Srinivas
Telephone: 609-275-5125
Fax: 609-275-3711
Email: gsrinivas@zydususa.com

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name:
Non-Proprietary Name (USAN): Mesalamine Delayed Release Tablets

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION:

This Abbreviated New Drug Application (ANDA) is based upon the reference listed drug (RLD) LIALDA®, NDA No. 22000, manufactured by Shire US Inc.. The firm has filed Paragraph IV certification for U.S. Patent Nos. 6,773,720 (exp. June 8, 2020). They have also indicated that according to the Orange Book, there is no unexpired exclusivity for the product.

10. PHARMACOL. CATEGORY:

Indicated for mild to moderate ulcerative colitis.

11. DOSAGE FORM:

Delayed Release Tablet

12. STRENGTH/POTENCY:

1200 mg

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. NANO TECHNOLOGY

 NANO product – Form Completed

 X Not a NANO product

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

Please see drug substance section

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CO DE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Inadequate	8/13/2012	By QMAjumper
	III				NA	(b) (4)	
	III				NA		
	III				NA		
	III				NA		
	III				NA		

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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA		

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Acceptable	7/17/12; Reevaluation Date: 9/24/13	FJNice
Methods Validation	NA		
Labeling	Deficiencies	7/16/12	C. Park
Bioequivalence	Incomplete (Dissolution only) Bioequivalence is pending	02/23/2012	ZHAO, ZHUOJUN
EA	Categorical Exclusion requested 21 CFR 25.31(a)		
Radiopharmaceutical	NA		

19. ORDER OF REVIEW

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

Chemistry Review for ANDA 91640

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable for CMC deficiency.

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

NA

II. Summary of Chemistry Assessments

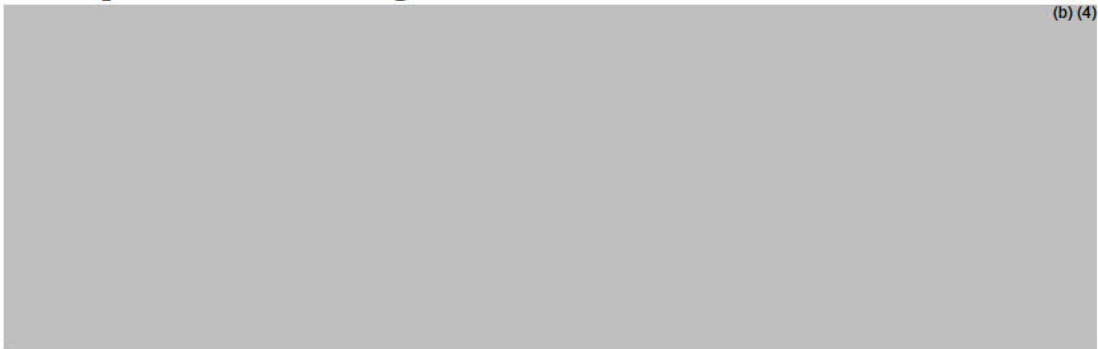
A. Description of the Drug Product(s) and Drug Substance(s)

(b) (4)



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

(b) (4)



Executive Summary Section

=

The usual dosage in adults is once daily with meal for a total daily dose of 2.4g or 4.8g. Treatment duration in controlled clinical trials was up to 8 weeks.

	<u>IT</u>	<u>QT</u>
DS	0.05%	0.05%
DP	0.10%	0.15%

C. Basis for Approvability or Not-Approval Recommendation

The application is not recommended for approval. Minor amendment is recommended.

Chemistry Assessment

QUALITY OVERALL SUMMARY

2.3 Introduction to the Quality Overall Summary

Proprietary Name of Drug Product	:	Not Applicable
Non-Proprietary Name of Drug Product	:	Mesalamine Delayed-release Tablets
Non-Proprietary Name of Drug Substance	:	Mesalamine, USP
Company Name	:	Zydus Pharmaceuticals USA Inc. (A subsidiary of Cadila Healthcare Ltd.)
Dosage Form	:	Delayed Release Tablets
Strength	:	1.2 g
Route of Administration	:	Oral
Proposed Indication(s)	:	(b) (4)

2.3.S DRUG SUBSTANCE

2.3.S.1 General Information

What are the nomenclature, molecular structure, molecular formula, and molecular weight?

Chemical Name: : 5-amino-2-hydroxybenzoic acid
5-amino-salicylic acid

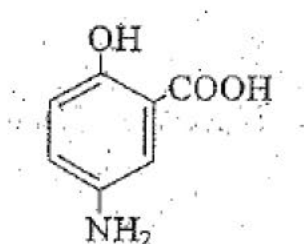
CAS Number : [89-57-6]

USAN Mesalamine

Molecular Structure :

Executive Summary Section

=

**Figure 1: Molecular Structure**

Molecular Formula : $C_7H_7NO_3$

Molecular Weight : 153.14

What are the physicochemical properties including physical description, pKa, polymorphism, aqueous solubility (as function of pH), hygroscopicity, melting points, and partition coefficient?

Physical Description: Light tan to pink colored, needle-shaped crystals.

(b) (4)

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

/s/

QUAMRUL MAJUMDER
08/20/2012

FRANK J NICE
08/21/2012

RADHIKA RAJAGOPALAN
08/21/2012

ANDA 91640

**Mesalamine Delayed Release Tablets, USP
1200 mg**

Zydus Pharmaceutical , Inc.

**Quamrul Majumder, Ph.D.
Chemistry Division II**

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5. PREVIOUS DOCUMENTS:.....	2
6. SUBMISSION(S) BEING REVIEWED:	2
7. NAME & ADDRESS OF APPLICANT:	2
8. DRUG PRODUCT NAME/CODE/TYPE:.....	2
9. LEGAL BASIS FOR SUBMISSION:	3
10. PHARMACOL. CATEGORY:.....	3
11. DOSAGE FORM:.....	3
Delayed Release Tablet.....	3
12. STRENGTH/POTENCY:	3
13. ROUTE OF ADMINISTRATION: Oral	3
14. Rx/OTC DISPENSED: X Rx ___ OTC	3
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A.2 Adventitious Agents Safety Evaluation NA	89

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Figure 1:	Molecular Structure	10
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Chemistry Review Data Sheet

1. ANDA #: 91640
2. REVIEW #: 2
3. REVIEW DATE: 5/3/2011
4. REVIEWER: Quamrul Majumder
5. PREVIOUS DOCUMENTS:

Previous Document(s)Document Date

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original Application

12/12/2009

Quality/Response To Information Request

02/11/2010

Quality/Response To Information Request

05/20/2010

7. NAME & ADDRESS OF APPLICANT:

Name: Zydus Pharmaceuticals, Inc.

Address: 210 Carnegie Center, Suite 103 • First Floor,
Princeton, NJ 08540

Representative: G. Srinivas

Telephone: 609-275-5125

Fax: 609-275-3711

Email: gsrinivas@zydususa.com

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name:

Non-Proprietary Name (USAN): Mesalamine Delayed Release Tablets

Chemistry Review Data Sheet

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This Abbreviated New Drug Application (ANDA) is based upon the reference listed drug (RLD) LIALDA®, NDA No. 22000, manufactured by Shire US Inc.. The firm has filed Paragraph IV certification for U.S. Patent Nos. 6,773,720 (exp. June 8, 2020). They have also indicated that according to the Orange Book, there is no unexpired exclusivity for the product.

10. PHARMACOL. CATEGORY:

Indicated for mild to moderate ulcerative colitis.

11. DOSAGE FORM:

Delayed Release Tablet

12. STRENGTH/POTENCY:

1200 mg

13. ROUTE OF ADMINISTRATION: Oral**14. Rx/OTC DISPENSED:** X Rx OTC**15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**

 SPOTS product – Form Completed

 X Not a SPOTS product

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

Please see drug substance section

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CO DE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Annual reports Reviewed	10/25/10	By QMAjunder
	III				NA	(b) (4)	
	III				NA		
	III				NA		
	III				NA		
	III				NA		

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1 – DMF Reviewed.

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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)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA		

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Pending	5/23/10	FJNice
Methods Validation	NA		
Labeling	Deficiencies	05/02/2011	SOOJUNG S PARK,
Bioequivalence	Incomplete (Dissolution only)	08/03/2010	MAHADEVAN, CHITRA
EA	Categorical Exclusion requested 21 CFR 25.31(a)		
Radiopharmaceutical	NA		

19. ORDER OF REVIEW

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

Chemistry Review for ANDA 91640

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable for CMC.

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

(b) (4)



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(b) (4)



Executive Summary Section

=

The usual dosage in adults is once daily with meal for a total daily dose of 2.4g or 4.8g. Treatment duration in controlled clinical trials was up to 8 weeks.

	<u>IT</u>	<u>QT</u>
DS	0.05%	0.05%
DP	0.10%	0.15%

C. Basis for Approvability or Not-Approval Recommendation

The application is not recommended for approval due to changes needed in drug product specifications, manufacturing, stability, and other minor issues.

Chemistry Assessment

QUALITY OVERALL SUMMARY

2.3 Introduction to the Quality Overall Summary

Proprietary Name of Drug Product	:	Not Applicable
Non-Proprietary Name of Drug Product	:	Mesalamine Delayed-release Tablets
Non-Proprietary Name of Drug Substance	:	Mesalamine, USP
Company Name	:	Zydus Pharmaceuticals USA Inc. (A subsidiary of Cadila Healthcare Ltd.)
Dosage Form	:	Delayed Release Tablets
Strength	:	1.2 g
Route of Administration	:	Oral
Proposed Indication(s)	:	(b) (4)

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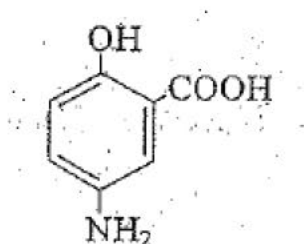
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USAN Mesalamine

Molecular Structure :

Executive Summary Section

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**Figure 1: Molecular Structure**

Molecular Formula : $C_7H_7NO_3$

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/s/

FRANK J NICE on behalf of QUAMRUL MAJUMDER
06/01/2011

FRANK J NICE
06/01/2011

RADHIKA RAJAGOPALAN
06/01/2011

ANDA 91640

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1200 mg**

Zydus Pharmaceutical , Inc.

**Quamrul Majumder
Chemistry Division II**

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3. REVIEW DATE: 9/13/2010	2
4. REVIEWER: Quamrul Majumder	2
5. PREVIOUS DOCUMENTS:	2
6. SUBMISSION(S) BEING REVIEWED:	2
7. NAME & ADDRESS OF APPLICANT:	2
8. DRUG PRODUCT NAME/CODE/TYPE:	2
9. LEGAL BASIS FOR SUBMISSION:	3
10. PHARMACOL. CATEGORY:	3
11. DOSAGE FORM:	3
Delayed Release Tablet	3
12. STRENGTH/POTENCY:	3
13. ROUTE OF ADMINISTRATION: Oral	3
14. Rx/OTC DISPENSED: X Rx ___ OTC	3
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):	3
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:	3
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Chemistry Review Data Sheet

1. ANDA #: 91640
2. REVIEW #: 1
3. REVIEW DATE: 9/13/2010
4. REVIEWER: Quamrul Majumder
5. PREVIOUS DOCUMENTS:

Previous Document(s)Document Date

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original Application

12/12/2009

Quality/Response To Information Request

02/11/2010

Quality/Response To Information Request

05/20/2010

7. NAME & ADDRESS OF APPLICANT:

Name: Zydus Pharmaceuticals, Inc.

Address: 210 Carnegie Center, Suite 103 • First Floor,
Princeton, NJ 08540

Representative: G. Srinivas

Telephone: 609-275-5125

Fax: 609-275-3711

Email: gsrinivas@zydususa.com

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name:

Non-Proprietary Name (USAN): Mesalamine Delayed Release Tablets

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION:

This Abbreviated New Drug Application (ANDA) is based upon the reference listed drug (RLD) LIALDA®, NDA No. 22000, manufactured by Shire US Inc.. The firm has filed Paragraph IV certification for U.S. Patent Nos. 6,773,720 (exp. June 8, 2020). They have also indicated that according to the Orange Book, there is no unexpired exclusivity for the product.

10. PHARMACOL. CATEGORY:

Indicated for mild to moderate ulcerative colitis.

11. DOSAGE FORM:

Delayed Release Tablet

12. STRENGTH/POTENCY:

1200 mg

13. ROUTE OF ADMINISTRATION: Oral**14. Rx/OTC DISPENSED:** X Rx OTC**15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**

 SPOTS product – Form Completed

 X Not a SPOTS product

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

Please see drug substance section

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CO DE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Annual reports Reviewed	10/25/10	By QMAjunder
	III				NA	(b) (4)	
	III				NA		
	III				NA		
	III				NA		
	III				NA		

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)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA		

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Pending	5/23/10	FJNice
Methods Validation	NA		
Labeling	Pending		
Bioequivalence	Incomplete (Dissolution only)	08/03/2010	MAHADEVAN, CHITRA
EA	Categorical Exclusion requested 21 CFR 25.31(a)		
Radiopharmaceutical	NA		

19. ORDER OF REVIEW

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

Chemistry Review for ANDA 91640

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable for CMC.

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

NA

II. Summary of Chemistry Assessments

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

(b) (4)



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

(b) (4)



Executive Summary Section

=

The usual dosage in adults is once daily with meal for a total daily dose of 2.4g or 4.8g. Treatment duration in controlled clinical trials was up to 8 weeks.

	<u>IT</u>	<u>QT</u>
DS	0.05%	0.05%
DP	0.10%	0.15%

C. Basis for Approvability or Not-Approval Recommendation

The application is not recommended for approval due to changes needed in the drug substance and drug product specifications, manufacturing, and other minor issues.

Chemistry Assessment

QUALITY OVERALL SUMMARY

2.3 Introduction to the Quality Overall Summary

Proprietary Name of Drug Product	:	Not Applicable
Non-Proprietary Name of Drug Product	:	Mesalamine Delayed-release Tablets
Non-Proprietary Name of Drug Substance	:	Mesalamine, USP
Company Name	:	Zydus Pharmaceuticals USA Inc. (A subsidiary of Cadila Healthcare Ltd.)
Dosage Form	:	Delayed Release Tablets
Strength	:	1.2 g
Route of Administration	:	Oral
Proposed Indication(s)	:	(b) (4)

2.3.S DRUG SUBSTANCE

2.3.S.1 General Information

What are the nomenclature, molecular structure, molecular formula, and molecular weight?

Chemical Name: : 5-amino-2-hydroxybenzoic acid
5-amino-salicylic acid

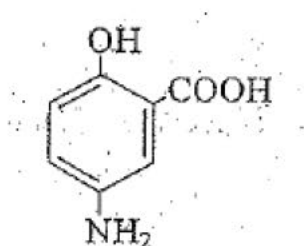
CAS Number : [89-57-6]

USAN : Mesalamine

Molecular Structure :

Executive Summary Section

=

**Figure 1: Molecular Structure**

Molecular Formula : $C_7H_7NO_3$

Molecular Weight : 153.14

What are the physicochemical properties including physical description, pKa, polymorphism, aqueous solubility (as function of pH), hygroscopicity, melting points, and partition coefficient?

Physical Description: Light tan to pink colored, needle-shaped crystals.

(b) (4)

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

/s/

QUAMRUL MAJUMDER
12/03/2010

FRANK J NICE
12/03/2010

RADHIKA RAJAGOPALAN
12/03/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091640

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	091640		
Drug Product Name	Mesalamine Delayed-release Tablets		
Strength (s)	1200 mg		
Applicant Name	Zydus Pharmaceuticals USA Inc.		
Applicant Address	210 Carnegie Center, 1 st Floor, Suite 103, Princeton, NJ-08540		
US Agent Name and the mailing address	G. Srinivas 210 Carnegie Center, 1 st Floor, Suite 103, Princeton, NJ-08540		
US Agent's Telephone Number	609-275-5125		
US Agent's Fax Number	609-275-3711		
Original Submission Date(s)	December 12, 2009 April 13, 2010 (Formulation Data) September 8, 2010 (Dissolution Acknowledgement) February 12, 2011 (Elemental Iron content update) October 23, 2013 (Study Amendment of PK BE study) May 23, 2014 (study amendment) December 8, 2014 (study amendment) 06/05/2015 Post CR meeting request		
Submission Date(s) of Amendment(s) Under Review	09/01/2015 amendment for complete response dated 5/29/2015 and for Post CR meeting response dated 08/21/2015		
First Generic	Yes		
Reviewer	Ping Ren, Ph.D.		
OVERALL REVIEW RESULT	☒ Adequate ☐ Inadequate		
Communication	☐ ECD ☐ IR ☒ Not Applicable		
OSI Status	Adequate		
Dissolution Review Results	Adequate Dissolution was reviewed in a separate document (DARRTS: REV-BIOEQ-02 (Dissolution Review), check-in date 07/14/2014)		
REVIEW RESULT	Adequate		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1	Fasting	1200 mg	Adequate
1	Fed	1200 mg	Adequate
2	Pilot Fed	1200 mg	Adequate
1	Pilot Fed	1200 mg	Adequate
1	In vitro BE	1200 mg	Adequate

	dissolution study		
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The Amendment Review of AND A091640

1 EXECUTIVE SUMMARY

This application contains the results of fasting and fed bioequivalence (BE) studies comparing a test product, Zydus Pharmaceuticals USA Inc.'s Mesalamine DR Tablets, 1200 mg to the corresponding reference product, Shire's Lialda® (Mesalamine) Delayed Release Tablets, 1200 mg. The firm's fasting and fed BE studies are acceptable. In addition to in vivo BE studies, the firm conducted *in vitro* comparative dissolution study over a range of represented pH in GI to demonstrate the bioequivalence between its test product and the reference product. The firm's in vitro BE dissolution results showed similar dissolution profiles between the test and reference products at pH 7.2 and pH 7.5 but not at pH 6.5 and 6.8.

After consulting with the science team, the testing at pH 6.5 is deemed acceptable due to the test product had minimal release at pH 6.5. However, in CR letter dated 5/29/2015, the firm was requested to re-conduct the study at (b) (4) pHs, 6.8, (b) (4) using fresh lots of test and RLD products due to the fact that dissolution data of the fresh test product (1 month) is significantly different from that of 31 month old product.

On June 05, 2015, Zydus requested a Post Complete Response Teleconference Meeting to discuss deficiencies noted in the Complete Response (CR) Letter dated May 29, 2015, for ANDA 091640, Mesalamine Delayed-release Tablets, 1.2 g. In its post CR response, the firm requested to waive-off the additional in vitro comparative dissolution data at pH 6.8, (b) (4)

After carefully re-evaluating the data of in vivo and in vitro studies, particularly for in vitro dissolution data at pH 6.8, DB II accepts the firm's request to waive-off the additional in vitro comparative dissolution data at pH 6.8 in post CR meeting written response dated 8/21/2015.

Based on the internal meeting minutes, the *in vitro* BE dissolution testing are acceptable for pH 6.5, 6.8, 7.2 and 7.5 for Mesalamine Delayed-release Tablets. In the amendment dated 09/01/2015, the firm acknowledged the agency's final decision. Therefore, both in vivo and in vitro BE studies are adequate for the current application.

No Division of Scientific Investigations (DSI) inspection is pending or necessary.

The application is acceptable without any deficiency.

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3 REVIEW OF SUBMISSION

Background

This application contains the results of fasting and fed bioequivalence (BE) studies comparing a test product, Zydus Pharmaceuticals USA Inc.'s Mesalamine DR Tablets, 1200 mg to the corresponding reference product, Shire's Lialda® (Mesalamine) Delayed Release Tablets, 1200 mg. The firm's fasting and fed BE studies are acceptable. In addition to in vivo BE studies, the firm conducted *in vitro* comparative dissolution study over a range of represented pH in GI to demonstrate the bioequivalence between its test product and the reference product. The firm's in vitro BE dissolution results showed similar dissolution profiles between the test and reference products at pH 7.2 and pH 7.5 but not at pH 6.5 and 6.8.

After consulting with the science team, the testing at pH 6.5 is deemed acceptable due to the test product had minimal release at pH 6.5. However, in CR letter dated 5/29/2015, the firm was requested to re-conduct the study at (b) (4) pHs, 6.8, (b) (4) using fresh lots of test and RLD products due to the fact that dissolution data of the fresh test product (1 month) is significantly different from that of 31 month old product.

On June 05, 2015, Zydus requested a Post Complete Response Teleconference Meeting to discuss deficiencies noted in the Complete Response (CR) Letter dated May 29, 2015, for ANDA 091640, Mesalamine Delayed-release Tablets, 1.2 g. In its post CR response, the firm requested to waive-off the additional in vitro comparative dissolution data at pH 6.8, (b) (4)

After carefully re-evaluating the data of in vivo and in vitro studies, particularly for in vitro dissolution data at pH 6.8, DB II accepts the firm's request to waive-off the additional in vitro comparative dissolution data at pH 6.8 in post CR meeting written response dated 8/21/2015 due to following reasons:

1. Acceptable in vivo BE studies with clinical and PK end points.
2. In vitro BE dissolution testing are acceptable for pH 6.5, 7.2 and 7.5. For pH 6.8, the dissolution is comparable to that of the RLD at 1, 2, 6 and 8 hours except at 4 hours (please note f2 criteria is not necessary to apply to this pH per previous consult to science team)
3. The RLD showed high variability from lots to lots in the current ANDAs as well as across ANDAs. The dissolution profiles of the test product (1 month) are similar to at least one batch of the RLD at pH 6.8, i.e.F2>50 (data from more than

one lots of the RLD is submitted) and are within the lot-to-lot variability of the RLD not only in the current ANDA but also across ANDAs.

4. The firm demonstrated that high within-batch variability of the test product at pH 6.8 is due to the inherent pH dependent solubility nature of the (b) (4)

Firm's submission in amendment dated 9/1/2015

BIOEQUIVALENCE:

1. Although your test product at 31 month (expired) met the shelf life specification, we noticed that the dissolution data of the fresh test product (1 month) in your submission dated October 23, 2013, is significantly different from that of 31 month old product (submitted in amendment December 6, 2014) under pH 6.8. Using bootstrapping method, the F2 value between the data of your 1 month and 31 month test product at pH 6.8 is only 25.66. Therefore, your dissolution testing data at pH 6.8, (b) (4) in the current amendment (December 6, 2014) is not acceptable. Please provide your explanation for the observed faster release of the aged product when compared to the fresh product.

2. Please re-conduct the study using fresh test (24 units) and RLD products (at least 24 units from two different lots or more) for the following conditions:

Apparatus: USP Apparatus 2 (paddle)

Pretreatment Stage 1: 2 hours in 100 mM HCl at 100 rpm (750 mL)

Pretreatment Stage 2: 1 hour in pH 6.4 Phosphate buffer at 100 rpm (950 mL)

Evaluation Stage: Each of

(1) pH 6.8 Phosphate buffer at 100 rpm
(b) (4)

Volume: 960 mL

Temperature: 37°C

Sample times: 1, 2, 3, 4, 5, 6 and 8 hours or as needed for profile comparison

3. As we recommended in the Complete Response letter dated September 23, 2014, due to the high variability of your in vitro BE dissolution data at pH 6.8 (i.e. percentage coefficient of variation > 10%), an f2 test using mean profiles of test vs. reference listed drug ("RLD") products is not sufficient as per the above "Dissolution Guidance". Therefore, we will calculate the f2 metric (an f2 confidence interval) using a bootstrapping method for the dissolution profile comparison. You may also consider the following options for your above new dissolution testing: 1) repeat comparative dissolution testing using one batch of freshly prepared buffer for both test and RLD products, 2) test a larger number of tablets (e.g. at least 24 units for each product) to provide a better estimate of the mean difference 3) use 2 or more batches of RLD products (at least 24 units; 12 unit for each batch) and 4) conduct the comparative dissolution testing for the test and reference products on the same day.

Firm's response:

Response for deficiency nos. #1, 2 and 3:

On June 5, 2015, Zydus Pharmaceuticals (USA) Inc. requested a Post Complete Response Teleconference Meeting to discuss deficiencies noted in the Complete Response letter dated May 28, 2015, for ANDA 091640, Mesalamine Delayed-release Tablets USP, 1.2 g. The Office of Generic Drugs provided the following responses to Zydus Pharmaceuticals (USA) Inc.'s questions as per the June 12, 2015, Meeting Request Granted – Written Responses Only correspondence.

“FDA POST CR MEETING REQUEST WRITTEN RESPONSES - BIOEQUIVALENCE¹”

The Division of Bioequivalence II (DBII) has re-evaluated the data for the in vitro BE dissolution studies, as well as your rationale for the high variability of dissolution data at pH 6.8. The DBII concludes that the in vitro BE dissolution testing at pH 6.8 is now acceptable. Therefore, DB II agrees with your request to waive the additional data requested in the complete response letter dated May 28, 2015.”

The [Post Complete Response Teleconference Meeting Request](#) was provided in Module 1.2 of amendment (0027) dated June 4, 2015. The [Meeting Request Granted Written Responses Only](#) received from the Agency in response to the meeting request is provided in Module 1.2 of this amendment.

Based on the communication received from the Agency dated August 21, 2015, the *Division of Bioequivalence II* has acknowledged that dissolution testing data at pH 6.8, (b) (4) submitted in the amendment dated December 6, 2014 (0026) are acceptable and additional dissolution data are not required.

Reviewer's Comment:

Based on the internal meeting minutes², the *in vitro* BE dissolution testing are acceptable for pH 6.5, 6.8, 7.2 and 7.5 for Mesalamine Delayed-release Tablets. In the amendment dated 09/01/2015, the firm acknowledged the agency's final decision. Therefore, both in vivo and in vitro BE studies are adequate for the current application.

¹ Panorama system: ANDA-091640-GI-1 MEETING-30: Respond to BE questions: A91640PostCRmeetLetter060515 final by Dr. Ping Ren. Final date: 07/28/2015.

² V:\DIVISION\BIO\BIO2\BIO Management Meeting Minutes\2015 Meeting Minutes\Non-BMM Internal Meeting Minutes: 7.16.15ANDA91640Post CR MR final date: 07/29/2015.

BIOEQUIVALENCE COMMENT TO BE PROVIDED TO THE APPLICANT

ANDA: 091640

APPLICANT: Zydus Pharmaceuticals USA Inc.

DRUG PRODUCT: Mesalamine Delayed-release Tablets, 1200 mg

The Division of Bioequivalence II (DB II) has completed its review of your post CR response on the cover sheet and has no further questions at this time.

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}

Ethan M. Stier, Ph.D., R.Ph.
Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

4 OUTCOME

ANDA: 091640

Completed Assignment for 091640 ID: 26755

Reviewer: Ren, Ping

Date Completed:

Verifier: ,

Date Verified:

Division: Division of Bioequivalence

Description: Mesalamine Delayed-release Tablets, 1200 mg

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>		
26755	9/1/2015	Other (REGULAR)	Study Amendment	0	0	Edit	Delete
				Total:	0		

To PM: Please do NOT communicate this review to the firm. The response letter to firm's POST CR request is in a separate file in GDRP.

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	091640
Drug Product Name	Mesalamine Delayed-release Tablets
Strength (s)	1200 mg
Applicant Name	Zydus Pharmaceuticals USA Inc.
Applicant Address	210 Carnegie Center, 1 st Floor, Suite 103, Princeton, NJ-08540
US Agent Name and the mailing address	G. Srinivas
US Agent's Telephone Number	609-275-5125
US Agent's Fax Number	609-275-3711
Original Submission Date(s)	December 12, 2009 April 13, 2010 (Formulation Data) September 8, 2010 (Dissolution Acknowledgement) February 12, 2011 (Elemental Iron content update) October 23, 2013 (Study Amendment of PK BE study) May 23, 2014 (study amendment) December 8, 2014 (study amendment)
Submission Date(s) of Document(s) Under Review	06/05/2015 Post CR meeting request
First Generic	Yes
Reviewer	Ping Ren, Ph.D.

The Review of Post Complete Response Teleconference Meeting Request

1. EXECUTIVE SUMMARY

In the Division of Bioequivalence II (DB II) deficiency letter dated 05/29/2015, the firm was requested to re-conduct the in vitro BE study (dissolution testing) at (b) (4) pHs, 6.8, (b) (4) using fresh lots of test and RLD products due to the fact that dissolution data of the fresh test product (1 month) is significantly different from that of 31 month old product.

On June 05, 2015, Zydus requested a Post Complete Response Teleconference Meeting to discuss deficiencies noted in the Complete Response (CR) Letter dated May 29, 2015, for ANDA 091640, Mesalamine Delayed-release Tablets, 1.2 g. In its post CR response, the firm requested to waive-off the additional in vitro comparative dissolution data at pH 6.8, (b) (4)

Based on careful re-evaluation of the data for in vivo and in vitro studies, particularly for in vitro dissolution data at pH 6.8 and consult response from ORS (see internal meeting

minutes¹ for the joint meeting of OB and ORS dated July 16, 2015), DB II concludes that dissolution profiles of the test and reference products at pH 6.8 are comparable and accepts the firm's request to waive-off the additional in vitro comparative dissolution data at pH 6.8 due to following reasons:

1. Acceptable in vivo BE studies with PK end points. The firm also submitted clinical endpoint study however the study was not reviewed.
2. In vitro BE dissolution testing are acceptable for pH 6.5, 7.2 and 7.5. For pH 6.8, the dissolution is comparable to that of the RLD at 1, 2, 6 and 8 hours except at 4 hours (please note f2 criteria is not necessary to apply to this pH per previous consult to science team because this pH is the triggering pH of the coating polymer and therefore dissolution is very sensitive to pH changes)
3. For the same reason, the RLD showed high variability from lots to lots in the current ANDAs as well as across ANDAs at pH 6.8. The dissolution profiles of the test product (1 month) are similar to at least one batch of the RLD at pH 6.8, i.e.F2>50 (data from more than one lots of the RLD was submitted) and are within the lot-to-lot variability of the RLD not only in the current ANDA but also across ANDAs.

4.

(b) (4)

5. The dissolution of 31 month old of test product is comparable to that of the RLD. The difference of dissolution profiles between 1 month and 31 month of test product is due to high within-batch variability of the test product at **transition pH, 6.8** but not due to the aging of the test product. This conclusion is supported by the fact that the dissolution profiles of test product at 31 month (expired) under pH 7.2 remain the same as compared to data at 1 month.

The PRM will inform the firm to submit formal response to the Complete Response letter dated May, 29, 2015. The firm can refer to our written response in their CR response. We will review the CR response and changes our BE outcome from inadequate to adequate.

¹ Internal meeting minutes at \\cdsnas\OGDS11\DIVISION\BIO\BIO2\BIO Management Meeting Minutes\2015 Meeting Minutes\Non-BMM Internal Meeting Minutes\ 7 16 15 ANDA 91640 Post CR internal meeting minutes mc.docx

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	Background	Error! Bookmark not defined.
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3. REVIEW OF SUBMISSION

On June 05, 2015, Zydus requested a Post Complete Response Teleconference Meeting to discuss deficiencies noted in the Complete Response Letter dated May 29, 2015, for ANDA 091640, Mesalamine Delayed-release Tablets, 1.2 g. Based on the firm's investigation in method validation experiment for high variability, Zydus concluded that day to day variability of both test and reference product at pH 6.8 is due to formulation characteristics resulting from pH dependent polymer (b) (4). By inference from this investigation, the significantly difference between dissolution data of the fresh test product (1 month) and 31 month old product under pH 6.8 is the result of inherent analytical variability due to day to day variability. The firm raised the following two questions: "1) Based on past complete response letter dated September 09, 2014, agency had acknowledged the day to day analytical variability expected in pH 6.8 buffer and recommended to perform testing of test and reference product on same day, we would like to understand agency's rational for comparing the dissolution data generated on two different days for F2 calculation (i.e. Data from 1 month and 31 month)?; 2) If agency accepts our scientific rational explained in above section, the firm requests agency to waive-off the additional data requested in the complete response letter dated May 29, 2015."

Reviewer's Comment:

In response to the firm's request, the DB carefully re-evaluated in vivo and in vitro data that firm submitted previously and concluded that, at pH 6.8, the vitro dissolution profile of the test product is comparable to that of reference product (although the fresh batch failed the f2 criterion). This conclusion is based on 1) pH 6.8 is a "transition point" and the test product showed high within-batch variability, 2) the dissolution profile of the test product at pH 6.8 is still within the lot-to-lot variability of the RLD in current ANDA as well as across ANDAs, and 3) the dissolution of 31 month old of test product meets F2 criteria and the difference of dissolution profiles between 1 month and 31 month of test product is due to high within-batch variability of the test product at transition pH, 6.8 but not due to aging of the test product.

The evidence and the rationale for the DB conclusion are presented/addressed in the following sections.

In Vivo and Vitro Results:

In vivo results:

Zydus Pharmaceuticals USA Inc. initially conducted a clinical endpoint BE study comparing the test product, Zydus Pharmaceuticals USA Inc.'s Mesalamine Delayed Release Tablets, 1200 mg to the corresponding reference product, Shire's Lialda® (Mesalamine) Delayed Release Tablets, 1200 mg. However, based on the FDA revised guidance on Mesalamine (2012), the clinical endpoints is no longer considered to be sufficiently sensitive to establish BE of this product. Therefore, the firm was requested to conduct BE studies with the recommended PK endpoints under both fasting and fed conditions and *in vitro* dissolution study over a range of represented pH in GI to demonstrate the bioequivalence between its test product and the reference product.

In the amendment dated October 23, 2013, the firm provided the results of the required fasting and fed bioequivalence (BE) studies comparing a test product, Zydus Pharmaceuticals USA Inc.'s Mesalamine DR Tablets, 1200 mg to the corresponding reference product, Shire's Lialda® (Mesalamine) Delayed Release Tablets, 1200 mg. Both fasting and fed BE studies are acceptable.

In vitro results:

The firm submitted in vitro comparative BE studies at pH 6.5, pH 6.8, pH 7.2, and pH 7.5 as follows:

Table 1: F2 values and 90% CI using bootstrapping method (24 units)

Bootstrapping method						
Treatment (# of units)	pH	Frequent	Original f2	F2 bootstrap mean	Lower CI (Percentile)	Upper CI (Percent ile)
T vs. R (two lots) (24 vs. 24)	6.5	10000	17.07561	16.45597458	14.8008	17.79041
	6.8	10000	34.30761	34.55327	29.30018	40.78859
	7.2	10000	69.02809	69.55844	54.56053	85.90782
	7.5	10000	77.17999	73.83384	57.09611	89.58673
R1 vs. R2 (12 vs 12)	6.5	10000	31.41539	30.92268	27.83892	34.34846
	6.8	10000	35.47665	35.57934	31.12492	40.74375
	7.2	10000	32.69056	33.06435	29.99618	37.0998
	7.5	10000	28.66241	28.6892	26.55906	30.78745

The results showed similar dissolution profiles between the test and reference products at pH 7.2 and pH 7.5 but not at pH 6.5 and 6.8. The firm's test product had minimal release at pH 6.5 and thus the testing at pH 6.5 is deemed acceptable per the science team consult. Since the f2 criteria do not apply to dissolution data at pH 6.8, new criteria for

pH 6.8 was established based on the consult of science team: “mean of test in the range of the RLD during 2-8 hrs”.

Time (hrs)	1	2	4	6	8
Mean of Test	2.7	5.1	28.4	70.9	98.2
Range of RLD	(b) (4)				

The dissolution profile at pH 6.8 between the test and reference are similar except 4 hours.

Thus, the firm was requested to provide its testing data for both test and reference product at pH 6.8, pH (b) (4) and pH (b) (4) in complete response letter dated September 23, 2014.

In the amendment dated 12/03/2014, the firm conducted the required dissolution testing at pH 6.8, (b) (4) as follows:

Table 2: F2 values and 90% CI using bootstrapping method (24 units)

Bootstrapping method						
Treatment (# of units)	pH	Frequent	Original f2	F2 bootstrap mean	Lower CI (Percentile)	Upper CI (Percentile)
T vs. R (two lots) (12 vs. 12)	6.8	10000	77.2262	69.1511	49.2400	86.1449 (b) (4)
R1 vs. R2 (12 vs 12)	6.8	10000	29.6235	29.6470	27.1077	32.2627 (b) (4)

All in vitro comparative dissolution data in pH 6.8, (b) (4) meet the acceptance criteria ($f_2 \geq 50$ and lower CI ≥ 46). However, the dissolution testing was conducted on expired test product (31 month) and significant difference was observed in the dissolution profile at pH 6.8 between the fresh (1 month) and expired (31 months) test products as follows:

**Table 3. Comparison of Dissolution Data for Test Product
(EMM196, Mfg Date: 03/2012)**

Submission	Amendment dated ²		Current Amendment	
Testing Date	April 7-12, 2012 (1 Month)		October 8, 2014 (31 Month)	
% Dissolved at Pretreatment Stages				
Statistics	2 hours in 0.1 N HCl	1 hour in pH 6.4 Phosphate Buffer	2 hours in 0.1 N HCl	1 hour in pH 6.4 Phosphate Buffer

² DARRTS: REV-BIOEQ-21 (Primary Review), final date 09/16/2014 and 03/01/2014

High variability was observed in the dissolution data between the fresh (one month) and expired (31 months) test products at pH 6.8, not pH 7.2. This data supports that the difference of dissolution profile at pH 6.8 between the 1 month and 31 month is due to high within-batch variability at transition point, pH 6.8 NOT age.

2. pH 6.8 is the transition point

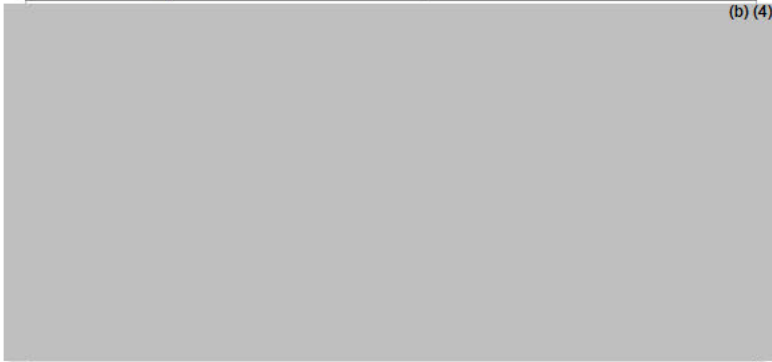
Since pH 6.8 is an intermediate, transitional pH, the dissolution profile at this pH is most sensitive to small variations in the medium pH and the two-polymer composition causing large variability especially at the early time points. A small variation in the two-polymer composition would result in large variability in the % mesalamine dissolved at this sensitive, transitional pH (6.8), especially at the early sampling time points of the dissolution test.

3. RLD Lot-to-lot Variability:

Across ANDAs

RLD Release at pH 6.8 from in-house ANDAs

(b) (4)



ANDA	Unit#	Formulaiton	1 hr	2 hrs	3 hrs	4 hrs	5 hrs	6 hrs	8 hrs
(b) (4)									
203574	24	RLD	(b) (4)						
91640	24	RLD1							
	24	RLD2							
	24	Test (1m)							
	24	Test (31m)							

The test product is within the lot variability of the RLD (e.g. 4 hrs)

Within same ANDA, dissolution profile is similar to at least one of the RLD lot (F2>50)

In current ANDA 91640:

(b) (4)



The RLD showed high variability from lots to lots in the current ANDA as well as across in house ANDAs. The fresh dissolution profiles of the test product are within the lot-to-lot variability of the RLDs and is similar to at least one batch of the RLD at pH 6.8, i.e. $F_2 > 50$ (data from more than one lots of the RLD is submitted). This data support that the dissolution profiles of the test and reference products at pH 6.8 is comparable.

ORS consult responses:

1. When comparing different RLDs used in several other ANDAs, it was observed that dissolution profiles were most variable at a lower pH (e.g. pH 6.5 and 6.8) compared to higher pHs (e.g. pH 7.2 and 7.5)
2. When comparing the test product profile with other RLDs used in other ANDAs, the pH 6.8 profile of the current application is in the range of the RLDs
3. When analyzing all RLD dissolution profiles that were used in the current ANDA, most RLDs from the same lot showed similar dissolution profiles on different days, but displayed large lot-to-lot variability
4. The test product showed high within batch variability but it was comparable to the lot-to-lot variability of the RLD in current ANDAs
5. ORS agrees with DB's recommendation to accept firm's request for the following reasons:
 - a. Although the within batch variability is high for ANDA 091640, it's comparable to the between lots variability of the RLD.
 - b. Assuming dissolution in pH 6.8 is in vivo relevant, in reality, patients won't completely avoid batch to batch variability.
 - c. Dissolution in pH 6.8 is not the QC method, so variability is not a concern from CMC perspective.
6. There are five RLDs for mesalamine modified release product. Different RLDs were designed to release the drug at different pH which mimics different location of the GI tract. For the pH condition lower or at the trigger pH of the coating polymer, we might not able to apply f_2 comparison. If the product follows similar pattern of release as the RLD, it may be reasonable to be acceptable.

Conclusions:

Based on the evidence and discussion above and consult response from ORS at internal meeting³, the DB concludes that the dissolution profiles of the test and reference products at pH 6.8 are comparable and accepts the firm's request to waive-off the additional in vitro comparative dissolution data at pH 6.8, (b) (4) on fresh test batch due to following reasons:

1. Acceptable in vivo BE studies with PK end points.
2. In vitro BE dissolution testing are acceptable for pH 6.5, 7.2 and 7.5. For pH 6.8, although, f2 values is less than 50 between the test and reference products, the dissolution profile of the test is still considered comparable to that of the RLD because it is within the lot-to-lot variability of the RLD in current ANDA as well as across ANDAs.
3. The dissolution of 31 month old of the test product is similar to that of reference product ($f_2 > 50$). The difference in dissolution between 1 month and 31 month of the test product is most likely due to within-batch variability of the test product at transition point, pH 6.8 not age.

³ Internal meeting minutes at \\cdsnas\OGDS11\DIVISION\BIO\BIO2\BIO Management Meeting Minutes\2015 Meeting Minutes\Non-BMM Internal Meeting Minutes

To PM: Please do NOT communicate this letter to the firm. The response letter to firm's POST CR request is in a separate file.

BIOEQUIVALENCE COMMENT TO BE PROVIDED TO THE APPLICANT

ANDA: 091640

APPLICANT: Zydus Pharmaceuticals USA Inc.

DRUG PRODUCT: Mesalamine Delayed-release Tablets, 1200 mg

The Division of Bioequivalence II (DB II) has completed the review of your request for a Post Complete Response Teleconference Meeting to discuss deficiencies noted in the Complete Response Letter dated May 29, 2015.

The Division of Bioequivalence II (DBII) has re-evaluated the data for the in vitro BE dissolution studies, as well as your rationale for the high variability of dissolution data at pH 6.8. The DBII concludes that the in vitro BE dissolution testing at pH 6.8 is now acceptable. Therefore, DB II agrees with your request to waive the additional data requested in the complete response letter dated May 29, 2015.

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}

Ethan M. Stier, Ph.D., R.Ph.
Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

OUTCOME

ANDA: 091640

APPEARS THIS WAY ON ORIGINAL



DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	091640		
Drug Product Name	Mesalamine Delayed-release Tablets		
Strength (s)	1200 mg		
Applicant Name	Zydus Pharmaceuticals USA Inc.		
Applicant Address	210 Carnegie Center, 1 st Floor, Suite 103, Princeton, NJ-08540		
US Agent Name and the mailing address	G. Srinivas		
US Agent's Telephone Number	609-275-5125		
US Agent's Fax Number	609-275-3711		
Original Submission Date(s)	December 12, 2009 April 13, 2010 (Formulation Data) September 8, 2010 (Dissolution Acknowledgement) February 12, 2011 (Elemental Iron content update) October 23, 2013 (Study Amendment of PK BE study)		
Submission Date(s) of Amendment(s) Under Review	May 23, 2014		
First Generic	Yes		
Reviewer	Zhuojun Zhao, Ph.D.		
OSI Status	Adequate		
Dissolution Review Results	Adequate Dissolution was reviewed in a separate document (DARRTS: REV-BIOEQ-02 (Dissolution Review), check-in date 07/14/2014)		
REVIEW RESULT	Inadequate		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1	Fasting	1200 mg	Adequate
1	Fed	1200 mg	Adequate
2	Pilot Fed	1200 mg	Adequate
1	Pilot Fed	1200 mg	Adequate
1	In vitro BE dissolution study	1200 mg	Inadequate

Review of Amendment

1 EXECUTIVE SUMMARY

Zydus Pharmaceuticals USA Inc. initially conducted a clinical endpoint BE study comparing the test product, Zydus Pharmaceuticals USA Inc.'s Mesalamine Delayed Release Tablets, 1200 mg to the corresponding reference product, Shire's Lialda® (Mesalamine) Delayed Release Tablets, 1200 mg. The application was received on

December 12, 2009. However, in the Agency's response to the Citizen's Petitions (CPs) FDA-2010-P-0111 and FDA-2008-P-0507, dated August 10, 2010, the BE study with clinical endpoints is no longer considered to be sufficiently sensitive to establish BE of this product. Therefore, the firm was requested to conduct BE studies with the recommended PK endpoints under both fasting and fed conditions and *in vitro* dissolution study to demonstrate the bioequivalence between its test product and the reference product in DB deficiency letter dated March 13, 2012.

In the amendment dated October 23, 2013, the firm provided the results of the required fasting and fed bioequivalence (BE) studies comparing a test product, Zydus Pharmaceuticals USA Inc.'s Mesalamine DR Tablets, 1200 mg to the corresponding reference product, Shire's Lialda® (Mesalamine) Delayed Release Tablets, 1200 mg. The tablet formulation composition for the Zydus' Mesalamine Delayed-Release Tablets 1200 mg used in the BE studies (Batch No. EMM196) is identical to the original ANDA exhibit batch (Batch No. EMH345), which was found acceptable in the original BE review (DARRTS: REV-BIOEQ-01 (General Review), final date 02/23/2012). The firm's BE studies was found incomplete pending its explanation for issues in its analytical reports.

In the current amendment, the firm provided its satisfactory explanation to the issues in the analytical report. The firm's BE studies are now adequate.

In addition to *in vivo* fasting and fed BE studies, the guidance also recommends comparative *in vitro* **BE** dissolution studies to be conducted in pH 6.5, 6.8, 7.2 and 7.5 phosphate buffer representative of the GI tract pH variations. In the amendment dated October 23, 2013, the firm's *in vitro* BE dissolution results showed similar dissolution profiles between the test and reference products at pH 7.2 and pH 7.5 but not at pH 6.5 and 6.8. The firm's test product had minimal release at pH 6.5 and thus the testing at pH 6.5 is deemed acceptable per the science team consult. However, we observed Day-to-Day high variability in pH 6.8 buffer on test and reference products, and thus the firm was requested to investigate its laboratory's performance of this method, provide explanation for the observed variability and re-conduct its testing in the pH 6.8 and pH

(b) (4)

In the current amendment, the firm investigated the day-to-day variability in the drug release data at pH 6.8 phosphate buffer and provided its method validation report MVR/4355. The firm observed that the dissolution testing at pH 6.8 is not robust over minor changes in the pH of dissolution medium (i.e. from pH 6.7 to pH (b) (4)) on its test product and provided its justification for the observed sensitivity on pH buffer at 6.8 of its test product due to the pH dependent solubility nature of (b) (4). However, the firm's validation report MVR/4355 was conducted on 6 units of test product only, the reviewer could not compare the performance of the test product with the RLD product. Considering the therapeutic purpose of this drug product for the treatment of ulcerative colitis and the reference product's design (release at pH above 6.8), the firm should be request to provide its testing data for both test and reference

product at pH 6.8, (b) (4) Thus, the in vitro BE dissolution testing is still incomplete.

No Division of Scientific Investigations (DSI) inspection is pending or necessary.

The application is incomplete.

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3 REVIEW OF SUBMISSION

3.1 In Vivo Bioequivalence (BE) Studies:

DB Deficiency #1:

Per your SOP (b) (4) and SOP (b) (4) sample coded as Above the Upper Limit of Quantitation (>ULQ) were diluted appropriately prior to reassay.

The code >ULQ is used where the calculated, un-rounded concentration of a sample falls above the nominal concentration of the ULQ (this does not apply to truncated calibration curves; refer to V.A.1.). Additionally, the >ULQ code is applied to QC and subject samples whose ratios have a greater value than the extrapolated curve's vertex, in the case of a quadratic equation. This code more often applies to subject samples, however, it may also apply to QC samples, e.g., high concentration QC samples assayed as part of sample analysis or method validation that produce concentrations above that of the ULQ calibrant. Subject samples coded >ULQ are generally diluted appropriately prior to re-assay. Refer to SOP (b) (4)

However, we could not locate the dilution factor in your study report or the related SOP (b) (4) Please provide the used dilution factors used for the fasting study MSN-P2-480 and the Fed study MSN-P3-482.

Firm's Response:

The regression tables of all accepted subject batches are presented in Module 5.3.1.4 for the fasting study [MSN-P2-480](#) and the Fed study [MSN-P3-482](#). Please refer to Appendix 5 of each analytical report. The dilution factor can be obtained in the regression tables via the column "Volume (mL)", where the undiluted sample volume is 0.200 mL as per analytical method. In the regression tables, all samples with a volume of 0.040 mL inscribed in this column were therefore diluted with a factor of 5, while samples with a volume of 0.050 mL were diluted with a factor of 4, and samples with a volume of 0.025 mL were diluted with a factor of 8.

Reviewer's Comment:

The firm's response is satisfactory.

The reviewer verified that ULP repeated samples in the Fasting study MSN-P3-480 and Fed study MSN-P3-482 were diluted with a factor up to 8, which is acceptable as the dilution factor of 20 was validated in the firm's analytical method validation report.

DB Deficiency #2:

It is noted that you reported all repeat assays values as the final concentration for repeat assay under code "SLP", "UIS", "SCI", ">ULQ" and "CR" but reported "Number of recalculated values used after reanalysis" as "NA" for those samples. For your future application, please report the actual number for "Number of recalculated values used after reanalysis" when the final concentration is reported from repeat assays.

Firm's Response:

We acknowledge the Agency's comment. Based on this comment, we have revised the Pivotal Bio Summary Table 9 "Reanalysis of Study Samples" and provided in word and .pdf format in Module 2.7 of this Amendment.

Reviewer's Comment:

The firm's response is satisfactory.

3.2 In Vitro BE Dissolution Studies:**DB Deficiency #3:**

*Day-to-Day variability is observed in your dissolution testing data on both of your Test and Reference product at pH 6.8. We could not locate your method validation report for the in vitro BE dissolution study. Please provide your method validation report, which should include precision and accuracy. In addition, to further investigate the observed high variability, please validate the method's system robustness to cover any possible deviation (e.g. buffer pH, operator, temperature, etc.) and include the data in the validation report. After revalidate your method, please re-conduct the in vitro BE dissolution testing and using unexpired test (24 units) and **at least two lots (more if needed)** of the reference product (using 12 tablets per lot) for the following conditions:*

Apparatus: USP Apparatus 2 (paddle)

Pretreatment Stage 1: 2 hours in 100mM HCl at 100 rpm (750 mL)
Pretreatment Stage 2: 1 hour in pH 6.4 Phosphate buffer at 100 rpm (950 mL)
Evaluation Stage: Each of

(1) pH 6.8 Phosphate buffer at 100 rpm
(b) (4)

Volume: 960 mL

Temperature: 37°C

Sample times: 1, 2, 4, 6 and 8 hours or as needed for profile comparison

Firm's Response:

We have performed analytical method validation for the in vitro BE dissolution study at pH 6.8 phosphate buffer for the evaluation stage. The complete method validation report (MVR/4355) along with findings to explain the comment regarding day-to-day variability in the dissolution test at evaluation stage pH 6.8 is provided in Module 3.2.P.5.3 of this Amendment.

The dissolution test method validation shows that systems suitability and precision are established; and the test method is specific, accurate and reproducible, and is robust over changes of UV absorbance wavelength, paddle speed and temperature.

From the intermediate precision data and pH robustness study, it becomes clear that the observed day-to-day variability in the pH 6.8 phosphate buffer dissolution test results especially at 1 hour and 2 hour sampling time points for both the test and reference products can be attributed to the inherent pH dependent solubility nature (b) (4) in the tablet coating, and not due to the analytical methods of the dissolution testing.

(b) (4)

The high day-to-day variability is actually reproducible and consistent for both the test and reference products at evaluation stage pH 6.8 and is attributed to the pH dependent solubility nature (b) (4)

Since pH 6.8 is an intermediate, transitional pH, the dissolution profile at this pH is most sensitive to small variations in the medium pH and the two-polymer composition causing large variability especially at the early time points.

The trend of the high day-to-day variability in dissolution behavior observed in method validation experiments at evaluation stage pH 6.8 (intermediate precision and pH robustness) is consistent with the dissolution data for both the reference and test products previously submitted to the Agency in the last complete response dated October 22, 2013. Since we have validated the dissolution test method and are able to provide a sound scientific basis for the observed high variability in the test results at evaluation stage pH 6.8, we believe that it would not be necessary to regenerate or repeat the dissolution test results at this pH using the unexpired reference and test products because the results will essentially be the same as those previously submitted.

The dissolution data generated at pH 7.2 and pH 7.5 do not show large variability (b) (4)

The respective dissolution data of test and reference batch in pH 7.2 and pH 7.5 were already submitted as a part of our previous response dated October 22, 2013.

Reviewer's Comment:

As required, the firm investigated the day-to-day variability in the drug release data at pH 6.8 phosphate buffer and provided its method validation report MVR/4355 in the current amendment.

The validation was conducted using the firm's Mesalamine DR Tablet, Batch # EMM196.

Following are the Standard, Sample and Placebo details used in the validation study.

1. Mesalamine working standard Lot No.: 12P0626
2. Mesalamine Delayed-Release Tablets Batch No.: EMM196
3. Placebo Batch No.: PL-F104

During the validation, the firm observed that the dissolution testing at pH 6.8 is not robust over minor changes in the pH of dissolution medium (b) (4) on its test product as shown below:



The firm provided 6 units data from the test product for each test above. However, no RLD product was tested for those conditions.

In addition, the firm provided its justification for the observed sensitivity on pH buffer at 6.8 rang of its test product and claimed that the observed day-to-day variabilit (b) (4)

Considering the therapeutic purpose of this drug product for the treatment of ulcerative colitis, it is important that the Test Product has almost identical dissolution profiles to those of the Reference product at pH levels associated with the site of local action of mesalamine (terminal ileum and colorectum), i.e., pH > 7, to have rapid and complete dissolution. As the RLD product is designed to release at pH above 6.8 and the formulation related variability from pH, the firm is required to re-conduct the test at pH 6.8, (b) (4) of 24 units from both test and RLD product (from two lots) (see DB II Management Discussion in [Section 7.4](#))¹.

The firm's response is incomplete.

DB Deficiency #4:

As stated in our complete response letter dated March 13, 2013, the in vitro BE dissolution testing should be conducted in pretreatment stages (0.1 N HCl and pH 6.4 Phosphate Buffer) and followed by each evaluation stage. However, we only received one set of pretreatment data in your amendment dated October 23, 2013. Please provide your complete study report with data from each pre-treatment stage for the following evaluation stages, pH 6.5, pH 7.2 and pH 7.5. If you did not analyze the drug release for those pretreatment stages or did not conduct pretreatment stage for each evaluation stage (pH 6.5, pH 7.2 and pH 7.5), please re-conduct in vitro BE dissolution testing with pretreatment stage for each evaluation stage (pH 6.5, 7.2 and 7.5) and submit the complete data.

¹ Per consult with the Science Team (see [Section 4.5](#) in DARRTS: REV-BIOEQ-21 (Primary Review), final date 03/01/2014), as no testing is currently required between pH 6.8 and 7.2 to compare the release similarity and as ulcerative colitis patients may have lower pH in the distal small bowel.

Firm's Response:

We indeed conducted pretreatment stage (0.1 N HCl and pH 6.4 Phosphate Buffer) for each evaluation stage (pH 6.5, pH 6.8, pH 7.2 and pH 7.5). We only included the results for the evaluation stage in the previous submission because they are the more critical data that differentiate the in vitro tablet performance. In response to the Agency's request, we are now providing the complete dissolution profiling data from each pre-treatment stage for the evaluation stages, pH 6.5, pH 7.2 and pH 7.5 in Module 5.3.1.3 of this amendment. A summary of the dissolution testing conditions and results for both the pretreatment stage and evaluation stage are presented in Table 1 to Table 4 as follows.

Reviewer's Comment:

As required, the firm provided its complete dissolution profile data from each stage in the current amendment. The summary for both pretreatment stages and evaluation stages are summarized below:

Table 1. Summary of Dissolution Data for Test and Reference Products Using Methods Defined by the FDA: Pretreatment Stage and Evaluation Stage pH 6.5

Product	TEST PRODUCT Mesalamine Delayed-Release Tablets, 1.2 g							REFERENCE PRODUCT LIALDA® (Mesalamine) Delayed- Release Tablets, 1.2 g						
Batch No.	EMM196 Mfg Date: March, 2012							FC207A (12 units), LC089A (12 units) Expiry Date: FC207A-March, 2014; LC089A-July, 2014						
Manufacturer	Cadila Healthcare Limited, India							Cosmo S.p.A. for Shire US Inc., USA						
Pretreatment Stage 1 and Stage 2														
	% Dissolved at							% Dissolved at						
Statistics	2 Hours in 0.1N HCl			1 Hour in pH 6.4 Phosphate Buffer				2 Hours in 0.1N HCl			1 Hour in pH 6.4 Phosphate Buffer			
Mean	0.0			0.1				0.0			0.0			
Min	(b) (4)													
Max														
%CV	176.9			30.8				111.0			120.9			
Evaluation Stage														
Condition	% Dissolved over Time (Hour)							% Dissolved over Time (Hour)						
	Stat.	1	2	4	6	8	10	1	2	4	6	8	10	
pH 6.5	Mean	0.4	0.3	0.3	0.8	1.2	2.6	0.7	2.1	13.6	32.5	65.3	87.2	
	Min	(b) (4)												
	Max													
	%CV	64.7	197.9	114.4	84.1	102.2	95.7	84.7	56.8	51.4	45.6	42.0	23.8	

Pretreatment Stage 1: 2 hours in 0.1 N HCl at 100 rpm (750 mL)

Pretreatment Stage 2: 1 hours in pH 6.4 phosphate buffer at 100 rpm (950 mL)

Evaluation Stage: pH 6.5 phosphate buffer at 100 rpm (960 mL)

Table 2. Summary of Dissolution Data for Test and Reference Products Using Methods Defined by the FDA: Pretreatment Stage and Evaluation Stage pH 6.8

Product		TEST PRODUCT Mesalamine Delayed-Release Tablets, 1.2 g					REFERENCE PRODUCT LIALDA® (Mesalamine) Delayed- Release Tablets, 1.2 g				
Batch No.		EMM196 Mfg Date: March, 2012					FC207A (12 units), LC089A (12 units) Expiry Date: FC207A-March, 2014; LC089A-July, 2014				
Manufacturer		Cadila Healthcare Limited, India					Cosmo S.p.A. for Shire US Inc., USA				
Pretreatment Stage 1 and Stage 2											
		% Dissolved at					% Dissolved at				
Statistics		2 Hours in 0.1N HCl		1 Hour in pH 6.4 Phosphate Buffer			2 Hours in 0.1N HCl		1 Hour in pH 6.4 Phosphate Buffer		
Mean		0.1		0.1			0.0		0.1		
Min		(b) (4)									
Max											
%CV		128.9		126.4			338.8		65.5		
Evaluation Stage											
Condition		% Dissolved over Time (Hour)					% Dissolved over Time (Hour)				
pH 6.8	Stat.	1	2	4	6	8	1	2	4	6	8
	Mean	2.7	5.1	28.4	70.9	98.2	4.5	17.5	61.6	91.9	102.8
	Min	(b) (4)									
	Max										
	%CV	87.1	71.7	62.1	24.1	5.4	112.9	54.9	31.3	13.9	2.9

Pretreatment Stage 1: 2 hours in 0.1 N HCl at 100 rpm (750 mL)

Pretreatment Stage 2: 1 hours in pH 6.4 phosphate buffer at 100 rpm (950 mL)

Evaluation Stage: pH 6.8 phosphate buffer at 100 rpm (960 mL)

Table 3. Summary of Dissolution Data for Test and Reference Products Using Methods Defined by the FDA: Pretreatment Stage and Evaluation Stage pH 7.2

Product		TEST PRODUCT Mesalamine Delayed-Release Tablets, 1.2 g					REFERENCE PRODUCT LIAALDA [®] (Mesalamine) Delayed- Release Tablets, 1.2 g				
Batch No.		EMM196 Mfg Date: March, 2012					FC207A (12 units), LC089A (12 units) Expiry Date: FC207A-March, 2014; LC089A-July, 2014				
Manufacturer		Cadila Healthcare Limited, India					Cosmo S.p.A. for Shire US Inc., USA				
Pretreatment Stage 1 and Stage 2											
		% Dissolved at					% Dissolved at				
Statistics		2 Hours in 0.1N HCl		1 Hour in pH 6.4 Phosphate Buffer			2 Hours in 0.1N HCl		1 Hour in pH 6.4 Phosphate Buffer		
Mean		0.0		0.1			0.0		0.1		
Min		(b) (4)									
Max											
%CV		131.9		54.6			199.1		79.1		
Evaluation Stage											
Condition		% Dissolved over Time (Hour)					% Dissolved over Time (Hour)				
	Stat.	1	2	4	6	8	1	2	4	6	8
pH 7.2	Mean	10.6	31.7	73.2	100.1	102.8	9.6	26.7	68.5	96.0	104.6
	Min	(b) (4)									
	Max										
	%CV	15.5	9.0	4.9	2.7	2.4	35.6	32.1	28.1	12.8	3.7

Pretreatment Stage 1: 2 hours in 0.1 N HCl at 100 rpm (750 mL)

Pretreatment Stage 2: 1 hours in pH 6.4 phosphate buffer at 100 rpm (950 mL)

Evaluation Stage: pH 7.2 phosphate buffer at 100 rpm (960 mL)

Table 4. Summary of Dissolution Data for Test and Reference Products Using Methods Defined by the FDA: Pretreatment Stage and Evaluation Stage pH 7.5

Product		TEST PRODUCT Mesalamine Delayed-Release Tablets, 1.2 g					REFERENCE PRODUCT LIALDA® (Mesalamine) Delayed- Release Tablets, 1.2 g				
Batch No.		EMM196 Mfg Date: March, 2012					FC207A (12 units), LC089A (12 units) Expiry Date: FC207A-March, 2014; LC089A-July, 2014				
Manufacturer		Cadila Healthcare Limited, India					Cosmo S.p.A. for Shire US Inc., USA				
Pretreatment Stage 1 and Stage 2											
		% Dissolved at					% Dissolved at				
Statistics		2 Hours in 0.1N HCl		1 Hour in pH 6.4 Phosphate Buffer			2 Hours in 0.1N HCl		1 Hour in pH 6.4 Phosphate Buffer		
Mean		0.1		0.0			0.0		0.0		
Min		(b) (4)									
Max											
%CV		133.1		111.0			489.9		176.9		
Evaluation Stage											
Condition		% Dissolved over Time (Hour)					% Dissolved over Time (Hour)				
	Stat.	1	2	4	6	8	1	2	4	6	8
pH 7.5	Mean	9.7	30.3	72.7	99.1	102.8	11.0	28.7	70.1	94.8	103.4
	Min	(b) (4)									
	Max										
	%CV	25.3	11.9	8.0	3.9	2.0	33.1	34.5	32.1	15.1	3.6

Pretreatment Stage 1: 2 hours in 0.1 N HCl at 100 rpm (750 mL)

Pretreatment Stage 2: 1 hours in pH 6.4 phosphate buffer at 100 rpm (950 mL)

Evaluation Stage: pH 7.5 phosphate buffer at 100 rpm (960 mL)

The complete profiles are attached in [Section VI.A](#), which confirms that the firm's in vitro BE was conducted in pretreatment stages (2 hours in 0.1 N HCl and 1 hour in pH 6.4 Phosphate buffer) and followed by evaluation stage of buffer (pH 6.5, 6.8, 7.2 and 7.5).

The firm's response is satisfactory.

DB Deficiency #5:

You provided mean dissolution profiles for various batches of RLD product in Figure 2 in the cover letter in the amendment dated 10/23/2013. However, we could not locate the raw data for those corresponding dissolution testing. Please provide dissolution testing report on RLD product batches VC011A, WD119A and LC105A. In addition, please provide those RLD products expiration date as well as the testing dates.

Firm's Response:

In response to the Agency's comment, we have provided the detailed dissolution raw data along with expiration dates and testing dates for RLD product batches VC011A, WD119A and LC105A in Module 5.3.1.3 of this Amendment.

Reviewer's Comment:

As required, the firm provided the dissolution raw data for three batches of the RLD product (attached in [Section VLB](#)).

Test Date			
Medium	RLD B No. VC001A (Expiry Date Sep 2014)	RLD B No. WD119A (Expiry Date May 2015)	RLD B No. LC105A (Expiry Date July 2014)
pH 6.5	April, 2012	June, 2013	April, 2012

pH 6.8			
pH 7.2		April, 2013	April, 2012 and Feb, 2013
pH 7.5		June, 2012	April, 2012

As shown in the above table, all testing was conducted within the expiration date of the batch.

The data of the above mentioned reference batches submitted in amendment dated 10/23/2013 is provided below:



As indicated in the above graph, the different batches of the reference product showed a large variability at pH 6.8

Based on the firm's raw data for other RLD batches in the current amendment, the reviewer generate the F2 values.

Bootstrapping method						
Treatment (24 vs. 12)	pH	Frequent	Original f2	F2 bootstrap mean	Lower CI (Percentile)	Upper CI (Percentile)
T vs. R1	6.8	10000	58.72	59.04	46.64	74.18
T vs. R2	6.8	10000	25.70	25.74	22.26	29.70
T vs. R3	6.8	10000	23.31	23.01	19.06	27.50

R1: VC011A; R2: WD119A ; R3: LC105A

The fact of large variability in drug release from different commercial batches of reference product impact the F2 values comparing the test and reference products, as shown in the table above.

Overall, the firm's response provided useful information regarding the performance of different batches of the reference product around pH 6.8. The firm's response is satisfactory.

4 DEFICIENCY COMMENTS

1. The firm investigated the day-to-day variability in the drug release data at pH 6.8 phosphate buffer and provided its method validation report MVR/4355 in the current amendment. The firm observed that the dissolution testing at pH 6.8 is not robust over minor pH changes in the dissolution medium (b) (4) on its test product and provided its justification for the observed sensitivity on pH buffer at 6.8 rang of its test product due to the pH dependent solubility nature of (b) (4). However, the firm's validation report MVR/4355 was conducted on 6 units of test

product, the reviewer could not compare the performance of the test product with the RLD product. Considering the therapeutic purpose of this drug product for the treatment of ulcerative colitis and the reference product's design (release at pH above 6.8), based DB II internal meeting (see [Section 7.4](#)), the firm should be request to provide its testing data for the following conditions:

Apparatus: USP Apparatus 2 (paddle)

Pretreatment Stage 1: 2 hours in 100mM HCl at 100 rpm (750 mL)

Pretreatment Stage 2: 1 hour in pH 6.4 Phosphate buffer at 100 rpm (950 mL)

Evaluation Stage: Each of

(1) pH 6.8 Phosphate buffer at 100 rpm

(b) (4)

Volume: 960 mL

Temperature: 37°C

Sample times: 1, 2, 3, 4, 5, 6 and 8 hours or as needed for profile comparison

2. The firm should be informed that due to the high variability of its in vitro BE dissolution data at pH 6.8 (i.e.. percentage coefficient of variation >10%), an f2 test using mean profiles of test vs. reference listed drug ("RLD") products is not sufficient as per the above "Dissolution Guidance". Therefore, DB II calculated the f2 metric (an f2 confidence interval) using a 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.

However, the testing data in evaluation stage at pH 6.8 Phosphate Buffer, the mean values and the lower bound of 90% confidence interval for the f2 test comparing Test vs. RLD are lower than 50 or those comparing the RLD against itself under the same condition. Those values suggest that the dissolution profiles of the test product are different from those of the corresponding reference under the condition. The test product is deemed not bioequivalent to the RLD.

3. The firm should also be informed to 1) repeat comparative dissolution testing using one batch of freshly prepared buffer for both test and RLD products, 2) test larger number of tablets (e.g. at least 24 units for each product) to provide a better estimate of the mean difference and 3) conduct the study on one day.

5 RECOMMENDATIONS

1. The Division of Bioequivalence accepts the fasting BE study (MSN-P2-480) conducted by Zydus Pharamceuticals USA Inc. on its Mesalemine DR Tablets, 1200 mg, lot # EMM196 comparing it to Shire's Lialda® (Mesalamine) DR Tablets, 1200 mg, lot # FC207A.
2. The Division of Bioequivalence accepts the fed BE study (MSN-P3-482) conducted by Zydus Pharamceuticals USA Inc. on its Mesalemine DR Tablets,

1200 mg, lot # EMM196 comparing it to Shire's Lialda® (Mesalamine) DR Tablets, 1200 mg, lot # FC207A.

3. The in vitro BE dissolution studies are incomplete due to the deficiency indicated above.

6 COMMENTS FOR OTHER OGD DISCIPLINES

Discipline	Comment
CSO/RPM	Dissolution was reviewed in a separate document (DARRTS: REV-BIOEQ-02 (Dissolution Review), check-in date 07/14/2014)

7 ATTACHMENTS

7.1 Dissolution profiles for the Pretreatment Stage 1 & 2

For Evaluation Stage at pH 6.5

Table 1a Pretreatment Stage 1: 2 hours in 0.1 N HCl at 100 rpm (750 mL)
Pretreatment Stage 2: 1 hour in pH 6.4 Phosphate buffer at 100 rpm (950 mL)

Product Name	Mesalamine Delayed-Release Tablets, 1.2 g		LIALDA® (Mesalamine) Delayed-Release Tablets, 1.2 g	
Batch No.	Lot No.: EMM 196 Mfg date: March, 2012		Lot No.: FC207A (Unit 1-12), LC089A (Unit 13-24) Expiry date: FC207A - March, 2014 LC089A - July, 2014	
Manufacturer:	Cadila Healthcare Limited, India		Cosmo S.p.A. for Shire US Inc., USA	
Time point	% Dissolved		% Dissolved	
	2 hours in 0.1 N HCl	1 hour in pH 6.4 Phosphate buffer	2 hours in 0.1 N HCl	1 hour in pH 6.4 Phosphate buffer
Unit-1	(b) (4)			
Unit-2				
Unit-3				
Unit-4				
Unit-5				
Unit-6				
Unit-7				
Unit-8				
Unit-9				
Unit-10				
Unit-11				
Unit-12				
Unit-13				
Unit-14				
Unit-15				
Unit-16				
Unit-17				
Unit-18				
Unit-19				
Unit-20				
Unit-21				
Unit-22				
Unit-23				
Unit-24				
Mean	0.0	0.1	0.0	0.0
Min	(b) (4)			
Max	(b) (4)			
% RSD	176.9	30.8	111.0	120.9
Date of analysis:	April 7, 2012 (1-12 units) April 13, 2012 (13-24 units)		March 25, 2012 (1-12 units) March 27, 2012 (13-18 units) April 2, 2012 (19-24 units)	

For Evaluation Stage at pH 6.8

Table 2a Pretreatment Stage 1: 2 hours in 0.1 N HCl at 100 rpm (750 mL)

Pretreatment Stage 2: 1 hour in pH 6.4 Phosphate buffer at 100 rpm (950 mL)

Product Name	Mesalamine Delayed-Release Tablets, 1.2 g		LIALDA [®] (Mesalamine) Delayed-Release Tablets, 1.2 g	
Batch No.	Lot No.: EMM 196 Mfg date: March, 2012		Lot No.: FC207A (Unit 1-12), LC089A (Unit 13-24) Expiry date: FC207A - March, 2014 LC089A - July, 2014	
Manufacturer:	Cadila Healthcare Limited, India		Cosmo S.p.A. for Shire US Inc., USA	
Time point	% Dissolved		% Dissolved	
	2 hours in 0.1 N HCl	1 hour in pH 6.4 Phosphate buffer	2 hours in 0.1 N HCl	1 hour in pH 6.4 Phosphate buffer
Unit-1	(b) (4)			
Unit-2				
Unit-3				
Unit-4				
Unit-5				
Unit-6				
Unit-7				
Unit-8				
Unit-9				
Unit-10				
Unit-11				
Unit-12				
Unit-13				
Unit-14				
Unit-15				
Unit-16				
Unit-17				
Unit-18				
Unit-19				
Unit-20				
Unit-21				
Unit-22				
Unit-23				
Unit-24				
Mean	0.1	0.1	0.0	0.1
Min	(b) (4)			
Max				
% RSD	128.9	126.4	338.8	65.5
Date of analysis:	April 7, 2012 (1-12 units) April 13, 2012 (13-24 units)		March 25, 2012 (1-12 units) March 27, 2012 (13-18 units) April 2, 2012 (19-24 units)	

For Evaluation Stage at pH 7.2

Table 3a Pretreatment Stage 1: 2 hours in 0.1 N HCl at 100 rpm (750 mL)

Pretreatment Stage 2: 1 hour in pH 6.4 Phosphate buffer at 100 rpm (950 mL)

Product Name	Mesalamine Delayed-Release Tablets, 1.2 g		LIALDA [®] (Mesalamine) Delayed-Release Tablets, 1.2 g	
Batch No.	Lot No.: EMM 196 Mfg date: March, 2012		Lot No.: FC207A (Unit 1-12), LC089A (Unit 13-24) Expiry date: FC207A - March, 2014 LC089A - July, 2014	
Manufacturer:	Cadila Healthcare Limited, India		Cosmo S.p.A. for Shire US Inc., USA	
Time point	% Dissolved		% Dissolved	
	2 hours in 0.1 N HCl	1 hour in pH 6.4 Phosphate buffer	2 hours in 0.1 N HCl	1 hour in pH 6.4 Phosphate buffer
Unit-1	(b) (4)			
Unit-2				
Unit-3				
Unit-4				
Unit-5				
Unit-6				
Unit-7				
Unit-8				
Unit-9				
Unit-10				
Unit-11				
Unit-12				
Unit-13				
Unit-14				
Unit-15				
Unit-16				
Unit-17				
Unit-18				
Unit-19				
Unit-20				
Unit-21				
Unit-22				
Unit-23				
Unit-24				
Mean	0.0	0.1	0.0	0.1
Min	(b) (4)			
Max				
% RSD	131.9	54.6	144.5	79.1
Date of analysis:	April 7, 2012 (1-12 units) April 13, 2012 (13-24 units)		March 25, 2012 (1-12 units) March 27, 2012 (13-18 units) April 2, 2012 (19-24 units)	

For Evaluation Stage at pH 7.5

Table 4a Pretreatment Stage 1: 2 hours in 0.1 N HCl at 100 rpm (750 mL)

Pretreatment Stage 2: 1 hour in pH 6.4 Phosphate buffer at 100 rpm (950 mL)

Product Name	Mesalamine Delayed-Release Tablets, 1.2 g		LIALDA® (Mesalamine) Delayed-Release Tablets, 1.2 g	
Batch No.	Lot No.: EMM 196 Mfg date: March, 2012		Lot No.: FC207A (Unit 1-12), LC089A (Unit 13-24) Expiry date: FC207A - March, 2014 LC089A - July, 2014	
Manufacturer:	Cadila Healthcare Limited, India		Cosmo S.p.A. for Shire US Inc., USA	
Time point	% Dissolved		% Dissolved	
	2 hours in 0.1 N HCl	1 hour in pH 6.4 Phosphate buffer	2 hours in 0.1 N HCl	1 hour in pH 6.4 Phosphate buffer
Unit-1	(b) (4)			
Unit-2				
Unit-3				
Unit-4				
Unit-5				
Unit-6				
Unit-7				
Unit-8				
Unit-9				
Unit-10				
Unit-11				
Unit-12				
Unit-13				
Unit-14				
Unit-15				
Unit-16				
Unit-17				
Unit-18				
Unit-19				
Unit-20				
Unit-21				
Unit-22				
Unit-23				
Unit-24				
Mean	0.1	0.0	0.0	0.0
Min	(b) (4)			
Max				
% RSD	133.1	111.0	489.9	176.9
Date of analysis:	April 7, 2012 (1-12 units) April 13, 2012 (13-24 units)		March 25, 2012 (1-12 units) March 27, 2012 (13-18 units) April 2, 2012 (19-24 units)	

7.2 Reference Product Dissolution Testing Data

7.2.1 Batch No. VC011A

pH 6.5

Product Name	LIALDA [®] (Mesalamine) Delayed-Release Tablets, 1.2 g							
Batch No.	Lot No.: VC011A; Expiry date: September, 2014							
Manufacturer:	Cosmo S.p.A. for Shire US Inc., USA							
Time point	% Dissolved							
	2 hours in 0.1 N HCl	1 hour in pH 6.4 Phosphate buffer	pH 6.5 Phosphate buffer					
			1 Hr	2 Hr	4 Hr	6 Hr	8 Hr	10 Hr (b) (4)
Unit-1								
Unit-2								
Unit-3								
Unit-4								
Unit-5								
Unit-6								
Unit-7								
Unit-8								
Unit-9								
Unit-10								
Unit-11								
Unit-12								
Mean	0.0	0.1	0.4	0.6	2.2	6.1	13.7	24.0 (b) (4)
Min								
Max								
% RSD	346.4	104.4	122.7	110.3	108.5	118.6	116.4	95.1
Date of analysis:	April 13, 2012 (1-12 Unit)							

pH 6.8

Product Name	LIALDA [®] (Mesalamine) Delayed-Release Tablets, 1.2 g						
Batch No.	Lot No.: VC011A; Expiry date: September, 2014						
Manufacturer:	Cosmo S.p.A. for Shire US Inc., USA						
Time point	% Dissolved						
	2 hours in 0.1 N HCl	1 hour in pH 6.4 Phosphate buffer	pH 6.8 Phosphate buffer				
			1 Hr	2 Hr	4 Hr	6 Hr	8 Hr
Unit-1	(b) (4)						
Unit-2	(b) (4)						
Unit-3	(b) (4)						
Unit-4	(b) (4)						
Unit-5	(b) (4)						
Unit-6	(b) (4)						
Unit-7	(b) (4)						
Unit-8	(b) (4)						
Unit-9	(b) (4)						
Unit-10	(b) (4)						
Unit-11	(b) (4)						
Unit-12	(b) (4)						
Mean	0.0	0.0	1.7	9.4	41.7	75.7	99.6
Min	(b) (4)						
Max	(b) (4)						
% RSD	0.0	147.7	122.2	30.6	15.6	5.5	2.4
Date of analysis:	April 13, 2012 (1-6 Unit); April 17, 2012 (7-12 Unit)						

pH 7.2

Product Name	LIALDA® (Mesalamine) Delayed-Release Tablets, 1.2 g						
Batch No.	Lot No.: VC011A; Expiry date: September, 2014						
Manufacturer:	Cosmo S.p.A. for Shire US Inc., USA						
Time point	% Dissolved						
	2 hours in 0.1 N HCl	1 hour in pH 6.4 Phosphate buffer	pH 7.2 Phosphate buffer				
			1 Hr	2 Hr	4 Hr	6 Hr	8 Hr
Unit-1	(b) (4)						
Unit-2							
Unit-3							
Unit-4							
Unit-5							
Unit-6							
Unit-7							
Unit-8							
Unit-9							
Unit-10							
Unit-11							
Unit-12							
Mean	0.0	0.1	5.1	16.1	47.1	80.3	100.6
Min	(b) (4)						
Max							
% RSD	0.0	104.4	38.2	13.9	10.5	6.5	1.2
Date of analysis:	April 13, 2012 (1-12 Unit)						

pH 7.5

Product Name	LIALDA® (Mesalamine) Delayed-Release Tablets, 1.2 g						
Batch No.	Lot No.: VC011A; Expiry date: September, 2014						
Manufacturer:	Cosmo S.p.A. for Shire US Inc., USA						
Time point	% Dissolved						
	2 hours in 0.1 N HCl	1 hour in pH 6.4 Phosphate buffer	pH 7.5 Phosphate buffer				
1 Hr			2 Hr	4 Hr	6 Hr	8 Hr	
Unit-1	(b) (4)						
Unit-2							
Unit-3							
Unit-4							
Unit-5							
Unit-6							
Unit-7							
Unit-8							
Unit-9							
Unit-10							
Unit-11							
Unit-12							
Mean	0.0	0.1	8.2	20.2	53.6	88.1	104.4
Min	(b) (4)						
Max							
% RSD	0.0	73.9	16.7	12.9	12.1	10.7	1.9
Date of analysis:	April 13, 2012 (1-12 Unit)						

7.2.2 Batch No. WD119A

pH 6.5

Product Name	LIALDA [®] (Mesalamine) Delayed-Release Tablets, 1.2 g							
Batch No.	Lot No.: WD119A; Expiry date: May, 2015							
Manufacturer:	Cosmo S.p.A. for Shire US Inc., USA							
Time point	% Dissolved							
	2 hours in 0.1 N HCl	1 hour in pH 6.4 Phosphate buffer	pH 6.5 Phosphate buffer					
			1 Hr	2 Hr	4 Hr	6 Hr	8 Hr	10 Hr
Unit-1	(b) (4)							
Unit-2								
Unit-3								
Unit-4								
Unit-5								
Unit-6								
Unit-7								
Unit-8								
Unit-9								
Unit-10								
Unit-11								
Unit-12								
Mean	0.0	0.0	0.1	0.2	4.1	21.5	37.0	64.7
Min	(b) (4)							
Max								
% RSD	147.7	233.5	104.4	78.4	82.5	46.6	47.6	43.3
Date of analysis:	June 19, 2013 (1-12 Unit)							

pH 6.8

Product Name	LIALDA [®] (Mesalamine) Delayed-Release Tablets, 1.2 g						
Batch No.	Lot No.: WD119A; Expiry date: May, 2015						
Manufacturer:	Cosmo S.p.A. for Shire US Inc., USA						
Time point	% Dissolved						
	2 hours in 0.1 N HCl	1 hour in pH 6.4 Phosphate buffer	pH 6.8 Phosphate buffer				
1 Hr			2 Hr	4 Hr	6 Hr	8 Hr	
Unit-1	(b) (4)						
Unit-2							
Unit-3							
Unit-4							
Unit-5							
Unit-6							
Unit-7							
Unit-8							
Unit-9							
Unit-10							
Unit-11							
Unit-12							
Mean	0.0	0.0	7.7	27.9	76.7	100.6	101.8
Min	(b) (4)						
Max							
% RSD	180.9	180.9	30.4	10.0	5.4	1.9	2.5
Date of analysis:	June 19, 2013 (1-12 Unit)						

pH 7.2

Product Name	LIALDA® (Mesalamine) Delayed-Release Tablets, 1.2 g						
Batch No.	Lot No.: WD119A; Expiry date: May, 2015						
Manufacturer:	Cosmo S.p.A. for Shire US Inc., USA						
Time point	% Dissolved						
	2 hours in 0.1 N HCl	1 hour in pH 6.4 Phosphate buffer	pH 7.2 Phosphate buffer				
			1 Hr	2 Hr	4 Hr	6 Hr	8 Hr
Unit-1	(b) (4)						
Unit-2							
Unit-3							
Unit-4							
Unit-5							
Unit-6							
Unit-7							
Unit-8							
Unit-9							
Unit-10							
Unit-11							
Unit-12							
Mean	0.0	0.1	11.9	32.1	81.6	100.7	102.8
Min	(b) (4)						
Max							
% RSD	0.0	116.8	25.3	16.8	7.0	2.2	1.8
Date of analysis:	April 27, 2013 (1-12 Unit)						

pH 7.5

Product Name	LIALDA [®] (Mesalamine) Delayed-Release Tablets, 1.2 g						
Batch No.	Lot No.: WD119A; Expiry date: May, 2015						
Manufacturer:	Cosmo S.p.A. for Shire US Inc., USA						
Time point	% Dissolved						
	2 hours in 0.1 N HCl	1 hour in pH 6.4 Phosphate buffer	pH 7.5 Phosphate buffer				
			1 Hr	2 Hr	4 Hr	6 Hr	8 Hr
Unit-1	(b) (4)						
Unit-2							
Unit-3							
Unit-4							
Unit-5							
Unit-6							
Unit-7							
Unit-8							
Unit-9							
Unit-10							
Unit-11							
Unit-12							
Mean	0.0	0.1	11.5	32.8	83.2	102.6	103.6
Min	(b) (4)						
Max							
% RSD	0.0	56.2	21.1	5.9	2.7	2.1	1.5
Date of analysis:	June 19, 2012 (1-12 Unit)						

7.2.3 Batch No. LC105A

pH 6.5

Product Name	LIALDA [®] (Mesalamine) Delayed-Release Tablets, 1.2 g							
Batch No.	Lot No.: LC105A; Expiry date: July, 2014							
Manufacturer:	Cosmo S.p.A. for Shire US Inc., USA							
Time point	% Dissolved							
	2 hours in 0.1 N HCl	1 hour in pH 6.4 Phosphate buffer	pH 6.5 Phosphate buffer					
			1 Hr	2 Hr	4 Hr	6 Hr	8 Hr	10 Hr (b) (4)
Unit-1								
Unit-2								
Unit-3								
Unit-4								
Unit-5								
Unit-6								
Unit-7								
Unit-8								
Unit-9								
Unit-10								
Unit-11								
Unit-12								
Mean	0.0	0.1	2.2	8.7	40.8	69.1	94.2	97.8 (b) (4)
Min								
Max								
% RSD	0.0	60.3	91.4	92.0	63.8	42.7	10.7	1.9
Date of analysis:	April 13, 2012 (1-12 Unit)							

pH 6.8

Product Name	LIALDA [®] (Mesalamine) Delayed-Release Tablets, 1.2 g							
Batch No.	Lot No.: LC105A; Expiry date: July, 2014							
Manufacturer:	Cosmo S.p.A. for Shire US Inc., USA							
Time point	% Dissolved							
	2 hours in 0.1 N HCl	1 hour in pH 6.4 Phosphate buffer	pH 6.8 Phosphate buffer					8 Hr
			1 Hr	2 Hr	4 Hr	6 Hr		
Unit-1	(b) (4)							
Unit-2								
Unit-3								
Unit-4								
Unit-5								
Unit-6								
Unit-7								
Unit-8								
Unit-9								
Unit-10								
Unit-11								
Unit-12								
Mean	0.0	0.0	8.7	33.5	83.0	100.1	102.8	(b) (4)
Min								
Max								
% RSD	0.0	147.7	32.3	41.5	14.8	4.9	1.9	
Date of analysis:	February 20, 2012 (1-6 Unit for Pre-Treatment stage) February 21, 2012 (1-6 Unit for Evaluation stage); April 13, 2012 (7-12 Unit)							

pH 7.2

Product Name	LIALDA [®] (Mesalamine) Delayed-Release Tablets, 1.2 g						
Batch No.	Lot No.: LC105A; Expiry date: July, 2014						
Manufacturer:	Cosmo S.p.A. for Shire US Inc., USA						
Time point	% Dissolved						
	2 hours in 0.1 N HCl	1 hour in pH 6.4 Phosphate buffer	pH 7.2 Phosphate buffer				
			1 Hr	2 Hr	4 Hr	6 Hr	8 Hr
Unit-1	(b) (4)						
Unit-2							
Unit-3							
Unit-4							
Unit-5							
Unit-6							
Unit-7							
Unit-8							
Unit-9							
Unit-10							
Unit-11							
Unit-12							
Mean	0.0	0.0	18.1	44.2	90.5	100.9	101.3
Min	(b) (4)						
Max							
% RSD	0.0	233.5	19.5	28.1	11.9	2.3	1.4
Date of analysis:	April 13, 2012 (1-6 Unit); February 21, 2013 (7-12 Unit)						

Product Name	LIALDA [®] (Mesalamine) Delayed-Release Tablets, 1.2 g						
Batch No.	Lot No.: LC105A; Expiry date: July, 2014						
Manufacturer:	Cosmo S.p.A. for Shire US Inc., USA						
Time point	% Dissolved						
	2 hours in 0.1 N HCl	1 hour in pH 6.4 Phosphate buffer	pH 7.5 Phosphate buffer				
			1 Hr	2 Hr	4 Hr	6 Hr	8 Hr
Unit-1	(b) (4)						
Unit-2							
Unit-3							
Unit-4							
Unit-5							
Unit-6							
Unit-7							
Unit-8							
Unit-9							
Unit-10							
Unit-11							
Unit-12							
Mean	0.0	0.1	9.0	25.3	74.3	103.0	104.6
Min	(b) (4)						
Max							
% RSD	0.0	104.4	19.3	11.5	7.7	1.7	0.9
Date of analysis:	April 13, 2012 (1-12 Unit)						

pH 7.5

7.3 Formulation

7.3.1 RLD Formulation²

Table 5: Components and Composition of SPD476 Tablets

Ingredient	Amount (mg)	Function	Reference to Standards
Drug substance(s) Mesalazine	1200.0	Active ingredient	EP and USP/NF
(b) (4)			
(b) (4)			
Sodium Carboxymethylcellulose (b) (4)	(b) (4)	(b) (4)	EP + USP/NF
(b) (4)			EP + USP/NF
Carnauba Wax			EP + USP/NF
Stearic Acid			EP + USP/NF
Silica, Colloidal Hydrated			EP + USP/NF
Sodium Starch Glycolate (Type A)			EP + USP/NF
Talc			EP + USP/NF
Magnesium Stearate			EP + USP/NF
(b) (4)			EP + USP/NF
(b) (4)			
Talc ²	(b) (4)	(b) (4)	EP + USP/NF
Methacrylic Acid Copolymer, Type A ²			EP + USP/NF
Methacrylic Acid Copolymer, Type B ²			EP + USP/NF
Triethylcitrate ²			EP + USP/NF
Titanium Dioxide ²			EP + USP/NF
Red Ferric Oxide (b) (4)	(b) (4)	(b) (4)	USP/NF
Polyethylene glycol 6000 ²			EP and USP
(b) (4)			EP and USP
(b) (4)	(b) (4)	(b) (4)	EP and USP
Total			
	1385.0		

EP: European Pharmacopoeia; NF: United States National Formulary; USP: United States Pharmacopoeia (b) (4)

7.3.2 Test Product Formulation³

Ingredient (s)	Mesalamine Delayed-release Tablets, 1.2 g	
	Unit Composition (mg/tablet)	% w/w ^s
Compaction		
Mesalamine (b) (4) USP	1200.000	(b) (4)
Colloidal Silicon Dioxide (b) (4) NF	(b) (4)	

² DARRTS: NDA 22000, REV-QUALITY-03 (General Review), final date 01/03/2007

³ DARRTS: REV-BIOEQ-01 (General Review), final date 02/23/2012

7.4 DB II Internal Meeting on September 8, 2014

Meeting Date: September 8, 2014
Meeting Time: 14:00 PM – 15:00 PM
Attendees: Ethan Stier, Xiaojian Jiang, Minglei Cui, Hongling Zhang and Zhuojun Zhao

ANDA No.	091640
Drug Product Name	Mesalamine Delayed-release Tablets
Strength (s)	1200 mg
Applicant Name	Zydus Pharmaceuticals USA Inc.
Applicant Address	210 Carnegie Center, 1 st Floor, Suite 103, Princeton, NJ-08540
US Agent Name and the mailing address	G. Srinivas
US Agent's Telephone Number	609-275-5125
US Agent's Fax Number	609-275-3711
Original Submission Date(s)	December 12, 2009 April 13, 2010 (Formulation Data) September 8, 2010 (Dissolution Acknowledgement) February 12, 2011 (Elemental Iron content update) October 23, 2013 (Study Amendment of PK BE study)
Submission Date(s) of Amendment(s) Under Review	May 23, 2014

1. Background

(b) (4)

(b) (4)

In the amendment dated October 23, 2013, the firm's dissolution results showed similar dissolution profiles between the test and reference products at pH 7.2 and pH 7.5 but not at pH 6.5 and 6.8. Based on the science consult, the firm's test product had minimal release at pH 6.5 and thus the testing at pH 6.5 is deemed acceptable. However, it is recommended that the test and reference products have comparable dissolution profiles at pH 6.8, since ulcerative colitis patients may have lower pH in the distal small bowel. Therefore, for the observed Day-to-Day high variability in pH 6.8 buffer on test and reference products, the firm was requested to investigate its laboratory's performance of this method, provide explanation for the observed variability.

2. Data in the Amendment dated October 23, 2014

Test Date			
Medium	Test Product	RLD 1 (FC207A) (Exp. Date: March 2014)	RLD 2 (LC089A) (Exp. Date: July 2014)
pH 6.8	April 7, 2012 (12 units)	March 25, 2012 (6 units)	April 2, 2012 (6 units)
	April 9, 2012 (6 units)	March 27, 2012 (6 units)	April 12, 2012 (6 units)
	April 12, 2012 (6 units)		

Bootstrapping method						
Treatment (# of units)	pH	Frequent	Original f2	F2 bootstrap mean	Lower CI (Percentile)	Upper CI (Percentile)
T vs. R (two lots) (24 vs. 24)	6.8	10000	34.30761	34.55327	29.30018	40.78859
R1 vs. R2 (12 vs 12)	6.8	10000	35.47665	35.57934	31.12492	40.74375

F2 values and 90% CI using bootstrapping method (12 units)

Bootstrapping method						
Treatment	pH	Frequent	Original f2	F2 bootstrap mean	Lower CI (Percentile)	Upper CI (Percentile)
T vs. R1 (12 vs 12)	6.8	10000	25.91946	26.03284	21.63071	31.14643
T vs. R2 (12 vs. 12)	6.8	10000	50.22053	50.61836	40.49969	63.76074

R1: FC207A (Exp. Date: March 2014) R2: LC089A(Exp. Date: July 2014)

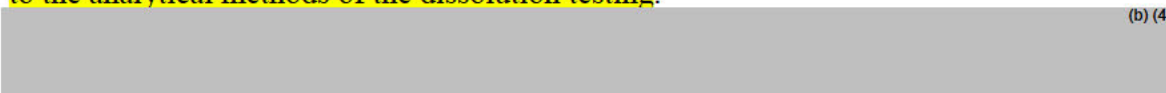
The firm stated that at pH 6.8, the Test Product shows slower dissolution rate than some of the Reference product batches, but the overall extent of dissolution at 8 hours is similar between the Test and Reference products



Per consult with the Science Team, as no testing is required between pH 6.8 and 7.2 to compare the release similarity, the test product should have comparable dissolution profiles at pH 6.8 as ulcerative colitis patients may have lower pH in the distal small bowel.

3. Data in the Amendment dated October 23, 2014

The firm performed analytical method validation for the in vitro BE dissolution study at pH 6.8 phosphate buffer for the evaluation stage to investigate the observed day-to-day variability. The firm found that the observed day-to-day variability in the pH 6.8 phosphate buffer dissolution test results especially at 1 hour and 2 hour sampling time points for both the test and reference products can be attributed to the inherent pH dependent solubility nature (b) (4) and not due to the analytical methods of the dissolution testing.



Thus, a small variation in the two-polymer composition would result in large variability in the % mesalamine dissolved at this sensitive, transitional pH (6.8), especially at the early sampling time points of the dissolution test.

During the validation, the firm observed that the dissolution testing at pH 6.8 is not robust over minor changes in the pH of dissolution medium (i.e. from (b) (4) on its test product as shown below:

The firm claimed that it validated the dissolution test method and provided a sound scientific basis for the observed high variability in the test results at evaluation stage pH 6.8. Thus, it believes that it would not be necessary to regenerate or repeat the dissolution test results at this pH using the unexpired reference and test products because the results will essentially be the same as those previously submitted.

4. Current Proposal:

a. Proposal I:

The firm provided 6 units data from the test product for each test in its method validation report. However, no RLD product was tested for those conditions. The firm is not required to re-conduct the test at pH 6.8 but to provide the data of 12 units from both test and RLD product at (b) (4)

b. Proposal II:

Based on the firm's raw data for other RLD batches in the current amendment, the reviewer generate the F2 values.

Bootstrapping method						
Treatment (24 vs. 12)	pH	Frequent	Original f2	F2 bootstrap mean	Lower CI (Percentile)	Upper CI (Percentile)
T vs. R1	6.8	10000	58.72	59.04	46.64	74.18
T vs. R2	6.8	10000	25.70	25.74	22.26	29.70
T vs. R3	6.8	10000	23.31	23.01	19.06	27.50

R1: VC011A; R2: WD119A ; R3: LC105A

The firm should be required to provide its dissolution testing using selected RLD product.

Test Date		
Medium	RLD B No. VC001A (Expiry Date Sep 2014)	RLD (LC089A) (Exp. Date: July 2014)
pH 6.8	April, 2012	April 2, 2012 (6 units) April 12, 2012 (6 units)

5. Attachments

a. Formulation

i. RLD Formulation

Table 5: Components and Composition of SPD476 Tablets

Ingredient	Amount (mg)	Function	Reference to Standards
Drug substance(s) Mesalazine	1200.0	Active ingredient	EP and USP/NF
(b) (4)			
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sodium Carboxymethylcellulose (b) (4)			EP + USP/NF
(b) (4)			EP + USP/NF
Carnauba Wax			EP + USP/NF
Stearic Acid			EP + USP/NF
Silica, Colloidal Hydrated			EP + USP/NF
Sodium Starch Glycolate (Type A)			EP + USP/NF
Talc			EP + USP/NF
Magnesium Stearate			EP + USP/NF
(b) (4)			EP + USP/NF
(b) (4)			
Talc ²			EP + USP/NF
Methacrylic Acid Copolymer, Type A ²			EP + USP/NF
Methacrylic Acid Copolymer, Type B ²			EP + USP/NF
Triethylcitrate ²			EP + USP/NF
Titanium Dioxide ²			EP + USP/NF
Red Ferric Oxide (b) (4)			USP/NF
Polyethylene glycol 6000 ²			EP and USP
(b) (4)			EP and USP
(b) (4)			EP and USP
Total	1385.0		

EP: European Pharmacopoeia; NF: United States National Formulary; USP: United States Pharmacopoeia
(b) (4)

ii. Test Product Formulation

Ingredient (s)	Mesalamine Delayed-release Tablets, 1.2 g	
	Unit Composition (mg/tablet)	% w/w ^s
(b) (4)		
Mesalamine (b) (4) USP	1200.000	(b) (4)
Colloidal Silicon Dioxide (b) (4) NF	(b) (4)	
Magnesium Stearate (b) (4) NF		
(b) (4)		
Carboxy methyl cellulose Sodium (b) (4) USP		
Sodium Starch Glycolate (b) (4) NF		

Hypromellose	(b) (4) USP	(b) (4)	(b) (4)
(b) (4)	(b) (4)		
Microcrystalline Cellulose	(b) (4) NF		
Colloidal Silicon Dioxide	(b) (4) NF		
Magnesium Stearate	(b) (4) NF		
(b) (4)			
Methacrylic Acid Copolymer	(b) (4) NF		
(b) (4)	(b) (4)		
Triethyl Citrate	(b) (4) NF		
Talc	(b) (4) USP		
(b) (4)	(b) (4)		
(b) (4)	(b) (4)		
(b) (4)	(b) (4)		
Total (Coated Tablets)		1465.000	100.00

⁵ Calculated based on the coated tablet average weight.

(b) (4)

b. Raw data for in vitro BE study at pH 6.8

Table 3 Evaluation Stage: pH 6.8 Phosphate buffer at 100 rpm

Table 3 Evaluation Stage: pH 6.8 Phosphate buffer at 100 rpm											
Product Name	Mesalamine Delayed-Release Tablets, 1.2 g					LIALDA [®] (Mesalamine) Delayed-Release Tablets, 1.2 g					
Batch No.	Lot No.: EMM 196 Mfg date: March, 2012					Lot No.: FC207A (Unit 1-12), LC089A (Unit 13-24) Expiry date: FC207A -March, 2014 LC089A-July, 2014					
Manufacture	Cadila Healthcare Limited, India					Cosmo S.p.A. for Shire US Inc., USA					
Time point	% Dissolved in Hours					% Dissolved in Hours					
	1	2	4	6	8	1	2	4	6	8	
Unit-1	(b) (4)					(b) (4)					
Unit-2	(b) (4)					(b) (4)					
Unit-3	(b) (4)					(b) (4)					
Unit-4	(b) (4)					(b) (4)					
Unit-5	(b) (4)					(b) (4)					
Unit-6	(b) (4)					(b) (4)					
Unit-7	(b) (4)					(b) (4)					
Unit-8	(b) (4)					(b) (4)					
Unit-9	(b) (4)					(b) (4)					
Unit-10	(b) (4)					(b) (4)					
Unit-11	(b) (4)					(b) (4)					
Unit-12	(b) (4)					(b) (4)					
Unit-13	(b) (4)					(b) (4)					
Unit-14	(b) (4)					(b) (4)					
Unit-15	(b) (4)					(b) (4)					
Unit-16	(b) (4)					(b) (4)					
Unit-17	(b) (4)					(b) (4)					
Unit-18	(b) (4)					(b) (4)					
Unit-19	(b) (4)					(b) (4)					
Unit-20	(b) (4)					(b) (4)					
Unit-21	(b) (4)					(b) (4)					
Unit-22	(b) (4)					(b) (4)					
Unit-23	(b) (4)					(b) (4)					
Unit-24	(b) (4)					(b) (4)					
Mean	2.7	5.1	28.4	70.9	98.2	4.5	17.5	61.6	91.9	102.8	
Min	(b) (4)					(b) (4)					
Max	(b) (4)					(b) (4)					
% RSD	87.1	71.7	62.1	24.1	5.4	112.0	54.0	31.3	13.0	2.0	
Date of analysis:	April 7, 2012 (1-12 units) April 9, 2012 (13-18 units) April 12, 2012 (19-24 units)					March 25, 2012 (1-6 units) March 27, 2012 (7-12 units) April 2, 2012 (13-18 units) April 12, 2012 (19-24 units)					

6. Management Decision

- 1) Since the firm reported that the dissolution testing at pH 6.8 is not robust over minor changes, the firm should be requested to conduct its testing using same batch of fresh prepared buffer and conducted the test on both test and RLD product on the same day.
- 2) The firm should be informed our criteria for F2 evaluation.
- 3) The firm should be requested to conduct testing for both test and reference product at pH 6.8, (b) (4)
- 4) The firm should be requested to provide dissolution testing with more time points for a complete dissolution profile comparison.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 091640

APPLICANT: Zydus Pharmaceuticals USA Inc.

DRUG PRODUCT: Mesalamine Delayed-release Tablets, 1200 mg

The Division of Bioequivalence II (DB II) has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

1. Due to the high variability of your **in vitro Bioequivalence (BE) dissolution** data at pH 6.8 (i.e., percentage coefficient of variation >10%), an f2 test using mean profiles of test vs. reference listed drug (“RLD”) products is not sufficient as per the above “Dissolution Guidance”. Therefore, we calculated the f2 metric (an f2 confidence interval) using a bootstrapping method for the dissolution profile comparison.

For your testing data in evaluation stage at pH 6.8 Phosphate Buffer, the mean values and the lower bound of 90% confidence interval for the f2 test comparing Test vs. the RLD are lower than 50 and those comparing the RLD against itself (comparison of 2 different lots of the RLD) under the same condition. Those values suggest that the dissolution profiles of your test product are different from those of the corresponding reference under the condition. Your in vitro BE dissolution testing at pH 6.8 is inadequate.

2. We acknowledge that you have submitted the justification for the observed Day-to-Day variability at pH 6.8. However, we could only locate dissolution testing data on 6 units of your test product at pH (b) (4) in your validation report MVR/4355. To address why your test product is different from the RLD product in the in vitro BE dissolution testing at evaluation stage (pH 6.8), please provide your comparative in vitro BE dissolution testing using both unexpired test (e.g. at least 24 units) and the reference products (24 units from 2 different lots, 12 units from each lot) for the following conditions:

Apparatus: USP Apparatus 2 (paddle)

Pretreatment Stage 1: 2 hours in 100mM HCl at 100 rpm (750 mL)

Pretreatment Stage 2: 1 hour in pH 6.4 Phosphate buffer at 100 rpm (950 mL)

Evaluation Stage: Each of

(1) pH 6.8 Phosphate buffer at 100 rpm
(b) (4)

Volume: 960 mL

Temperature: 37°C

Sample times: 1, 2, 3, 4, 5, 6 and 8 hours or as needed for profile comparison

Please conduct the dissolution testing of the test and reference products on the same day and at the same location to reduce the Day-to-Day variability. The DB will perform an f2 test on your submitted dissolution data. If the variability of the dissolution data is such that mean data cannot be used for the f2 test, as per the Dissolution Guidance, the bootstrapping approach will be employed.

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. The 90% confidence intervals of the f2 values are calculated using the percentile approach. 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. Please note only one measurement after 85% dissolution of both the products should be included in the f2 calculation.

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D., R.Ph.
Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

8 OUTCOME

ANDA: 091640

Enter Review Productivity and Generate Report

Reviewer: Zhao, Joan

Date Completed:

Verifier: ,

Date Verified:

Division: Division of Bioequivalence

Description: Mesalamine Delayed Release Tablets, 1.2 g

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
24062	5/23/2014	Other (REGULAR)	Study Amendment	1	1
24062	5/23/2014	Bioequivalence Study (REGULAR)	In Vitro BE Dissolution Study on New Data from three reference batches	1	1
				Total:	2

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

/s/

ZHUOJUN ZHAO
09/16/2014

MINGLEI CUI
09/16/2014

ETHAN M STIER
09/16/2014

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	091640
Drug Product Name	Mesalamine Delayed-release Tablets
Strength (s)	1200 mg
Applicant Name	Zydus Pharmaceuticals USA Inc.
Applicant Address	210 Carnegie Center, 1 st Floor, Suite 103, Princeton, NJ-08540
US Agent Name and the mailing address	G. Srinivas
US Agent's Telephone Number	609-275-5125
US Agent's Fax Number	609-275-3711
Original Submission Date(s)	December 12, 2009 April 13, 2010 (Formulation Data) September 8, 2010 (Dissolution Acknowledgement) February 12, 2011 (Elemental Iron content update) October 23, 2013 (Study Amendment of PK BE study)
Submission Date(s) of Amendment(s) Under Review	May 23, 2014
First Generic	Yes
Reviewer	Zhuojun Zhao, Ph.D.
OVERALL DISSOLUTION REVIEW RESULT	ADEQUATE

Review of a Dissolution Amendment

I. EXECUTIVE SUMMARY

This is a review of the dissolution amendment only.

There is no USP method for this product but there is an FDA-recommended method. The firm's dissolution testing procedure in the original application dated December 12, 2009 is slightly different from the FDA-recommended method in the medium volume (See table below).

Dissolution Method		FDA	Zydus
Medium Volume:	Acid A:	750 mL	(b) (4)
	Buffer B:	950 mL	
	Buffer C:	960 mL	

Nevertheless, the firm's dissolution testing data was accepted and the firm was requested to acknowledge the following FDA-recommended method and specifications in deficiency letter dated August 3, 2010¹.

¹ DARRTS: REV-BIOEQ-02 (Dissolution Review), final date 07/28/2010.

Acid stage A: NMT (b) (4) % in 2 hours
 Buffer stage B: NMT (b) (4) % in 1 hour
 Buffer stage C:
 1 hour: NMT (b) (4) %
 2 hours: (b) (4) %
 6 hours: NLT (b) (4) %

In firm's amendment dated September 8, 2010, the firm acknowledged the FDA-recommended method and specifications and submitted documents for the updates. The dissolution testing on batch (EMH345, Manufacture Date August 2008) was deemed acceptable².

In the amendment dated October 23, 2013, the firm submitted its dissolution testing using the FDA-recommended method on the new batch test product (Lot No. EMM196, Manufacture date March 2012). The firm's dissolution testing meets the FDA-recommended specifications. (b) (4)

(b) (4) 3 volumes in the FDA-recommended method (Acid stage A: 750 mL, Buffer stage B; 950 mL and Buffer stage C: 960 mL) and the specification was not updated.. Therefore, the firm was requested to submit its explanation on the observed discrepancy and provided the updated table.

In the current amendment, the firm clarified the observed discrepancy was its typographical error. The reviewer verified that the correct dissolution volume is listed in the firm's Raw Data Sheet of Finished Product. The firm's response is satisfactory.

The firm's dissolution testing is now found acceptable.

II. TABLE CONTENTS

I. EXECUTIVE SUMMARY	1
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IV. Deficiency Comments for Dissolution Testing	3
V. Dissolution Recommendations.....	4
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III. Review of Submission

DB Deficiency #1:

We acknowledge that you conduct your dissolution testing on the new batch test product (Lot No. EMM196, Manufacture date March 2012). (b) (4)

Please note that you acknowledged the following FDA-recommended method and specifications in your amendment dated September 8, 2010.

² DARRTS: REV-BIOEQ-01 (General Review), final date 02/23/2012

Method:

Acid Stage A: 750mL of 100 mM HCl (Acid Stage A)

Buffer Stage B: 950 mL of Phosphate buffer, pH 6.4

(Buffer Stage B: A+ 200 mL 200 mM Na₃PO₄)

Buffer Stage C: 960 mL of Phosphate buffer, pH 7.2

(Buffer Stage C: B + 9 mL 2M NaOH adjusting pH with 2M NaOH or 2M HCl)

Apparatus: USP apparatus 2 (Paddle)

Speed: 100 rpm.

Specifications:

Acid stage A: NMT (b) (4) % in 2 hours

Buffer stage B: NMT (b) (4) % in 1 hour

Buffer stage C: 1 hour: NMT (b) (4) %

2 hours: (b) (4) %

6 hours: NLT (b) (4) %

Please explain the observed discrepancy on dissolution volume and specifications and provide the updated table with correct dissolution volume and specifications.

Firm's Response:

(b) (4)
(b) (4) 950 mL (Buffer Stage B) or 960 mL (Buffer Stage C) in the bio summary Table 5: summary of in vitro dissolution studies provided in last complete response dated October 22, 2013.

We confirmed that all the dissolution tests have been performed using methods consistent with the FDA recommended methods. We assure the Agency that specification and parameters used in the dissolution tests for Mesalamine Delayed-Release Tablets, 1.2 g are same as those acknowledged in the submission dated September 8, 2010. For verification, please refer to the raw data sheet for the dissolution test in [Annexure-I](#) (pages 2 and 3 of 5 for Buffer Stage B and C, respectively) attached to this cover letter.

Reviewer's Comment:

The firm's response is satisfactory. The firm clarified the observed discrepancy was its typographical error. The reviewer verified that the correct dissolution volume is listed in the firm's Raw Data Sheet of Finished Product.

IV. Deficiency Comments for Dissolution Testing

None.

V. Dissolution Recommendations

The dissolution testing conducted by Zydus Pharmaceuticals USA Inc. on its Mesalamine Delayed-release Tablets, 1200 mg, is **acceptable**. The dissolution testing should be conducted in the following FDA-recommended method and specifications

Method: **Acid Stage A:** 750mL of 100 mM HCl (Acid Stage A)
 Buffer Stage B: 950 mL of Phosphate buffer, pH 6.4
 (Buffer Stage B: A+ 200 mL 200 mM Na₃PO₄)
 Buffer Stage C: 960 mL of Phosphate buffer, pH 7.2
 (Buffer Stage C: B + 9 mL 2M NaOH adjusting pH with 2M NaOH or 2M HCl)
 Apparatus: USP apparatus 2 (Paddle)
 Speed: 100 rpm.

Specifications:

Acid stage A: NMT $\frac{(b)(4)}{(4)}\%$ in 2 hours
Buffer stage B: NMT $\frac{(b)(4)}{(4)}\%$ in 1 hour
Buffer stage C: 1 hou NMT $\frac{(b)(4)}{(4)}\%$
 2 hours: $\frac{(b)(4)}{(4)}\%$
 6 hours: NLT $\frac{(b)(4)}{(4)}\%$

BIOEQUIVALENCE COMMENTS

ANDA: 091640

APPLICANT: Zydus Pharmaceuticals USA Inc.

DRUG PRODUCT: Mesalamine Delayed-release Tablets, 1200 mg

The Division of Bioequivalence II (DBII) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet and has no further questions at this time. The review of the bioequivalence studies will be conducted later.

We acknowledge that you will conduct the dissolution testing of your test product using the following FDA-recommended method for Mesalamine Delayed-release Tablets:

Method: **Acid Stage A:** 750mL of 100 mM HCl (Acid Stage A)
Buffer Stage B: 950 mL of Phosphate buffer, pH 6.4
(Buffer Stage B: A+ 200 mL 200 mM Na₃PO₄)
Buffer Stage C: 960 mL of Phosphate buffer, pH 7.2
(Buffer Stage C: B + 9 mL 2M NaOH adjusting pH with 2M NaOH or 2M HCl)
Apparatus: USP apparatus 2 (Paddle)
Speed: 100 rpm.

Specifications:

Acid stage A: NMT (b)(4)0% in 2 hours
Buffer stage B: NMT (b)(4)0% in 1 hour
Buffer stage C: 1 hour NMT (b)(4)0%
2 hours: (b)(4)0%
6 hours: NLT (b)(4)0%

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D., R.Ph.
Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

VI. OUTCOME

ANDA: 091640

Reviewer: Zhao, Joan

Date Completed:

Verifier: ,

Date Verified:

Division: Division of Bioequivalence

Description: Mesalamine Delayed-release Tablets, 1200 mg

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
23159	5/23/2014	Dissolution Data (REGULAR)	Dissolution Amendment	1	1
				Total:	1

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/s/

ZHUOJUN ZHAO
07/14/2014

MINGLEI CUI
07/16/2014

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	091640	
Drug Product Name	Mesalamine Delayed-release Tablets	
Strength(s)	1200 mg	
Applicant Name	Zydus Pharmaceuticals USA Inc.	
Address	210 Carnegie Center, 1 st Floor, Suite 103, Princeton, NJ-08540	
Applicant's Point of Contact	G. Srinivas	
Contact's Telephone Number	609-275-5125	
Contact's Fax Number	609-275-3711	
Original Submission Date(s)	December 12, 2009 April 13, 2010 (Formulation Data) September 8, 2010 (Dissolution Acknowledgement) February 12, 2011 (Elemental Iron content update)	
Submission Date(s) of Amendment(s) Under Review	October 23, 2013	
First Generic	Yes	
Reviewer	Zhuojun Zhao, Ph.D.	
Study Number (s)	MSN-P2-480	MSN-P3-482
Study Type (s)	Fasting	Fed
Strength (s)	1200 mg	1200 mg
Clinical Site	Algorithme Pharma Inc.	
Clinical Site Address	1200 Beaumont Ave. Mount-Royal, Quebec, Canada H3P 3P1 Telephone: (514) 858-6077 Fax: (514) 380-5261	
Analytical Site	(b) (4)	
Analytical Site Address	(b) (4)	
Study Number (s)	MSN-P2-481	MSN-P2-602
Study Type (s)	Failed Pilot Fed	Failed Pilot Fed
Strength (s)	1200 mg	1200 mg
Clinical Site	Algorithme Pharma Inc.	
Clinical Site Address	1200 Beaumont Ave. Mount-Royal, Quebec, Canada H3P 3P1 Telephone: (514) 858-6077 Fax: (514) 380-5261	
Analytical Site	(b) (4)	
Analytical Site Address	(b) (4)	
OSI Status	Adequate	
REVIEW RESULT	Inadequate	

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1	Fasting	1200 mg	Inadequate
1	Fed	1200 mg	Inadequate
2	Pilot Fed	1200 mg	Adequate
1	Pilot Fed	1200 mg	Adequate
1	Dissolution	1200 mg	Inadequate
1	In vitro BE dissolution study	1200 mg	Inadequate
OUTCOME DECISION		Inadequate	

NOTE: This is a combined dissolution (QC) and BE review.

This is the review of study amendment

1 EXECUTIVE SUMMARY

Zydus Pharamceuticals USA Inc. initially conducted a clinical endpoint BE study comparing the test product, Zydus Pharmaceuticals USA Inc.'s Mesalamine Delayed Release Tablets, 1200 mg to the corresponding reference product, Shire's Lialda® (Mesalamine) Delayed Release Tablets, 1200 mg. The application was received on December 12, 2009. However, in the Agency's response to the Citizen's Petitions (CPs) FDA-2010-P-0111 and FDA-2008-P-0507, dated August 10, 2010, the BE study with clinical endpoints is no longer considered to be sufficiently sensitive to establish BE of this product. Therefore, the firm was requested to conduct BE studies with the recommended PK endpoints under both fasting and fed conditions and *in vitro* dissolution study to demonstrate the bioequivalence between its test product and the reference product in DB deficiency letter dated March 13, 2012.

In the current amendment, the firm provided the results of the required fasting and fed bioequivalence (BE) studies comparing a test product, Zydus Pharamceuticals USA Inc.'s Mesalamine DR Tablets, 1200 mg to the corresponding reference product, Shire's Lialda® (Mesalamine) Delayed Release Tablets, 1200 mg. The tablet formulation composition for the Zydus' Mesalamine Delayed-Release Tablets 1200 mg used in the BE studies (Batch No. EMM196) is identical to the original ANDA exhibit batch (Batch No. EMH345), which was found acceptable in the original BE review (DARRTS: REV-BIOEQ-01 (General Review), final date 02/23/2012). Each of the BE studies was designed as a single-dose, three-way, partial reference-replicated crossover study in healthy subjects. The applicant provided evidence that, the reference product met FDA's criteria to be classified as a highly variable drug, with respect to $AUC_{8-48 \text{ hr}}$, AUC_{0-t} and C_{max} under both fasting and fed conditions. The reference-scaled average bioequivalence (ABE) approach was used to calculate bioequivalence statistics for $AUC_{8-48 \text{ hr}}$, AUC_{0-t} and C_{max} in the fasting and fed conditions. The firm's BE studies are incomplete pending its explanation for issues in its analytical reports. The results of the BE studies are summarized in the tables below.

Mesalamine Delayed Release Tablets, 1 × 1200 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals								
Fasting Bioequivalence Study, Study No. MSN-P2-480, N=58								
SUMMARY OF STATISTICAL ANALYSIS – SCALED DATA								
Parameter (units)	T/R Ratio	Lower90% CI	Upper90% CI	s2wr	sWR [#]	Criteria Bound	Method Used	OUTCOME
AUC _{8-48 hr} (hr *ng/ml)	1.05	N/A	N/A	0.3002033	0.5479081	-0.170822	Scaled/PE	PASS
AUC _{0-t} (hr *ng/ml)	1.02	N/A	N/A	0.0870697	0.2950757	-0.047687	Scaled/PE	PASS
C _{max} (ng/ml)	0.88	N/A	N/A	0.3348601	0.578671	-0.149502	Scaled/PE	PASS

Mesalamine Delayed Release Tablets, 1 × 1200 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals								
Fed Bioequivalence Study, Study No. MSN-P3-482 n=58								
SUMMARY OF STATISTICAL ANALYSIS – SCALED DATA								
Parameter (units)	T/R Ratio	Lower90% CI	Upper90% CI	s2wr	sWR [#]	Criteria Bound	Method Used	OUTCOME
AUC _{8-48 hr} (hr *ng/ml)	0.91	N/A	N/A	0.1819849	0.4265969	-0.083179	Scaled/PE	PASS
AUC _{0-t} (hr *ng/ml)	0.91	N/A	N/A	0.1924678	0.4387115	-0.086809	Scaled/PE	PASS
C _{max} (ng/ml)	0.91	N/A	N/A	0.4596764	0.6779944	-0.242166	Scaled/PE	PASS

The firm also submitted two failed pilot fed studies no MSN-P2-481 and MSN-P2-602 on the same exhibition test lot. The Reference Product used in Study MSN-P2- 481 was the same batch (Batch No. FC207A) as that in the pivotal fed BE study, but different RLD batch (Batch No. LC089A) for the Study MSN-P2-602. The study design for both pilot studies is the same as the pivotal study MSNP3- 482, except that the plasma sampling time points. The statistical analysis results indicate that the Test Product, Zydus's Mesalamine Delayed-Release Tablets 1.2 g is bioequivalent to the Reference product in both fed studies, in terms of AUC_{0-t} and AUC_{8-48hr} of mesalamine, but not for C_{max}. The failed C_{max} indicates that the firm did not have accurately designed sampling time points to demonstrate bioequivalence of the test product to the RLD product.

There is no USP method for this product but there is an FDA-recommended method. The firm stated it re-conducted its dissolution testing using the FDA-recommended method [750mL of 100 mM HCl (Acid Stage A) for 2 hrs, followed by 950 mL of Phosphate buffer, pH 6.4 (Buffer Stage B) for 1 hr and 960 mL of Phosphate buffer, pH 7.2 (Buffer Stage C) using apparatus 2 (Paddle) at 100 rpm on the new batch test product (Lot No. EMM196). The firm's dissolution testing meets the FDA-recommended specifications.

(b) (4)

In addition to in vivo fasting and fed BE studies, the guidance also recommends comparative in vitro BE dissolution studies to be conducted in pH 6.5, 6.8, 7.2 and 7.5 phosphate buffer representative of the GI tract pH variations. The firm's dissolution results show similar dissolution profiles between the test and reference products at pH 7.2 and pH 7.5 but not at pH 6.5 and 6.8. The firm's test product had minimal release at pH 6.5 and thus the testing at pH 6.5 is deemed acceptable per the science team consult (see section 3.9). However, since ulcerative colitis patients may have lower pH in the distal small bowel^{1,2}, we currently recommend the test and reference products have comparable dissolution profiles at pH 6.8. Therefore, for the observed Day-to-Day high variability in pH 6.8 buffer on test and reference products, the firm should investigate its laboratory's performance of this method, provide explanation for the observed variability and re-conduct its testing in the pH 6.8 and (b) (4). In addition, the firm should submit its full study report or the complete dissolution profiles for the testing conditions.

A Routine inspection of the Clinical site, Algorithm Pharma Inc. (1200 Beaumont Ave., Mount-Royal, Quebec, H3P 3P1, Canada) and the Analytical site, (b) (4)

Therefore, no Division of Scientific Investigations (DSI) inspection is pending or necessary.

The application is incomplete.

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¹ Digestive Diseases and Sciences, Vol. 38, No. 11 (November 1993), pp. 1989-1993:

² Gut 2001;48:571-577

³ DARRTS: CONSULT REV-DSI-05 (Bioequivalence Establishment Inspection Report Review), final date 09/26/13.

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3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Mesalamine Delayed Release Tablets, 1200 mg
Reference Product	Lialda® (Mesalamine) Delayed Release Tablets, 1200 mg
RLD Manufacturer	Shire
NDA No.	N022000
RLD Approval Date	January 16, 2007
Indication	LIALDA is a locally acting 5-aminosalicylic acid (5-ASA) indicated for

	the induction of remission in adults with active, mild to moderate ulcerative colitis and for the maintenance of remission of ulcerative colitis.
Product Description of RLD	The tablet core consists of 5-ASA incorporated in microparticles of a lipophilic matrix that are in turn dispersed within a hydrophilic matrix. The inner lipophilic matrix gives an extended release fashion. This modified matrix system is coated with a gastro-resistant polymer film that breaks down at pH 6.8, usually in the terminal ileum. This gives the delayed release fashion (see 4.2.2 for the RLD formulation).
Mechanism of Action	The mechanism of action of mesalamine is not fully understood, but appears to have a topical anti-inflammatory effect on the colonic epithelia cells. The pharmacodynamic action of mesalamine occur in the colonic/rectal mucosae local to the delivery of drug from Lialda into lumen, Gamma-scintigraphy studies have shown that a single dose of LIALDA 1.2g (one tablet) passed intact through the upper gastrointestinal tract of fasted healthy volunteers. Scintigraphic images showed a trail of radio-labeled tracer in the colon, suggesting that mesalamine had distributed throughout this region of the gastrointestinal tract.

3.2 PK/PD Information⁴

Bioavailability	The total absorption of mesalamine from LIALDA 2.4 g or 4.8 g given once daily for 14 days to healthy volunteers was found to be approximately 21-22% of the administered dose.
Food Effect	Administration of a single dose of LIALDA 4.8 g with a high fat meal resulted in further delay in absorption, and plasma concentrations of mesalamine were detectable 4 hours following dosing. However, a high fat meal increased systemic exposure of mesalamine (mean C_{max} : (91%; mean AUC: (16%) compared to results in the fasted state.
T_{max}	Plasma concentrations of mesalamine were detectable after 2 hours and reached a maximum by 9-12 hours on average for the doses studied.
Metabolism	The only major metabolite of mesalamine (5-aminosalicylic acid) is N-acetyl-5-aminosalicylic acid. Its formation is brought about by N-acetyltransferase (NAT) activity in the liver and intestinal mucosa cells, principally by NAT-1.
Excretion	Elimination of mesalamine is mainly via the renal route following metabolism to N-acetyl-5-aminosalicylic acid (acetylation). However, there is also limited excretion of the parent drug in urine. Of the approximately 21-22% of the dose absorbed, less than 8% of the dose was excreted unchanged in the urine after 24 hours, compared with greater than 13% for N-acetyl-5-aminosalicylic acid.
Half-life	The apparent terminal half-lives for mesalamine and its major metabolite after administration of LIALDA 2.4 g and 4.8 g were, on average, 7-9 hours and 8-12 hours, respectively.
Dosage and Administration	The recommended dosage for the induction of remission in adult patients

⁴ Labeling repository: <http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=3098a080-be86-4265-9818-7fc4beab77b7#nmlm34068-7>.

	with active, mild to moderate ulcerative colitis is two to four 1.2 g tablets taken once daily with a meal for a total daily dose of 2.4 g or 4.8 g.
Maximum Daily Dose	4.8 g/day
Drug Specific Issues (if any)	None

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	3, fasting and fed studies and <i>in vitro</i> comparative dissolution study
---------------------------------------	--

1.	Type of study:	Fasting
	Design:	Single-dose, partially or fully replicated crossover design, in vivo
	Strength:	1200 mg
	Subjects:	Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstinence or contraception during the study.
	Additional Comments:	Bioequivalence based on (Scaled Average Bioequivalence): (1). Applicants may consider using a reference-scaled average bioequivalence approach for mesalamine. If using this approach, the applicant should provide evidence of high variability in the bioequivalence parameters (i.e., within-subject variability $\geq 30\%$) for the reference product. For general information on this approach refer to the Progesterone Capsule Guidance for additional information regarding highly variable drugs. (2). For both fasting and fed studies, the following PK parameters are recommended to be evaluated: Log-transformed AUC₈₋₄₈, AUC_{0-t}, and C_{max}, where AUC₈₋₄₈ is the area under the plasma concentration vs. time curve from 8 to 48 hours, AUC_{0-t} is the area under the curve from 0 hours to the last measurable time point, and C_{max} is the maximum plasma concentration. Applicants should have extensive sampling points around T_{max} to have accurate estimation of C_{max} and T_{max}, and at least four non-zero measurements of concentration are recommended before T_{max} and between T_{max} and 24 hours. Other partial AUCs may be evaluated as supporting material to evaluate similarity of drug release throughout the gastrointestinal tract. (3). As AUC_{0-t}, is recommended in place of AUC_{0-∞}, the last sampling time point should be at least at 72 hours.

2.	Type of study:	Fed
	Design:	Single-dose, partially or fully replicated crossover design, in vivo
	Strength:	1200 mg
	Subjects:	Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstinence or contraception during the study.
	Additional Comments:	See additional comments above

Analytes to measure (in plasma/serum/blood):	Mesalamine in plasma
Bioequivalence based on:	90% CI of mesalamine
Waiver request of in-vivo testing:	N/A

3.	Type of study:	<i>In vitro</i> comparative dissolution study
	Strength:	1200 mg
	Apparatus:	USP Apparatus 2 (Paddle)
	Pretreatment Stage 1:	2 hours in 0.1 N HCl at 100 rpm (750 mL)
	Pretreatment Stage 2:	1 hour in pH 6.4 Phosphate buffer at 100 rpm (950 mL)
	Evaluation Stage 1:	Each of 960 mL (1) pH 6.5 Phosphate buffer at 100 rpm (2) pH 6.8 Phosphate buffer at 100 rpm (3) pH 7.2 Phosphate buffer at 100 rpm (4) pH 7.5 Phosphate buffer at 100 rpm
	Temperature:	37°C
	Sample times:	1, 2, 4, 6 and 8 hours or as needed for profile comparison
	Additional comments:	The applicant should use at least 12 tablets per test. The f2 metric will be used to compare dissolution profiles

Source of most recent recommendations:	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM320004.pdf (Recommended Sep 2012) ⁵
Summary of OGD or DB History	The DB has received and/or reviewed the following ANDAs: (b) (4) 203817 (WATSON LABORATORIES INC FLORIDA) 203574 (MYLAN PHARMACEUTICALS INC) Summary of OGD History (for detail, see Appendix 4.4)

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	--
In vitro dissolution	Yes	1
Waiver requests	No	--
BCS Waivers	No	--
Clinical Endpoints	No	--
Failed Studies	No	2 failed fed Studies

⁵ V:\Science Group\Mesalamine_BE\mesalamine_oral_BE_summary.doc

In vitro BE studies	Yes	4
Amendments	Yes	1

3.5 Pre-Study Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation report location	MSN-V9-475 (R4)
Analyte	Mesalamine
Internal standard (IS)	Mesalamine-D3
Method description	Liquid-liquid extraction with derivatization Hilic HPLC with MS/MS detection
Limit of quantitation	2.60 ng/mL
Average recovery of drug (%)	74.1% (LQC), 79.3% (MQC), 77.7% (HQC)
Average recovery of IS (%)	46.3 % (339.7ng/mL)
Standard curve concentrations (ng/mL)	2.60 ng/mL, 5.00 ng/mL, 10.00 ng/mL, 30.00 ng/mL, 75.00 ng/mL, 225.00 ng/mL, 375.00 ng/mL, 600.00 ng/mL, 1050.00 ng/mL, 1275.00 ng/mL, 1500.00 ng/mL
QC concentrations (ng/mL)	2.60 ng/mL, 7.60 ng/mL, 150.00 ng/mL, 1100.00 ng/mL
QC Intraday precision range (%)	2.1% - 7.9%
QC Intraday accuracy range (%)	98.2% - 100.3%
QC Interday precision range (%)	3.3% - 10.2%
QC Interday accuracy range (%)	92.1% - 101.0%
Bench-top stability (hrs)	31.5 hours at 22°C nominal
Stock stability (days)	41 days in ACN:H ₂ O 50:50% v/v at a concentration of 1000.00 µg/mL at 4°C nominal for Mesalamine 16 days in ACN:H ₂ O 50:50% v/v at a concentration of 0.13 µg/mL at 4°C nominal for Mesalamine 245 days in ACN:H ₂ O 50:50% v/v at a concentration of 250.00 µg/mL at 4°C nominal for Mesalamine-D3
Processed stability (hrs)	163.0 hours at 4°C nominal
Freeze-thaw stability (cycles)	3 cycles
Long-term storage stability (days)	313 days at -80°C nominal
Dilution integrity	10500.00 ng/mL diluted 5-fold
Selectivity	No significant interference was observed in the 10 blank matrix lots screened.

Updated for Fed Study

Dilution integrity	11250.00 ng/mL diluted 20-fold
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Comments on the Pre-Study Method Validation:
Acceptable.

APPEARS THIS WAY ON ORIGINAL



3.6 In Vivo Studies

Table 1. 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 (years): Mean (Range)	Mean Parameters (%CV)						Study Report Location
					C_{max}^a (ng/mL)	t_{max}^{ab} (hr)	AUC_{0-t}^a (ng h/mL)	AUC_{8-48}^a (ng h/mL)	t_{Half}^c (hr)	K_{el}^c (hr ⁻¹)	
Study MSN-P2-480	Single Dose, Partial Replicate, Crossover Comparative Bioavailability Study of Mesalamine 1.2 g Delayed-Release Tablets in Healthy Male and Female Volunteers / Fasting State	Randomized single-dose replicated, crossover	Mesalamine 1.2 g Delayed-Release Tablet p.o. [Batch # EMM196]	58 completing (27M/31F) Healthy subjects	1046.93 (95.3%)	11.02 (4.00-36.00)	9855.11 (38.7%)	7731.56 (44.3%)	11.37 (69.1%)	0.1009 (117.0%)	Refer Module 5.3.1.2
			Lialda™ 1.2 g Delayed-Release Tablet, p.o. [Batch # FC207A]	39 (18-63)	1207.07 (93.3%)	10.00 (4.00-48.00)	10116.06 (46.1%)	7800.74 (45.5%)	11.99 (73.5%)	0.0995 (107.4%)	

^a For MSN-P2-480, n= 58 for the Test and n= 116 for the Reference.

^b Median (range) is presented.

^c For MSN-P2-480, n= 50 for the Test and n= 96 for the Reference.

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age (years): Mean (Range)	Mean Parameters (%CV)						Study Report Location
					C _{max} ^a (ng/mL)	T _{max} ^{ab} (hr)	AUC _{0-t} ^a (ng·h/mL)	AUC ₈₋₄₈ ^a (ng·h/mL)	t _{half} ^c (hr)	Kel ^c (hr ⁻¹)	
MSN-P3-482	Single Dose, Partial Replicate, Crossover Comparative Bioavailability Study of Mesalamine 1.2 g Delayed-Release Tablets in Healthy Male and Female Volunteers / Fed State	Randomized single-dose partial-replicate crossover	Mesalamine 1.2 g Delayed-Release Tablet, p.o. [EMM196]	58 (33/25) Healthy subjects	1648.09 (83.0%)	21.00 (8.00-36.00)	9245.43 (51.8%)	8314.51 (54.7%)	11.12 (71.9%)	0.0950 (80.2)	Refer Module 5.3.1.2
			Lialda™ 1.2 g Delayed-Release Tablet, p.o. [FC207A]	Mean age: 41 years (19-69)	1890.43 (85.0%)	17.06 (8.00-48.00)	10491.37 (54.4%)	9454.29 (59.3%)	11.33 (82.9%)	0.1019 (88.4%)	

^a n= 58 for the Test and n= 116 for the Reference.^b Median (range) is presented.^c n= 43 for the Test and n= 77 for the Reference

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Mesalamine Delayed Release Tablets, 1 × 1200 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals								
Fasting Bioequivalence Study, Study No. MSN-P2-480								
SUMMARY OF STATISTICAL ANALYSIS –SCALED DATA								
Parameter (units)	T/R Ratio	Lower90% CI	Upper90% CI	s2wr	sWR [#]	Criteria Bound	Method Used	OUTCOME
AUC _{8-48 hr} (hr *ng/ml)	1.05	N/A	N/A	0.3002033	0.5479081	-0.170822	Scaled/PE	PASS
AUC _{0-t} (hr *ng/ml)	1.02	N/A	N/A	0.0870697	0.2950757	-0.047687	Scaled/PE	PASS
C _{max} (ng/ml)	0.88	N/A	N/A	0.3348601	0.578671	-0.149502	Scaled/PE	PASS

Mesalamine Delayed Release Tablets, 1 × 1200 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals								
Fed Bioequivalence Study, Study No. MSN-P3-482								
SUMMARY OF STATISTICAL ANALYSIS –SCALED DATA								
Parameter (units)	T/R Ratio	Lower90% CI	Upper90% CI	s2wr	sWR [#]	Criteria Bound	Method Used	OUTCOME
AUC _{8-48 hr} (hr *ng/ml)	0.91	N/A	N/A	0.1819849	0.4265969	-0.083179	Scaled/PE	PASS
AUC _{0-t} (hr *ng/ml)	0.91	N/A	N/A	0.1924678	0.4387115	-0.086809	Scaled/PE	PASS
C _{max} (ng/ml)	0.91	N/A	N/A	0.4596764	0.6779944	-0.242166	Scaled/PE	PASS

Table 3. Reanalysis of Study Samples

Study No. MSN-P2-480								
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
Pharmacokinetic	NA	NA	NA	NA	NA	NA	NA	NA
Laboratory Investigation (LI)	1	0	0.0	0.0	1	0	0.0	0.0

Sample Lost in Processing (SLP)	3	7	0.1	0.2	NA	NA	NA	NA
Unexpected Internal Standard Response (UIS)	17	41	0.4	0.9	NA	NA	NA	NA
Suspected Contamination or Interference (SCI)	2	2	0.0	0.0	NA	NA	NA	NA
Above the Upper Limit of Quantification (>ULQ)*	19	49	0.4	1.1	NA	NA	NA	NA
Total	42	99	0.9	2.2	1	0	0.0	0.0

Study No. MSN-P3-482								
Additional information in Volume(s), Page(s)								
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
Pharmacokinetic	NA	NA	NA	NA	NA	NA	NA	NA
Sample Lost in Processing (SLP)	0	3	0.0	0.1	NA	NA	NA	NA
Unexpected Internal Standard Response (UIS)	2	9	0.0	0.2	NA	NA	NA	NA
Outside Truncated Curve Range (CR)	5	12	0.1	0.3	NA	NA	NA	NA
Suspected Contamination or Interference (SCI)	1	0	0.0	0.0	NA	NA	NA	NA
Above the Upper Limit of Quantification (>ULQ)*	54	107	1.3	2.6	NA	NA	NA	NA
Total	62	131	1.5	3.1	NA	NA	NA	NA

* Initial repeat reasons are accounted.

Did use of recalculated plasma concentration data change study outcome? No

Comments from the Reviewer:

1. There was 1 sample repeated as Laboratory Investigation (LI) in the Fasting study MSN-P2-480. It is noted that the definition below for Laboratory Investigation (LI) in firm's SOP (b) (4) is not clear for the criteria on how to judge the data (as shown below). Also, the reviewer could not locate the reference of SOP (b) (4)

9. Laboratory Investigation (LI)

The code LI is used as part of a laboratory investigation of aberrant subject sample values or subject sample values where an inversion is suspected. Refer to SOP (b) (4) for further details about laboratory investigations. Samples coded LI are repeated in duplicate (refer to the * in section V.A.), if sufficient sample volume permits. When insufficient sample volume remains to perform duplicate re-assays, consider the possibility of diluting the sample in order to obtain duplicate re-assay values (note that if insufficient sample volume remains to perform duplicate re-assays with dilution, a single re-assay may be performed). The criteria for reporting final concentration values for subject samples coded LI are detailed in section VI. The code LI applies to subject samples only.

Thus, the samples repeated with LI is deemed as PK repeat and thus the reviewer conducted statistical analysis using the original value for the fasting study and found the study results were not impacted.

2. Per firm's SOP (b) (4) and SOP (b) (4) sample coded as Above the Upper Limit of Quantitation (>ULQ) were diluted appropriately prior to reassay.

The code >ULQ is used where the calculated, un-rounded concentration of a sample falls above the nominal concentration of the ULQ (this does not apply to truncated calibration curves; refer to V.A.1.). Additionally, the >ULQ code is applied to QC and subject samples whose ratios have a greater value than the extrapolated curve's vertex, in the case of a quadratic equation. This code more often applies to subject samples, however, it may also apply to QC samples, e.g., high concentration QC samples assayed as part of sample analysis or method validation that produce concentrations above that of the ULQ calibrant. Subject samples coded >ULQ are generally diluted appropriately prior to re-assay. Refer to SOP (b) (4)

However, the firm did not provide the dilution factor in its study report or the related SOP (b) (4). The firm should be requested to provide the used dilution factors for those samples.

3. It is noted that the firm reported all repeat assays values as the final concentration for repeat assay under code "SLP", "UIS", "SCI", ">ULQ" and "CR" but report "Number of recalculated values used after reanalysis" as "NA" for those samples. The firm should be notified for its future application, the firm should report the actual number for "Number of recalculated values used after reanalysis" when the final concentration is reported from repeat assays.

3.7 Formulation

The submitted tablet formulation composition for the Zydus's Mesalamine Delayed-Release Tablets 1.2 g in the current amendment (Batch No. EMM196) is identical to the original ANDA exhibit batch (Batch No. EMH345), which was found acceptable in the original BE review (DARRTS: REV-BIOEQ-01 (General Review), final date 02/23/2012)⁶.

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	DARRTS: REV-BIOEQ-02 (Dissolution Review), final date 07/28/2010 DARRTS: REV-BIOEQ-01 (General Review), final date 02/23/2012
Source of Method (USP, FDA or Firm)	FDA
Medium	Acid stage A: 100 mM HCl; Buffer stage B: Phosphate buffer, pH 6.4; Buffer stage C: Phosphate buffer, pH 7.2
Volume (mL)	Acid A: 750 mL Buffer B: 950 mL (A + 200mL 200mM Na ₃ PO ₄)* Buffer C: 960 mL (B+ 9mL 2M NaOH)* *Adjust pH with 2M NaOH or 2M HCl
USP Apparatus type	USP II (Paddle)
Rotation (rpm)	100 rpm
DB-recommended specifications	Acid Stage A: NMT $\frac{(b)(4)}{(4)}\%$, Buffer Stage B: NMT $\frac{(b)(4)}{(4)}\%$, Buffer Stage C: 1 hr: NMT $\frac{(b)(4)}{(4)}\%$, 2 hr: $\frac{(b)(4)}{(4)}\%$, 6h NLT $\frac{(b)(4)}{(4)}\%$
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	Yes
If no, reason why F2 not calculated	
Is method acceptable?	METHOD ACCEPTABLE
If not then why?	

F2 metric, Test (Batch # EMH196) compared to RLD (FC207A)
82.53

Comments:

There is no USP method for this product but there is an FDA-recommended method. The firm's dissolution testing procedure in the original application dated December 12, 2009

(b) (4)

is slightly different from the FDA-recommended method in the medium volume (See table below).

Dissolution Method		FDA	Zydus
Medium Volume:	Acid A:	750 mL	(b) (4)
	Buffer B:	950 mL	
	Buffer C:	960 mL	

Nevertheless, the firm's dissolution testing data was accepted and the firm was requested to acknowledge the following FDA-recommended method and specifications in deficiency letter dated August 3, 2010⁷.

Acid stage A: NMT $\frac{(b) (4)}{(4)}\%$ in 2 hours

Buffer stage B: NMT $\frac{(b) (4)}{(4)}\%$ in 1 hour

Buffer stage C:

1 hour: NMT $\frac{(b) (4)}{(4)}\%$

2 hours: $\frac{(b) (4)}{(4)}\%$

6 hours: NLT $\frac{(b) (4)}{(4)}\%$

In firm's amendment dated September 8, 2010, the firm acknowledged the FDA-recommended method and specifications and submitted documents for the updates. The dissolution testing on batch (EMH345, Manufacture Date August 2008) is deemed acceptable⁸.

In the current amendment, the firm submits its dissolution testing using the FDA-recommended method on the new batch test product (Lot No. EMM196, Manufacture date March 2012). The dissolution data is attached in [section 4.3](#). The firm's dissolution testing meets the FDA-recommended specifications. The reviewer verified that the firm's dissolution data is reported by the first 12 units of test and RLD products (for pH 7.2 as a part of multi-media dissolution testing) in the submission module 5.3.1.3 (see individual data in section 4.3.4). However, the firm listed the volume of dissolution medium as $\frac{(b) (4)}{(4)}$ in bio-summary table 5 instead of 3 volumes in the FDA-recommended method (Acid stage A: 750 mL, Buffer stage B; 950 mL and Buffer stage C: 960 mL) and the specification was not updated.. Therefore, the firm should be requested to submit its explanation on the observed discrepancy and provided the updated table.

The firm's dissolution testing is incomplete.

3.9 In Vitro BE Studies (in pH 6.5, pH 6.8, pH 7.2 and pH 7.5 Phosphate buffer)

The performance of the enteric coating of Lialda[®] is an essential attribute of the product. Demonstration of equivalence in multistage dissolution ensures the equivalent integrity of the enteric coat at acidic pH and at pH 6.4-7.2. The firm was request to conduct in vitro BE studies comparing its test product to the RLD Lialda[®] tablets at pH 6.5-7.5 as per the OGD recommendations in deficiency letter dated March 13, 2012 and Complete Response letter dated March 13, 2013.

⁷ DARRTS: REV-BIOEQ-02 (Dissolution Review), final date 07/28/2010.

⁸ DARRTS: REV-BIOEQ-01 (General Review), final date 02/23/2012

As required, the firm conducted the studies on 24 units of Test product and two lots of RLD (12 units from each RLD lot), as shown below:

Table 4 . Product information in dissolution testing

Test	Reference1	Reference 2
Lot No. EMM 196 Mfg. Date: March 2012	Lialda® (Mesalamine) Delayed Release Tablets Lot. No. FC207A ⁹ Exp. Date: March 2014	Lialda® (Mesalamine) Delayed Release Tablets Lot. No. LC089A Exp. Date: July 2014

Table 5 Test dates for in vitro BE studies for both test and reference products:

Test Date			
Medium	Test Product	RLD 1 (FC207A) (Exp. Date: March 2014)	RLD 2 (LC089A) (Exp. Date: July 2014)
Pretreatment Stage 1 (0.1 N HCl) Pretreatment Stage 2 (pH 6.4)	April 7, 2012 (12 units) April 13, 2012 (12 units)	March 25, 2012 (12 units)	March 27, 2012 (6 units) April 2, 2012 (6 units)
pH 6.5	April 7, 2012 (12 units) April 12, 2012 (12 units)	March 25, 2012 (6 units) March 27, 2012 (6 units)	April 2, 2012 (6 units) April 12, 2012 (6 units)
pH 6.8	April 7, 2012 (12 units) April 9, 2012 (6 units) April 12, 2012 (6 units)	March 25, 2012 (6 units) March 27, 2012 (6 units)	April 2, 2012 (6 units) April 12, 2012 (6 units)
pH 7.2	April 13, 2012 (12 units) April 11, 2012 (12 units)	March 25, 2012 (6 units) March 27, 2012 (6 units)	April 2, 2012 (6 units) April 11, 2012 (6 units)
pH 7.5	April 8, 2012 (12 units) April 11, 2012 (12 units)	March 26, 2012 (6 units) March 27, 2012 (6 units)	April 2, 2012 (6 units) April 11, 2012 (6 units)

Comments on Study:

- The firm provided *in vitro* BE study on the new test product batch (EMM 196) and two RLD lots (FC207A and LC089A). All studies were conducted on product within the expiration date using the FDA-recommended condition as following:

Apparatus: USP Apparatus 2 (paddle)

Pretreatment Stage 1: 2 hours in 0.1 N HCl at 100 rpm (750 mL)

Pretreatment Stage 2: 1 hour in pH 6.4 Phosphate buffer at 100 rpm (950 mL)

Evaluation Stage: Each of

(1) pH 6.5 Phosphate buffer at 100 rpm

(2) pH 6.8 Phosphate buffer at 100 rpm

(3) pH 7.2 Phosphate buffer at 100 rpm

(4) pH 7.5 Phosphate buffer at 100 rpm

Volume: 960 mL

Temperature: 37°C

Sample times: 1, 2, 4, 6 and 8 hours or as needed

⁹ Used for in vivo BE studies

- Based on the firm's data in [section 4.4](#), the means of F2 values (T24 vs. R24) are not calculated due to the observed high variability (i.e. percent coefficient of variation more than 15%).

Because of the highly variability of the dissolution data (high %CV) (i.e. percentage coefficient of variation (CV%) >10% at later time points as per *the CDER Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms*), a comparison of mean profiles with f2 test is not sufficient. The reviewer calculated f2 confidence interval (a statistical evaluation of f2 values) using a bootstrapping procedure¹⁰ (see below).

Table 6: F2 values and 90% CI using bootstrapping method (24 units)

Bootstrapping method						
Treatment (# of units)	pH	Frequent	Original f2	F2 bootstrap mean	Lower CI (Percentile)	Upper CI (Percent ile)
T vs. R (two lots) (24 vs. 24)	6.5	10000	17.07561	16.45597458	14.8008	17.79041
	6.8	10000	34.30761	34.55327	29.30018	40.78859
	7.2	10000	69.02809	69.55844	54.56053	85.90782
	7.5	10000	77.17999	73.83384	57.09611	89.58673
R1 vs. R2 (12 vs 12)	6.5	10000	31.41539	30.92268	27.83892	34.34846
	6.8	10000	35.47665	35.57934	31.12492	40.74375
	7.2	10000	32.69056	33.06435	29.99618	37.0998
	7.5	10000	28.66241	28.6892	26.55906	30.78745

R1: FC207A (Exp. Date: March 2014) **R2: LC089A**(Exp. Date: July 2014)

As shown in table above, the similarity dissolution profile for pH7.2 and pH 7.5 is indicated by the fact that f2 are greater than 50 and the lower bound of 90% CIs for the f2 test comparing T vs. R are greater than 46¹¹. Therefore, the firm's dissolution data showed that the test and reference products have a similar dissolution profile for pH 7.2 and pH 7.5.

- For pH 6.5, the test product showed slower dissolution rate than the reference product through 10 hours (data in [section 4.3.2](#)). The f2 using mean profiles is lower than 50, and their lower bound of 90% CIs of f2 comparing test vs. RLD are not only less than 46, but also lower than those comparing the RLD against itself under the same conditions. This result suggests that the dissolution profile of the test product is significantly different from that of reference product in pH 6.5 Phosphate buffer.

¹⁰ Please see statistical consult review for ANDA 065490 (DARRTS, ANDA-065490, REV-BIOMETRICS-01(General Review), Duan John Z, 12/04/2009) and ANDA 065510 (DARRTS, ANDA-065510, REV-BIOMETRICS-01(General Review), Duan John Z, 12/04/2009) for detail description of the bootstrap method.

¹¹ Per the internal meeting of OGD vancomycin review team (see the Attachment in Section 4.7), the dissolution profiles of the test and reference products are considered similar and acceptable when the f2 for the mean test and reference profiles are >50 and the lower bound of 90% confidence interval (CI) for f2 test is >46.

The pharmacodynamic actions of mesalamine occur in the colonic/rectal mucosae local to the delivery of drug from LIALDA® into the lumen. Mesalamine is rapidly absorbed by the upper small intestine, and thus absorption must be delayed until mesalamine reaches the terminal ileum or the colon. Lialda® DR tablets are coated with a gastro-resistant pH dependent polymer film, which dissolve at pH greater than 6.8¹², normally in the terminal ileum where mesalamine then begins to be released from the tablet core. Per consult with the Science Team (see [section 4.5](#)), F2 values might not be applied to pH 6.5 testing since the goal of this product is not to release at this pH. Instead, the dissolution profiles should be compared for the product release after 4 hours at pH 6.5. The test product **should not have more release** than the RLD product for 4 hours under pH 6.5.

The firm's test product had minimal release at pH 6.5 and thus the testing at pH 6.5 is deemed acceptable.

4. For pH 6.8, the f2 using mean profiles is lower than 50, and their lower bound of 90% CIs of f2 comparing test vs. RLD are less than 46 when the test product (24 units) compared with 2 lots of RLD (24 units). This result indicates that the dissolution profiles of test product are significantly different from those of the reference product. However, when the test product (12 units) compared with one batch of the RLD (Batch LC089A, 12 units), the F2 mean value is more than 50 and the lower bound of 90% CIs of f2 comparing test (12 unit) vs. reference 2 (Batch LC089A, 12 units) are higher than that comparing the RLD against itself under the same conditions (40.49 vs 31.12), as shown in table below:

Table 7: F2 values and 90% CI using bootstrapping method (12 units)

Bootstrapping method						
Treatment (# of units)	pH	Frequent	Original f2	F2 bootstrap mean	Lower CI (Percentile)	Upper CI (Percent ile)
T vs. R1 (12 vs 12)	6.8	10000	25.91946	26.03284	21.63071	31.14643
T vs. R2 (12 vs. 12)	6.8	10000	50.22053	50.61836	40.49969	63.76074

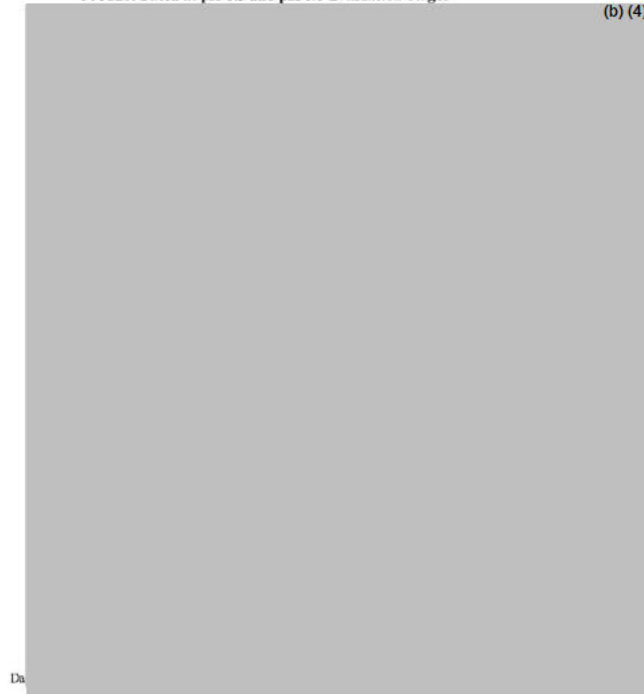
R1: FC207A (Exp. Date: March 2014) **R2: LC089A**(Exp. Date: July 2014)

This result indicated that the RLD showed high variability at pH 6.8 between **different batches**. The firm stated in the report that although the dissolution profiles at pH 6.5 and pH 6.8 for the Test Product Batch EMM196 were not "similar to" those of the Reference Product Batches FC207A and LC089A based on f2 values due to the large lot-to-lot differences in the Reference Product batches, the dissolution profiles of certain Reference batches (e.g. Batch VC011A

¹² Per Lialda® label

) at pH 6.5 and pH 6.8 were similar to those of the Test Product Batch EMM196 (Figure 2). Considering the therapeutic purpose of this drug product for the treatment of ulcerative colitis, it is important that the Test Product has almost identical dissolution profiles to those of the Reference product at pH levels associated with the site of local action of mesalamine (terminal ileum and colorectum), i.e., pH > 7, to have rapid and complete dissolution. Since mesalamine is almost completely absorbed into the blood stream from the proximal small intestine, it is essential to limit systemic absorption by minimizing dissolution of this "delayed-release" drug product at the lower pH levels associated with the proximal small intestine. Therefore, the overall dissolution profiles of Zydus's Mesalamine Delayed-Release Tablets 1.2 g are consistent with the intended formulation design and therapeutic purpose of this drug product. The firm concludes that the dissolution profiles of the Test Product, Zydus Mesalamine Delayed-Release Tablets 1.2 g, are similar to those of the Reference product (RLD), LIALDA®(Mesalamine) Delayed-Release Tablets 1.2 g, at pH 7.2 and pH 7.5. At pH 6.8, the Test Product shows slower dissolution rate than some of the Reference product batches, but the overall extent of dissolution at 8 hours is similar between the Test and Reference products (The consult from Science team also suggest that "the mean of the test is within the range of the RLD data at pH 6.8 over the 2-8 hour range" if f2 criteria is not applied to dissolution profiles under pH 6.8, see below) .

Figure 2 Mean Dissolution Profiles of Various Batches of Reference Product and a Test Product Batch at pH 6.5 and pH 6.8 Evaluation Stages



Per consult with the Science Team (see [section 4.5](#)), as no testing is required between pH 6.8 and 7.2 to compare the release similarity, the test product should

have comparable dissolution profiles at pH 6.8 as ulcerative colitis patients may have lower pH in the distal small bowel^{13,14}.

Table 3 Intestinal luminal pH, measured using radiotelemetry capsules, in patients with ulcerative colitis (UC)

Study	Patients with UC	Small bowel pH		Caecum/right colon pH	Left colon/rectal pH
		Proximal	Distal		
Raimundo, 1992 ⁶	7 active	6.1	7.2	4.7	N/A
	6 inactive	5.9–6.6	6.9–7.4	4.9–5.5	N/A
Fallingborg, 1993 ⁷	3 active	Normal range	Normal range	Normal range	N/A
	3 very active	Normal range	Normal range	2.3–3.4	N/A
Press, 1998 ¹⁰	7 active	6.8	8.2	7.2	6.8
	4 inactive	6.6	7.9	6.5	6.5
Ewe, 1999 ¹¹	4 active	6.5	6.8	5.5	7.5
Nugent, 2000 ¹²	6 active	7.3	8.3	6.7 (5.8–7.3)	6.7 (4.8–7.3)

N/A, data not available.

As the RLD product is designed to release at pH above 6.8, F2 values might not be applied to pH 6.8 testing. However, the mean of the test product should be within the range of the RLD data at pH 6.8 over 2-8 hours range (Science team consult in section 4.5). Based on the current submission, the test product meet the requirements for all time points except for Time point at 4-hour (Mean_{test}=28.4, Range_{RLD}=34.6-95.6). In addition, high variability at pH 6.8 was observed in the current application and other in-house ANDAs, but not in ANDA 203574, as shown below:

Table 8: 0.1N HCl Followed by pH 6.4 Phosphate Buffer and pH 6.8 Phosphate Buffer (RLD Products)

ANDA #	Unit #	Testing Date	Exp Date		Collection Times (hr)							
					1	2	3	4	5	6	8	10
(b) (4)												
203574	24	7/20/12 7/21/12	9/2014	Mean	16	30	54	82		103	105	
				% CV	12.5	7.8	5.6	3.2		2.5	1.2	
091640	24	3/25/2012 3/27/2012	FC207A 3/2014	Mean	6.03	21.80		77.41		102.33	104.35	
				% CV	111.04	54.15		18.41		2.90	1.64	
		4/2/2012 4/12/2012	LC089A 7/2014	Mean	2.88	13.12		45.76		81.52	101.30	
				% CV	56.03	26.22		11.32		12.18	3.16	

Also, different release rate of RLD at pH 6.8 were shown in table above and figure below.

¹³ Digestive Diseases and Sciences, Vol. 38, No. 11 (November 1993), pp. 1989-1993.

¹⁴ Gut 2001;48:571–577

Reference product release at pH 6.8 from in-house ANDAs



Based on the our in-house RLD data, the reference product exhibit high lot to lot variability. We noted that RLD batch#LC089A used in this ANDA showed similar release profiles comparing to the test product, while, RLD batch#FC207A showed faster release than the test product. The F2 values in Table 7 above also confirmed this observation.



5. The reviewer summarized the **test product** profiles at pH 6.8 from our in-house ANDAs, as shown below:

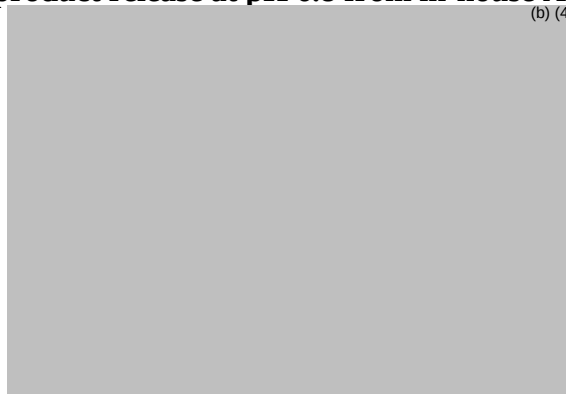
Table 9: 0.1N HCl Followed by pH 6.4 Phosphate Buffer and pH 6.8 Phosphate Buffer (Test Products)

ANDA #	unit #	Testing Date	Mfg Date		Collection Times (hr)							
					1	2	3	4	5	6	8	10
(b) (4)												

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203574	24	101/12 10/2/12	8/2012	Mean	12	28	50	75		100	102	
				% CV	11.4	7.9	5.5	4.3		1.4	0.8	
091640	24	4/7/2012 4/12/2012	3/2012	Mean	2.7	5.1		28.4		70.9	98.2	
				% CV	87.1	71.7		62.1		24.1	5.4	

Test product release at pH 6.8 from in-house ANDAs



As shown in table above, **only the test product in the current ANDA** shows high variability profiles in pH 6.8. It is noted the firm's dissolution testing were conducted on 2 or 3 separate dates for test product and 4 separate dates for the two lots RLD product. Day-to-Day variability is observed in the data, e.g. Test product at pH 6.8, which is much higher than the observed value for ANDA 204304 (testing were conducted on 5 separate dates). The firm did not provide its method validation for the in vitro BE dissolution study. Thus we currently could not judge the cause for such high variability on its test product. The firm should be requested to provide the method validation report, which should include precision and accuracy. In addition, to further investigate the observed high variability, the firm should also be requested to validate its method's system robustness to cover any possible deviation (e.g. buffer pH, operator, temperature, etc.). When the method is optimized, the firm should re-conduct the comparative dissolution testing on both test and RLD products for the evaluation condition at pH 6.8.

6. The in vitro BE dissolution testing should be conducted in pretreatment stage (Acid stage A and Buffer stage B) and followed by evaluation stage of buffer stage C (pH 6.5, 6.8, 7.2 and 7.5). The firm only submitted one set of pretreatment data (see section 4.3.1) for the QC method (i.e. pH 7.2) and did not submit the complete dissolution profiles for other pH conditions. Thus, the firm should be requested to provide its complete study report with data from pretreatment stages for each evaluation stage, i.e. pH 6.5, pH 6.8, pH 7.2 and pH 7.8. If the firm did not analyze the drug release for those pretreatment stages or did not conduct pretreatment stage for each evaluation pH stage, the firm should re-conduct dissolution testing. The firm should not only provide the data for evaluation stages, i.e. Buffer stage C (pH 6.5, 6.8, 7.2 and 7.5) but also the corresponding pretreatment stage in Acid stage A of 100 mM HCl and Buffer stage B of pH 6.4 for each evaluation stage.

7. The firm provided mean dissolution profiles for various batches of RLD product in Figure 2 of its cover letter. However, the reviewer could not locate the raw data for those corresponding dissolution testing. The firm should be requested to provide dissolution testing report on RLD product batches VC011A, WD119A and LC105A. In addition, the firm should also provide the used RLD product expiration date as well as the testing dates.

3.10 Deficiency Comments

In vivo BE Studies:

1. Per firm's SOP (b) (4) and SOP (b) (4) sample coded as Above the Upper Limit of Quantitation (>ULQ) were diluted appropriately prior to reassay.

The code >ULQ is used where the calculated, un-rounded concentration of a sample falls above the nominal concentration of the ULQ (this does not apply to truncated calibration curves; refer to V.A.1.). Additionally, the >ULQ code is applied to QC and subject samples whose ratios have a greater value than the extrapolated curve's vertex, in the case of a quadratic equation. This code more often applies to subject samples, however, it may also apply to QC samples, e.g., high concentration QC samples assayed as part of sample analysis or method validation that produce concentrations above that of the ULQ calibrant. Subject samples coded >ULQ are generally diluted appropriately prior to re-assay. Refer to SOP (b) (4)

However, the firm did not provide the dilution factor in its study report or the related SOP (b) (4). The firm should be requested to provide the used dilution factors for those samples.

2. It is noted that the firm reported all repeat assays values as the final concentration for repeat assay under code "SLP", "UIS", "SCI", ">ULQ" and "CR" but report "Number of recalculated values used after reanalysis" as "NA" for those samples. The firm should be notified for its future application, the firm should report the actual number for "Number of recalculated values used after reanalysis" when the final concentration is reported from repeat assays.

In vitro Dissolution Testing:

1. The firm acknowledged the FDA-recommended method and specifications in its amendment dated September 8, 2010. In the current amendment, the firm submitted its dissolution testing on the new batch test product (Lot No. EMM196, Manufacture date March 2012). The firm's dissolution testing meets the FDA-recommended specifications. However, the firm listed the volume of dissolution medium as (b) (4) in bio-summary table 5 instead of 3 volumes in the FDA-recommended method (Acid stage A: 750 mL, Buffer stage B: 950 mL and Buffer stage C: 960 mL) and the specification was not updated. Therefore, the firm should be requested to submit its explanation on the observed discrepancy and provided the updated table.

In vitro BE Studies:

1. Day-to-Day variability is observed in the firm's dissolution testing data on both of your Test and reference product at pH 6.8. The reviewer could not locate the firm's method validation report for the in vitro BE dissolution study. The firm should be request to provide its method validation report, which should include precision and accuracy. The firm should be informed that the report should validate the method's system robustness to cover any possible deviation (e.g. buffer pH, operator, temperature, etc.). The firm should be requested to revalidate its method and re-conduct the in vitro BE dissolution method for the following conditions:

Apparatus: USP Apparatus 2 (paddle)

Pretreatment Stage 1: 2 hours in 0.1 N HCl at 100 rpm (750 mL)

Pretreatment Stage 2: 1 hour in pH 6.4 Phosphate buffer at 100 rpm (950 mL)

Evaluation Stage: Each of

(1) pH 6.8 Phosphate buffer at 100 rpm

(b) (4)

Volume: 960 mL

Temperature: 37°C

Sample times: 1, 2, 4, 6 and 8 hours or as needed

2. The in vitro BE dissolution testing should be conducted in pretreatment stages (0.1 N HCl and pH 6.4 Phosphate Buffer) and followed by each evaluation stage. However, only one set of pretreatment data was provided in the firm's amendment dated October 23, 2013. The firm should be informed to provide its complete study report with data from each pre-treatment stage for the following evaluation stages, pH 6.5, pH 7.2 and pH 7.5. If the firm did not analyze the drug release for those pretreatment stages or did not conduct pretreatment stage for each evaluation stage (pH 6.5, pH 7.2 and pH 7.5), it should re-conduct in vitro BE dissolution testing with pretreatment stage for each evaluation stage (pH 6.5, 7.2 and 7.5) and submit the complete data.
3. The firm provided mean dissolution profiles for various batches of RLD product in Figure 2 of its cover letter in the amendment dated 10/23/2013. However, the reviewer could not locate the raw data for those corresponding dissolution testing. The firm should be requested to provide dissolution testing report on RLD product batches VC011A, WD119A and LC105A. In addition, the firm should also provide those RLD products expiration date as well as the testing dates.

3.11 Recommendations

1. The Division of Bioequivalence finds the fasting BE study (MSN-P2-480) incomplete due to the deficiencies mentioned above. Zydus Pharamceuticals USA Inc. conducted the fasting BE study on its Mesalemine DR Tablets, 1200 mg, lot # EMM196 comparing it to Shire's Lialda® (Mesalamine) DR Tablets, 1200 mg, lot # FC207A.
2. The Division of Bioequivalence finds the fed BE study (MSN-P3-482) incomplete due to the deficiencies mentioned above. Zydus Pharamceuticals USA Inc.

conducted the fed BE study on its Mesalamine DR Tablets, 1200 mg, lot # EMM196 comparing it to Shire's Lialda® (Mesalamine) DR Tablets, 1200 mg, lot # FC207A.

3. The firm stated it re-conducted its dissolution testing using the FDA-recommended method [750mL of 100 mM HCl (Acid Stage A) for 2 hrs, followed by 950 mL of Phosphate buffer, pH 6.4 (Buffer Stage B) for 1 hr and 960 mL of Phosphate buffer, pH 7.2 (Buffer Stage C) using apparatus 2 (Paddle) at 100 rpm on the new batch test product (Lot No. EMM196). The firm's dissolution testing meets the FDA-recommended specifications. However, the firm listed the volume of dissolution media as (b) (4). The firm should be requested to submit its explanation on the observed discrepancy and provide the updated table.
4. The in vitro BE dissolution studies are incomplete due to the deficiency indicated above.

3.12 Comments for Other OGD Disciplines

Discipline	Comment
CSO/RPM	This is a combined dissolution (QC) and BE review

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 10 Study Information

Study Number	MSN-P2-480
Study Title	Single Dose, Partial Replicate, Crossover Comparative Bioavailability Study of Mesalamine 1.2 g Delayed-Release Tablets in Healthy Male and Female Volunteers / Fasting State
Clinical Site (Name & Address)	Algorithme Pharma Inc. 1200 Beaumont Ave. Mount-Royal, Quebec, Canada H3P 3P1 Telephone: (514) 858-6077 Fax: (514) 380-5261
Principal Investigator	Eric Sicard, M.D. esicard@algopharm.com
Dosing Dates	Period 1: 2012/04/29 Period 2: 2012/05/06 Period 3: 2012/05/13
Analytical Site (Name & Address)	(b) (4)

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	(b) (4)
Analysis Dates	2012/05/24 to 2012/06/12
Analytical Director	(b) (4)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	a) 44 days b) -80°C ± 20°C nominal

Table 11. Product information

Product	Test	Reference
Treatment ID	A	B
Product Name	Mesalamine	Lialda™
Manufacturer	Cadila Healthcare Limited, India	Giullani S.p.A., Italy for Shire US Inc., USA
Batch/Lot No.	EMM196	FC207A
Manufacture Date	03/2012	N/A
Expiration Date	N/A	03/2014
Strength	1.2 g	1.2 g
Dosage Form	delayed-release tablet	delayed-release tablet
Bio-Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency (Assay)	102.2% of label claim	99.5% of label claim
Content Uniformity (mean, %CV)	Acceptance value : 2.9	Acceptance value : 1.9
Dose Administered	1.2 g	1.2 g
Route of Administration	Oral	Oral

Table 12. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	66 dosed, 59 completed and 58 included in the statistical analysis ¹⁵
No. of Sequences	3
No. of Periods	3
No. of Treatments	2
No. of Groups	1
Washout Period	7 days

¹⁵ Subject # (b) (6) completed all periods of the study but was removed from the pharmacokinetic and statistical analysis after bioanalysis due to positive pre-dose mesalamine concentration greater than 5% of the C_{max} in Period 3 (C₀=24.47 ng/mL and C_{max}=308.59). The firm excluded the subject from its statistical analysis according to its protocol, which is acceptable.

Randomization Scheme	TRR: 1, 5, 7, 10, 14, 16, 21, 24, 25, 29, 31, 34, 37, 41, 45, 46, 49, 54, 56, 58, 63, 64, RRT: 2, 6, 9, 12, 13, 18, 19, 23, 26, 28, 32, 35, 39, 40, 44, 47, 50, 52, 57, 60, 62, 65 RTR: 3, 4, 8, 11, 15, 17, 20, 22, 27, 30, 33, 36, 38, 42, 43, 48, 51, 53, 55, 59, 61, 66
Blood Sampling Times	0.00 (Pre-dose), 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 20, 22, 24, 26, 28, 30, 36, 48 and 72 hours after dosing
Blood Volume Collected/Sample	4 mL in K ₂ EDTA vacutainers
Blood Sample Processing/Storage	Blood samples were collected in pre-cooled K ₂ EDTA Vacutainers. As soon as possible following blood collection, samples were centrifuged at a temperature of 4°C nominal and at approximately 1500g for 10 minutes. The plasma obtained was separated into duplicate polypropylene culture tubes, when feasible. The samples were frozen in an upright position and retained in the clinic's freezers at a temperature of -80°C nominal or on dry ice until shipment to the Analytical facility. The samples were stored frozen at the temperature of -80°C nominal until assayed.
IRB Approval	Yes (April 12, 2012)
Informed Consent	Yes (April 12, 2012)
Length of Fasting	At least 10 hours
Length of Confinement	At least 72 hours (at least 24 hours before dosing and 48 hours after dosing)
Safety Monitoring	Vital signs will be monitored if judged necessary by the physician in charge. ECG will be recorded if judged necessary by the physician in charge. No other measurements are required during this study unless judged necessary by the physician in charge.

Comments on Study Design:

The study design is acceptable.

4.1.1.2 Clinical Results

Table 13. Demographics Profile of Subjects Completing the Bioequivalence Study

Study No. MSN-P2-480			
		Treatment Groups	
		Test Product N = 58	Reference Product N = 58
Age (years)	Mean ± SD	39 ± 13	39 ± 13
	Range	18 - 63	18 - 63
Age Groups	< 18	0	0
	18 – 40	33 (56.9%)	33 (56.9%)
	41 – 64	25 (43.1%)	25 (43.1%)
	65 – 75	0	0
	> 75	0	0

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Sex	Male	27 (46.6%)	27 (46.6%)
	Female	31 (53.4%)	31 (53.4%)
Race	White	52 (89.7%)	52 (89.7%)
	Black	4 (6.9%)	4 (6.9%)
	Asian	1 (1.7%)	1 (1.7%)
	American Native or Alaska Native	0	0
	Pacific Islander	0	0
	Others	1 (1.7%)	1 (1.7%)
BMI (kg/m ²)	Mean ± SD	23.97 ± 2.98	23.97 ± 2.98
	Range	18.74 – 29.55	18.74 – 29.55
Other Factors		NA	NA

Table 14. Dropout Information, Fasting Bioequivalence Study

Subject No.	Reason	Period	Replaced?
(b) (6)	Withdrew consent after dosing of period 3 for personal reasons (not related to clinical event(s)).	3	No
	Withdrawn before dosing of period 2 due to a change in the subjects' smoking habits.	2, 3	No
	Withdrew consent before dosing of period 3 for personal reasons (not related to clinical event(s)).	2, 3	No
	Withdrawn by the Investigator before dosing of period 2 for safety reasons (pain in extremity of mild severity).	2, 3	No
	Withdrew consent before dosing of period 2 for personal reasons (not related to clinical event(s)).	2, 3	No
	Completed all periods of the study but was removed from the pharmacokinetic and statistical analysis after bioanalysis due to positive pre-dose mesalamine concentration greater than 5% of the C _{max} .	3	No
	Withdrawn by the physician before dosing of period 3 for safety reasons (positive pregnancy test).	3	No
	Withdrew consent after dosing of period 1 for personal reasons (not related to clinical event(s)).	2, 3	No

Table 15. Study Adverse Events, Fasting Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fasted Bioequivalence Study Study No. MSN-P2-480	
	Test	Reference
INJURY, POISONING AND PROCEDURAL COMPLICATIONS [n(%)]	6 (9.5)	6 (4.8)

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Vessel Puncture Site Pain [n(%)]	1 (1.6)	3 (2.4)
Procedural Dizziness [n(%)]	0	3 (2.4)
Procedural Complication [n(%)]	1 (1.6)	1 (0.8)
Vessel Puncture Site Haematoma [n(%)]	2 (3.2)	0
Injury [n(%)]	1 (1.6)	0
Procedural Nausea [n(%)]	0	1 (0.8)
Vessel Puncture Site Reaction [n(%)]	1 (1.6)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS [n(%)]	3 (4.8)	2 (1.6)
Back Pain [n(%)]	0	2 (1.6)
Myalgia [n(%)]	1 (1.6)	0
Neck Pain [n(%)]	1 (1.6)	0
Pain In Extremity [n(%)]	1 (1.6)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS [n(%)]	3 (4.8)	1 (0.8)
Oropharyngeal Pain [n(%)]	2 (3.2)	1 (0.8)
Sneezing [n(%)]	1 (1.6)	0
EYE DISORDERS [n(%)]	1 (1.6)	1 (0.8)
Eye Irritation [n(%)]	1 (1.6)	0
Ocular Hyperaemia [n(%)]	0	1 (0.8)
GASTROINTESTINAL DISORDERS [n(%)]	1 (1.6)	1 (0.8)
Dyspepsia [n(%)]	1 (1.6)	1 (0.8)
NERVOUS SYSTEM DISORDERS [n(%)]	0	2 (1.6)
Somnolence [n(%)]	0	2 (1.6)
RENAL AND URINARY DISORDERS [n(%)]	1 (1.6)	1 (0.8)
Polyuria [n(%)]	1 (1.6)	1 (0.8)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS [n(%)]	0	1 (0.8)
Erythema [n(%)]	0	1 (0.8)
VASCULAR DISORDERS [n(%)]	0	1 (0.8)
Peripheral Coldness [n(%)]	0	1 (0.8)
Total	13 (20.6)	16 (12.8)
Note: Population is the sum of all drug administrations. Each adverse event is counted only once for each subject per drug administration within each System Organ Class and Preferred Term.		

Table 16. Protocol Deviations, Fasting Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
Blood sampling time deviations	(b) (6)	

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	(b) (6)
Collection time not recorded	
Collection time incorrectly recorded	
Subjects not housed at least 24 hours prior to drug administration.	

NA: Not Applicable

* Subject had deviation for both administrations of the same treatment.

Comments on Dropouts/Adverse Events/Protocol Deviations:

1. 59 out of 66 dosed subjects completed all three study periods and 58 were included in the statistical analysis¹⁵.

1. There were time deviations great than 5% of the scheduled time. Thus, the reviewer used the actual time for those time points.

<i>subject ID</i>	<i>Period</i>	<i>Deviation (minutes)</i>	<i>Time(hr)</i>	<i>%</i>
(b) (6)	1	7	2	5.83%
	2	409	72	9.47%
	3	225	72	5.21%

3. 24 out of 66 dosed subjects experienced 39 adverse events. The severity of adverse events ranged from mild to moderate. No severe adverse events were observed during the study.

4. The protocol deviations and adverse events did not compromise the integrity of the study.

4.1.1.3 Bioanalytical Results

Table 17. Assay Validation – Within the Fasting Bioequivalence Study

Bioequivalence Study No. MSN-P2-480 Mesalamine											
Parameter	Standard Curve Samples										
Conc. (ng/mL)	2.60	5.00	10.00	30.00	75.00	225.00	375.00	600.00	1050.00	1275.00	1500.00
Inter day Precision (%CV)	2.9	4.9	6.5	4.3	5.0	3.7	4.5	3.4	3.6	4.7	3.4
Inter day Accuracy (%Actual)	98.5	104.0	98.1	100.7	101.0	100.6	101.1	101.4	95.6	99.2	100.1
Linearity	0.9908 – 0.9994										
Linearity Range (ng/mL)	2.60 to 1500.00										
Sensitivity/LOQ (ng/mL)	2.60										
Bioequivalence Study No. MSN-P2-480 Mesalamine											

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Parameter	Quality Control Samples			
Concentration (ng/mL)	7.60	150.00	750.00	1100.00
Inter day Precision (%CV)	5.6	4.1	4.9	4.8
Inter day Accuracy (%Actual)	105.6	106.4	103.6	100.1

Comments on Study Assay Validation:

Acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially (Subjects (b) (6))

Comments on Chromatograms:

Acceptable.

Table 18. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
	(b) (4)	Sample Coding and Re-assay

Table 19. Additional Comments on Repeat Assays

Were all SOPs followed?	No (see comments in section 3.6)
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	No
If no, reason for disagreement	See comments in section 3.6 and 3.10

Summary/Conclusions, Study Assays:

Incomplete.

4.1.1.4 Pharmacokinetic Results

Table 20. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in [Table 24](#) and [Figure 1](#)

Fasting Bioequivalence Study, Study No. MSN-P2-480 (Reviewer calculated by regular 3 way SAS program) ¹⁶									
Parameter (Unit)	Test		Reference 1		Reference 2		RatioT/R1	RatioT/R2	RatioR1/R2
	Mean	CV%	Mean	CV%	Mean	CV%	(T/R1)	(T/R2)	(R1/R2)

¹⁶ Since the current 3-way Highly Variable Drug program does not provide summary of arithmetic mean, the reviewer used the regular 3-way crossover program to get the results.

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AUC _{0-t} (hr *ng/ml)	9855.111	38.73	9632.914	44.72	10599.21	47.04	1.02	0.93	0.91
AUC _{8-48 hr} (hr *ng/ml)	7731.560	44.34	7225.651	40.66	8375.823	48.00	1.07	0.92	0.86
C _{max} (ng/ml)	1046.926	95.29	1146.457	100.49	1267.683	87.31	0.91	0.83	0.90
T _{max} (hr)	11.017	.	10.000	.	10.000	.	1.10	1.10	1.00
Composite									
	Test		Reference#		Ratio T/R				
AUC _{0-t} (hr *ng/ml)	9855.111		10116.06		0.974204				
AUC _{8-48 hr} (hr *ng/ml)	7731.560		7800.737		0.991132				
C _{max} (ng/ml)	1046.926		1207.07		0.867328				
T _{max} * (hr)	11.017		10		1.1017				

* T_{max} values are presented as median, range

Note: The values of three PK parameters of the reference product in this study are comparable with those from Lialda® Label Mean PK Parameters¹⁷, AUC_{0-t} (9039 hr*ng/ml), AUC_{8-48hr} (N/A), C_{max} (857 ng/mL) and T_{max} (9 hr).

Table 21. Geometric Means and 90% Confidence Intervals - Firm Calculated

Mesalamine (No of subjects completed = 58), Dose (1 x 1.2 g)				
Fasting Bioequivalence Study, Study No. MSN-P2-480				
Parameter (units)	Test	Reference	Ratio	90% C.I.
AUC _{0-t} (hr *ng/ml)	9049.60	8953.69	101.07	92.21-110.78
Parameter (units)	Ratio of Least Square Means %	s ² wr	sWR	95 % Upper Confidence Bound
AUC ₄₋₄₈ (hr *ng/ml)	104.85	0.29475	0.54291	-0.16849
C _{max} (ng/ml)	87.86	0.34567	0.58794	-0.15960

Table 22. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Mesalamine Delayed Release Tablets, 1 × 1200 mg					
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. MSN-P2-480					
SUMMARY OF STATISTICAL ANALYSIS – UNSCALED DATA					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{8-48 hr} (hr *ng/ml)	7017.89	6703.45	1.05	90.82	120.68
AUC _{0-t} (hr *ng/ml)	9051.89	8957.16	1.01	91.12	112.07

¹⁷ Table 3: Mean (SD) PK Parameters for Mesalamine Following single dose administration of 1.2 g Lialda® under fasting conditions

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C _{max} (ng/ml)	768.81	862.51	0.89	74.93	106.03			
SUMMARY OF STATISTICAL ANALYSIS –SCALED DATA								
Parameter (units)	T/R Ratio	Lower90% CI	Upper90% CI	s2wr	sWR [#]	Criteria Bound	Method Used	OUTCOME
AUC _{8-48 hr} (hr *ng/ml)	1.05	90.82	120.68	0.3002033	0.5479081	-0.170822	Scaled/PE	PASS
AUC _{0-t} (hr *ng/ml)	1.02	91.12	112.07	0.0870697	0.2950757	-0.047687	Scaled/PE	PASS
C _{max} (ng/ml)	0.88	74.93	106.03	0.3348601	0.578671	-0.149502	Scaled/PE	PASS

Table 23. Additional Study Information, Fasting Study No. MSN-P2-480

Root mean square error, AUC _{0-t}	0.3451	
Root mean square error, AUC _{8-48 hr}	0.4525	
Root mean square error, C _{max}	0.6119	
	Test	Reference
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	2 (b) (6)	1 (b) (6)
first measurable drug concentration as C _{max}	None	None
Were the subjects dosed as more than one group?	No	No

Comments on Pharmacokinetic and Statistical Analysis:

Scaled average bioequivalence approach is recommended in the draft Guidance on Mesalamine DR Tablets (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM320004.pdf> (Recommended Sep 2012)).

The current approach calls for using scaled average BE with a point estimate constraint, if sWR (the estimated within-subject standard deviation on the log scale for the RLD) is greater than or equal to 0.294 (meaning that s²wr is greater than or equal to 0.086436)¹⁹. This was true for C_{max}, AUC_{0-t} and AUC_{8-48hr} in this study. Hence, the reviewer performed the statistical analysis by using reference scaled approach for establishing bioequivalence.

The method used for calculating the Average BE in the fasting study is as follows:

¹⁸ Subject # (b) (6) has reported pre-dose value in Period 3, which was less than 5% of C_{max} for the corresponding period and thus was included in the statistical analysis.

¹⁹ The firm used 30% instead of 29.4% as the scale-BE criteria in its protocol. Thus for its calculated R/R ISCV (29.9%), the average BE is applied to AUC_{0-t}.

In the analysis of a bioequivalence study, the measurements of $C_{\max}$ and both AUC are subject to the following procedure. The measurement for each subject is log-transformed and the averages, μ_T and μ_R , of the test and reference products are calculated. The within subject variability σ^2_{WR} of the reference product is also calculated.

There are two parts to the proposed bioequivalence criteria, a scaled average bioequivalence evaluation and a point estimate constraint. In order to demonstrate bioequivalence both parts must pass. Scaled average bioequivalence for AUC and $C_{\max}$ is evaluated by testing the following null hypothesis:

$$H_0: \frac{(\mu_T - \mu_R)^2}{\sigma^2_{WR}} > \theta$$

(for given $\theta > 0$) versus the alternative hypothesis

$$H_1: \frac{(\mu_T - \mu_R)^2}{\sigma^2_{WR}} \leq \theta$$

where μ_T and μ_R are the averages of the log-transformed measure for the test and reference products, respectively; usually testing is done at level $\alpha=0.05$; and θ is the scaled average BE limit. Furthermore,

$$\theta = \frac{(\ln \Delta)^2}{\sigma^2_{W0}}$$

where Δ is 1.25, the usual average BE upper limit for the untransformed Test/Reference ratio of geometric means, and $\sigma_{W0} = 0.25$. Note that rejection of the null hypothesis H_0 supports the conclusion of equivalence.

A 95% upper confidence bound for $\frac{(\bar{Y}_T - \bar{Y}_R)^2}{s^2_{WR}}$ determined in a BE study must be $\leq \theta$, or

equivalently, a 95% upper confidence bound for $(\bar{Y}_T - \bar{Y}_R)^2 - \theta s^2_{WR}$ must be ≤ 0 . Where s_{WR} is within reference standard deviation determined in the BE study.

Additionally, the point estimate (test/reference geometric mean ratio) must fall within [0.80, 1.25]. The test drug must pass both conditions before it is judged bioequivalent to the reference product.

In order to be considered bioequivalent to the RLD, the test drug must pass the following two conditions:

$$\frac{(\bar{Y}_T - \bar{Y}_R)^2}{S_{WR}^2}$$

- a. A 95% upper confidence bound for S_{WR}^2 (calculated as explained in the above equation) must be less than or equal to θ (where $\theta = 0.7967$).
- b. The point estimate (test/reference geometric mean ratio) must fall within [0.80, 1.25].

The 95% Upper confidence bound for $(\bar{Y}_T - \bar{Y}_R)^2 - \theta S_{WR}^2$ for $C_{\max}$, AUC_{0-t} and AUC_{8-48hr} in the fasting BE study was -0.149502, -0.047687 and -0.170822. Since the value is less than 0, it meets the first condition.

The point estimate (test/reference geometric mean ratio) for $C_{\max}$, AUC_{0-t} and AUC_{8-48hr} in the fasting BE study are 0.88, 1.02 and 1.05, respectively. It is within [0.80, 1.25], and thus it meets the second condition.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

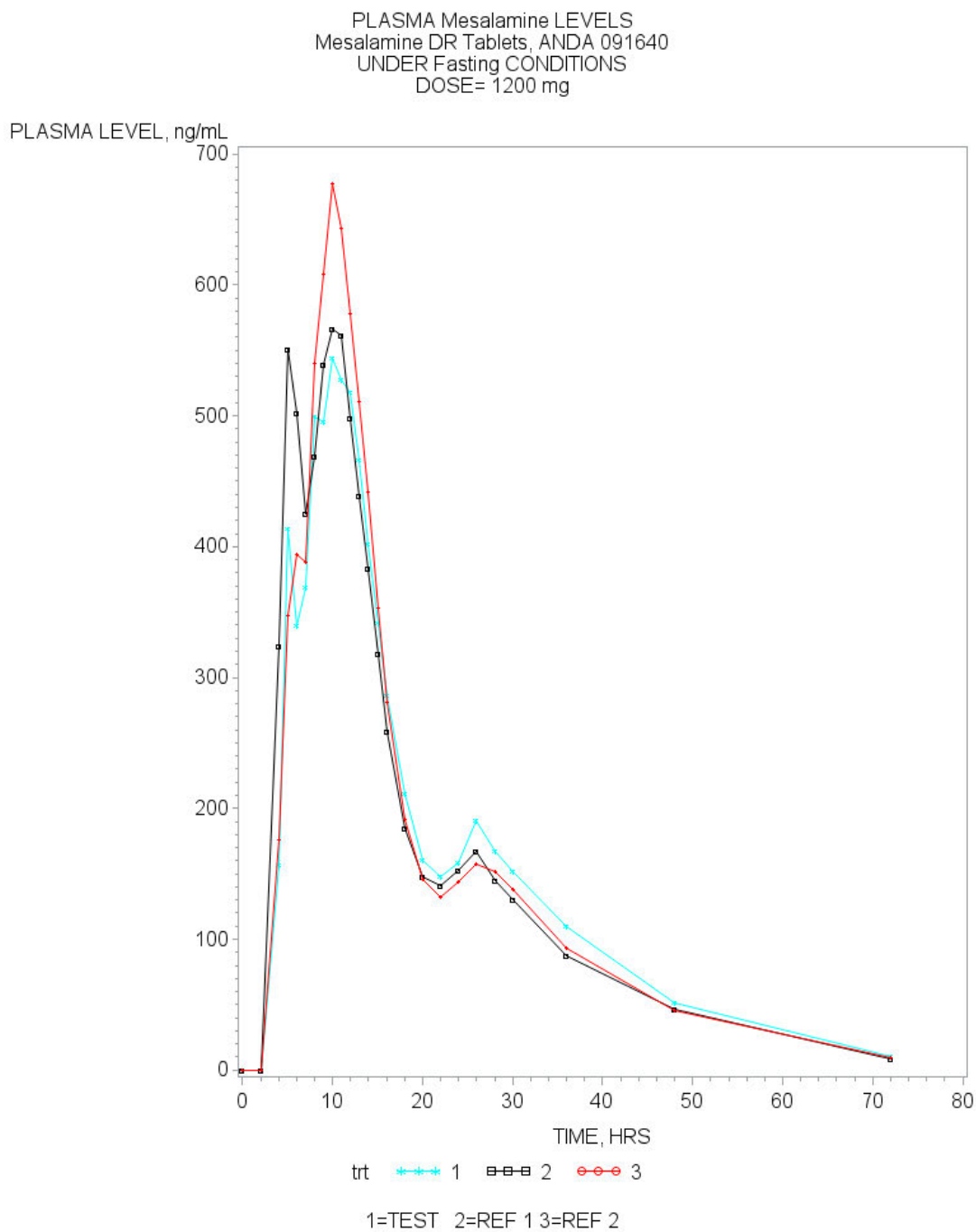
The fasting study met the BE acceptance criteria of reference scaled analysis for log-transformed $C_{\max}$, AUC_{0-t} , and $AUC_{8-48 hr}$ of Mesalamine Delayed Release Tablets.

The fasting study is acceptable.

Table 24. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

	Test 1 (n=58)		Reference 1 (n=58)		Reference 2 (n=58)		RatioT1R1	RatioT1R2	RatioR1R2
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T1/R1)	(T1/R2)	(R1/R2)
0.00	0.05	761.58	0.00	.	0.00	.	.	.	.
2.00	0.06	761.58	0.12	535.36	0.21	445.17	0.49	0.28	0.56
4.00	188.86	237.72	295.84	225.72	166.58	250.48	0.64	1.13	1.78
5.00	434.86	210.77	411.93	201.26	454.33	169.70	1.06	0.96	0.91
6.00	384.53	223.26	444.31	203.93	398.87	197.43	0.87	0.96	1.11
7.00	349.42	120.71	379.59	169.88	448.10	105.31	0.92	0.78	0.85
8.00	352.18	89.38	463.55	145.31	690.50	127.43	0.76	0.51	0.67
9.00	399.36	88.57	527.27	122.80	717.56	96.19	0.76	0.56	0.73
10.00	442.00	88.89	596.73	101.54	749.67	92.24	0.74	0.59	0.80
11.00	453.93	84.76	580.96	71.41	698.59	75.94	0.78	0.65	0.83
12.00	459.92	73.28	523.97	57.09	613.70	67.94	0.88	0.75	0.85
13.00	426.50	65.58	448.09	51.54	546.52	62.87	0.95	0.78	0.82
14.00	385.55	58.83	392.04	52.90	452.56	55.55	0.98	0.85	0.87
15.00	330.68	57.77	321.19	53.29	360.62	54.11	1.03	0.92	0.89
16.00	288.87	64.10	259.39	58.69	277.39	53.83	1.11	1.04	0.94
18.00	214.18	64.87	186.11	60.53	186.55	61.85	1.15	1.15	1.00
20.00	170.02	63.32	143.11	64.52	140.02	73.18	1.19	1.21	1.02
22.00	164.34	67.42	129.57	68.33	126.91	84.18	1.27	1.29	1.02
24.00	177.12	80.98	134.57	72.81	143.54	88.96	1.32	1.23	0.94
26.00	210.27	95.26	146.99	71.15	157.86	87.77	1.43	1.33	0.93
28.00	172.77	87.11	134.22	62.43	157.19	93.97	1.29	1.10	0.85
30.00	155.73	92.28	120.30	75.18	144.30	92.77	1.29	1.08	0.83
36.00	115.88	107.73	81.40	86.51	92.34	106.05	1.42	1.25	0.88
48.00	57.01	98.40	43.71	115.64	42.22	136.81	1.30	1.35	1.04
72.00	10.03	229.72	10.36	244.79	7.71	240.58	0.97	1.30	1.34

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

Table 25. Study Information

Study Number	MSN-P3-482
Study Title	Single Dose, Partial Replicate, Crossover Comparative Bioavailability Study of Mesalamine 1.2 g Delayed-Release Tablets in Healthy Male and Female Volunteers / Fed State
Clinical Site (Name & Address)	Algorithme Pharma Inc. 1200 Beaumont Ave. Mount-Royal, Quebec, Canada H3P 3P1 Telephone: (514) 858-6077 Fax: (514) 380-5261
Principal Investigator	Eric Sicard, M.D. esicard@algopharm.com
Dosing Dates	Period 1: 2013/04/22 Period 2: 2013/04/29 Period 3: 2013/05/06
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	2013/05/10 to 2013/05/24
Analytical Director	(b) (4)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	a) 32 days b) -80°C ± 20°C nominal

Table 26. Product Information

Product	Test	Reference
Treatment ID	A	B
Product Name	Mesalamine	Lialda™
Manufacturer	Cadila Healthcare Limited, India	Giullani S.p.A., Italy for Shire US Inc., USA
Batch/Lot No.	EMM196	FC207A
Manufacture Date	03/2012	N/A
Expiration Date	N/A	03/2014
Strength	1.2 g	1.2 g
Dosage Form	delayed-release tablet	delayed-release tablet
Bio-Batch Size	(b) (4)	N/A
Production Batch Size		N/A

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Potency (Assay)	102.2% of label claim	99.5% of label claim
Content Uniformity (mean, %CV)	Acceptance value : 2.9	Acceptance value : 1.9
Dose Administered	1.2 g	1.2 g
Route of Administration	Oral	Oral

Table 27. Study Design, Single-Dose Fed Bioequivalence Study

No. of Subjects	63 dosed and 58 completed and included in the statistical analysis
No. of Sequences	3
No. of Periods	3
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	RTR: 1, 4, 7, 11, 15, 18, 19, 24, 27, 29, 33, 36, 37, 41, 43, 46, 49, 52, 56, 58, 63 TRR: 2, 6, 8, 12, 14, 17, 21, 23, 25, 30, 31, 34, 39, 42, 45, 48, 50, 53, 55, 60, 62 RRT: 3, 5, 9, 10, 13, 16, 20, 22, 26, 29, 32, 35, 38, 40, 44, 47, 51, 54, 57, 59, 61
Blood Sampling Times	0.0 (Pre-dose), 2, 4, 8, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, 28, 30, 36, 42, 48 and 72 hours post dose
Blood Volume Collected/Sample	4 mL in K ₂ EDTA vacutainers
Blood Sample Processing/Storage	Blood samples will be centrifuged at 4°C nominal (approximately 1500g for 10 minutes) as soon as possible after blood collection. The plasma obtained will be transferred in polypropylene culture tubes. When feasible, the plasma will be separated into duplicate tubes. All samples will be frozen in an upright position and stored at -80°C nominal until assayed. Samples will be shipped on dry ice to the analytical facility. The time from blood samples collection to plasma aliquot storage should be within 90 minutes. The tubes will be labeled according to clinical SOP.
IRB Approval	Yes (April 4, 2013)
Informed Consent	Yes (April 4, 2013)
Length of Fasting Before Meal	At least 10 hours
Length of Confinement	At least 72 hours (at least 24 hours before dosing and 48 hours after dosing)
Safety Monitoring	Vital signs will be monitored if judged necessary by the physician in charge. ECG will be recorded if judged necessary by the physician in charge. No other measurements are required during this study unless judged necessary by the physician in charge.
Standard FDA Meal Used?	No
If No, then meal components and composition is listed in the tables below	
Components of Non-standard FDA Meal Used in Fed Bioequivalence Study	

Ingredients	Amount (g)	Energy (kcal)	Protein (kcal)	Fat (kcal)	Carbohydrate (kcal)
240 mL Whole Milk (3.25%)	29	156	36	72	48
2 Large Eggs	24	146	48	90	8
4 oz Hash Brown Potatoes / 2 patties	46	264	8	144	112
1 English Muffin	34	141	20	9	112
4.5 g of Butter	3.5	31.5	0	31.5	0
2 Slices of Bacon	26	199	24	171	4
TOTAL	162.5	937.5	136	517.5	284
PERCENTAGE	--	--	14.5%	55.2%	30.3%

The details of the calories from fat, carbohydrate and protein for each individual component were provided. The test meal meets the high fat and high calorie recommendation.

Comments on Study Design:

The study design is acceptable.

4.1.2.2 Clinical Results

Table 28. Demographics Profile of Subjects Completing the Bioequivalence Study

Study No. MSN-P3-482				
		Treatment Groups		
		Test Product N = 58	Reference Product N = 58	
Age (years)	Mean ± SD	41 ± 14	41 ± 14	
	Range	19 - 69	19 - 69	
Age Groups	< 18	0	0	
	18 – 40	29 (50.0%)	29 (50.0%)	
	41 – 64	27 (46.6%)	27 (46.6%)	
	65 – 75	2 (3.4%)	2 (3.4%)	
	> 75	0	0	
Sex	Male	33 (56.9%)	33 (56.9%)	
	Female	25 (43.1%)	25 (43.1%)	
Race	White	52 (89.7%)	52 (89.7%)	
	Black	4 (6.9%)	4 (6.9%)	
	Asian	0	0	
	American Native or Alaska Native	0	0	
	Pacific Islander	0	0	
	Others	2 (3.4%)	2 (3.4%)	
BMI (kg/m ²)	Mean ± SD	25.36 ± 2.74	25.36 ± 2.74	
	Range	18.69 - 29.70	18.69 - 29.70	
Other Factors		NA	NA	

Table 29. Dropout Information, Fed Bioequivalence Study

Subject No.	Reason	Period	Replaced?
(b) (6)	Withdrawn from the study after dosing of period 1 due to emesis within the restriction period; this subject experienced a gastrointestinal adverse event (vomiting of unknown intensity) that could have an impact on his pharmacokinetic profile.	2, 3	No
	Withdrew consent from the study before dosing of period 2 for personal reasons (not related to clinical event(s)).	2, 3	No
	Withdrawn from the study before dosing of period 3 due to a positive cannabinoids (THC50) test.	3	No
	Withdrawn from the study before dosing of period 3 for pharmacokinetic reasons. This subject missed the 72-hour blood sample collection in period 2 and consequently, it was considered that characterization of the pharmacokinetic profile and estimation of the parameter AUC _{0-∞} would be inaccurate.	3	No
	Withdrawn from the study before dosing of period 3 due to a positive amphetamines test.	3	No

Table 30. Study Adverse Events, Fed Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fed Bioequivalence Study Study No. MSN-P3-482	
	Test	Reference
NERVOUS SYSTEM DISORDERS [n(%)]	6 (10.0)	7 (5.7)
Headache [n(%)]	2 (3.3)	5 (4.1)
Somnolence [n(%)]	3 (5.0)	1 (0.8)
Dizziness [n(%)]	1 (1.7)	2 (1.6)
GASTROINTESTINAL DISORDERS [n(%)]	2 (3.3)	5 (4.1)
Diarrhoea [n(%)]	1 (1.7)	3 (2.5)
Abdominal Pain [n(%)]	0	1 (0.8)
Dyspepsia [n(%)]	1 (1.7)	0
Nausea [n(%)]	0	1 (0.8)
Vomiting [n(%)]	0	1 (0.8)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS [n(%)]	3 (5.0)	3 (2.5)
Vessel Puncture Site Reaction [n(%)]	2 (3.3)	0
Chemical Injury [n(%)]	1 (1.7)	0
Injury [n(%)]	0	1 (0.8)
Procedural Complication [n(%)]	0	1 (0.8)
Vessel Puncture Site Haematoma [n(%)]	1 (1.7)	0
Vessel Puncture Site Pain [n(%)]	0	1 (0.8)

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RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS [n(%)]	2 (3.3)	3 (2.5)
Epistaxis [n(%)]	1 (1.7)	1 (0.8)
Oropharyngeal Pain [n(%)]	1 (1.7)	1 (0.8)
Nasal Congestion [n(%)]	0	1 (0.8)
Rhinorrhoea [n(%)]	0	1 (0.8)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS [n(%)]	0	2 (1.6)
Pruritus Generalised [n(%)]	0	2 (1.6)
EYE DISORDERS [n(%)]	0	1 (0.8)
Dry Eye [n(%)]	0	1 (0.8)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS [n(%)]	0	1 (0.8)
Discomfort [n(%)]	0	1 (0.8)
INFECTIONS AND INFESTATIONS [n(%)]	1 (1.7)	0
Oral Herpes [n(%)]	1 (1.7)	0
VASCULAR DISORDERS [n(%)]	0	1 (0.8)
Hot Flush [n(%)]	0	1 (0.8)
Total	12 (20.0)	18 (14.8)
Note: Population is the sum of all drug administrations. Each adverse event is counted only once for each subject per drug administration within each System Organ Class and Preferred Term.		

Table 31. Protocol Deviations, Fed Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
Blood sampling time deviations	(b) (6)	
Blood sampling collection time incorrectly recorded		
Medication restriction not followed		
Xanthines restriction not followed		
Meal consumption requirements not followed		
Housing		

restriction followed	not		
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* Subject had deviation for both administrations of the same treatment.

Comments on Adverse Events/Protocol Deviations:

1. 58 out of 63 dosed subjects completed all three study periods and were included in the statistical analysis.
2. All time deviations were less than 5% of the scheduled time. Thus, the reviewer used the scheduled time points in the statistical analysis.
3. 23 out of 63 dosed subjects experienced 41 adverse events. The severity of adverse events ranged from mild to severe. Two severe AEs were observed for Subject (b) (6) Period II (diarrhea ,RLD) and Subject (b) (6) period III (Procedural complication: fainted due to blood draw, RLD). In addition, subject (b) (6) vomited in period I (RLD) and was withdraw from the study.
4. The protocol deviations and adverse events did not compromise the integrity of the study.

4.1.2.3 Bioanalytical Results

Table 32. Assay Validation – Within the Fed Bioequivalence Study

Bioequivalence Study No. MSN-P3-482											
Parameter	Standard Curve Samples										
Conc. (ng/mL)	2.60	5.00	10.00	30.00	75.00	225.00	375.00	600.00	1050.00	1275.00	1500.00
Inter day Precision (%CV)	2.8	4.8	5.7	4.4	4.0	3.2	3.3	3.4	3.2	3.5	3.4
Inter day Accuracy (%Actual)	99.3	102.2	98.4	99.6	101.3	102.1	101.5	99.8	100.3	98.4	97.2
Linearity	0.9945 – 0.9994										
Linearity Range (ng/mL)	2.60 to 1500.00										
Sensitivity/LOQ (ng/mL)	2.60										
Bioequivalence Study No. MSN-P3-482											
Parameter		Quality Control Samples									
Concentration (ng/mL)		7.60		100.00		150.00		750.00		1100.00	
Inter day Precision (%CV)		6.9		4.2		3.9		4.1		4.7	
Inter day Accuracy (%Actual)		103.0		104.1		106.0		104.5		100.8	

Comments on Study Assay Validation:

Acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially (b) (6)

Comments on Chromatograms:

Acceptable.

Table 33. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
	(b) (4)	Sample Coding and Re-assay

Table 34. Additional Comments on Repeat Assays

Were all SOPs followed?	No (see comments in section 3.6)
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	No
If no, reason for disagreement	See comments in section 3.6 and 3.10

Summary/Conclusions, Study Assays:

Incomplete.

4.1.2.4 Pharmacokinetic Results

Table 35. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 39 and Figure 2

Fed Bioequivalence Study, Study No. MSN-P3-482 (Reviewer calculated by regular 3 way SAS program) ²⁰									
Parameter (Unit)	Test		Reference 1		Reference 2		RatioT/R1	RatioT/R2	RatioR1/R2
	Mean	CV%	Mean	CV%	Mean	CV%	(T/R1)	(T/R2)	(R1/R2)
AUC _{0-t} (hr *ng/ml)	9245.433	51.78	10501.37	55.35	10481.36	54.00	0.88	0.88	1.00
AUC _{8-48 hr} (hr *ng/ml)	8314.508	54.71	9586.914	57.94	9321.666	61.08	0.87	0.89	1.03
C _{max} (ng/ml)	1648.092	82.99	2030.634	80.20	1750.224	90.72	0.81	0.94	1.16

²⁰ Since the current 3-way Highly Variable Drug program does not provide summary of arithmetic mean, the reviewer used the regular 3-way crossover program to get the results.

T _{max} (hr)	21.000	.	17.058	.	17.500	.	1.23	1.20	0.97
Composite									
	Test		Reference#		Ratio T/R				
AUC _{0-t} (hr *ng/ml)	9245.433		10491.365		0.881242				
AUC _{8-48 hr} (hr *ng/ml)	8314.508		9454.29		0.879443				
C _{max} (ng/ml)	1648.092		1890.429		0.871808				
T _{max} * (hr)	21		17.279		1.215348				

* T_{max} values are presented as median, range

Note: The values of three PK parameters of the reference product in this study are comparable with those from NDA 022000, AUC_{0-t} (9286.5 hr*ng/ml), AUC_{8-48hr} (N/A), C_{max} (1466 ng/mL)²¹.

T_{max} analysis is in section 4.1.2.5

Table 36. Geometric Means and 90% Confidence Intervals - Firm Calculated

Mesalamine Delayed Release Tablets, 1 × 1200 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study, Study No. MSN-P3-482				
Parameter (units)	Ratio of Least Square Means %	s ² wr	sWR	Criteria Bound
LAUC _{0-t}	91.06	0.19247	0.43871	-0.08681
LAUC ₈₋₄₈	91.19	0.18199	0.42660	-0.08318
LC _{max}	91.30	0.45967	0.67799	-0.24217

Table 37. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Mesalamine Delayed Release Tablets, 1 × 1200 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals								
Fed Bioequivalence Study, Study No. MSN-P3-482								
SUMMARY OF STATISTICAL ANALYSIS – UNSCALED DATA								
Parameter (units)	Test	Reference	Ratio	90% C.I.				
AUC _{8-48 hr} (hr *ng/ml)	7187.51	7892.34	0.91	80.05	103.60			
AUC _{0-t} (hr *ng/ml)	8031.67	8829.85	0.91	79.31	104.33			
C _{max} (ng/ml)	1123.93	1234.23	0.91	74.40	111.46			
SUMMARY OF STATISTICAL ANALYSIS – SCALED DATA								
Parameter (units)	T/R Ratio	Lower 90% CI	Upper 90% CI	s _{2wr}	sWR [#]	Criteria Bound	Method Used	OUTCOME
AUC _{8-48 hr} (hr *ng/ml)	0.91	80.05	103.60	0.1819849	0.4265969	-0.083179	Scaled/PE	PASS

²¹ Data used is from NDA fed study on 2.4 g dose, which was found dose proportional to the 1.2 g strength.

AUC_{0-t} (hr *ng/ml)	0.91	79.31	104.33	0.1924678	0.4387115	-0.086809	Scaled/PE	PASS
C_{max} (ng/ml)	0.91	74.40	111.46	0.4596764	0.6779944	-0.242166	Scaled/PE	PASS

Table 38. Additional Study Information

Root mean square error, AUC_{0-t}	0.4742	
Root mean square error, AUC_{8-48 hr}	0.4525	
Root mean square error, C_{max}	0.7192	
	Test	Reference
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	1 (b) (6)	None
first measurable drug concentration as C_{max}	None	None
Were the subjects dosed as more than one group?	No	No

Comments on Pharmacokinetic and Statistical Analysis:

Acceptable.

Summary/Conclusions, Single-Dose Fed Bioequivalence Study:

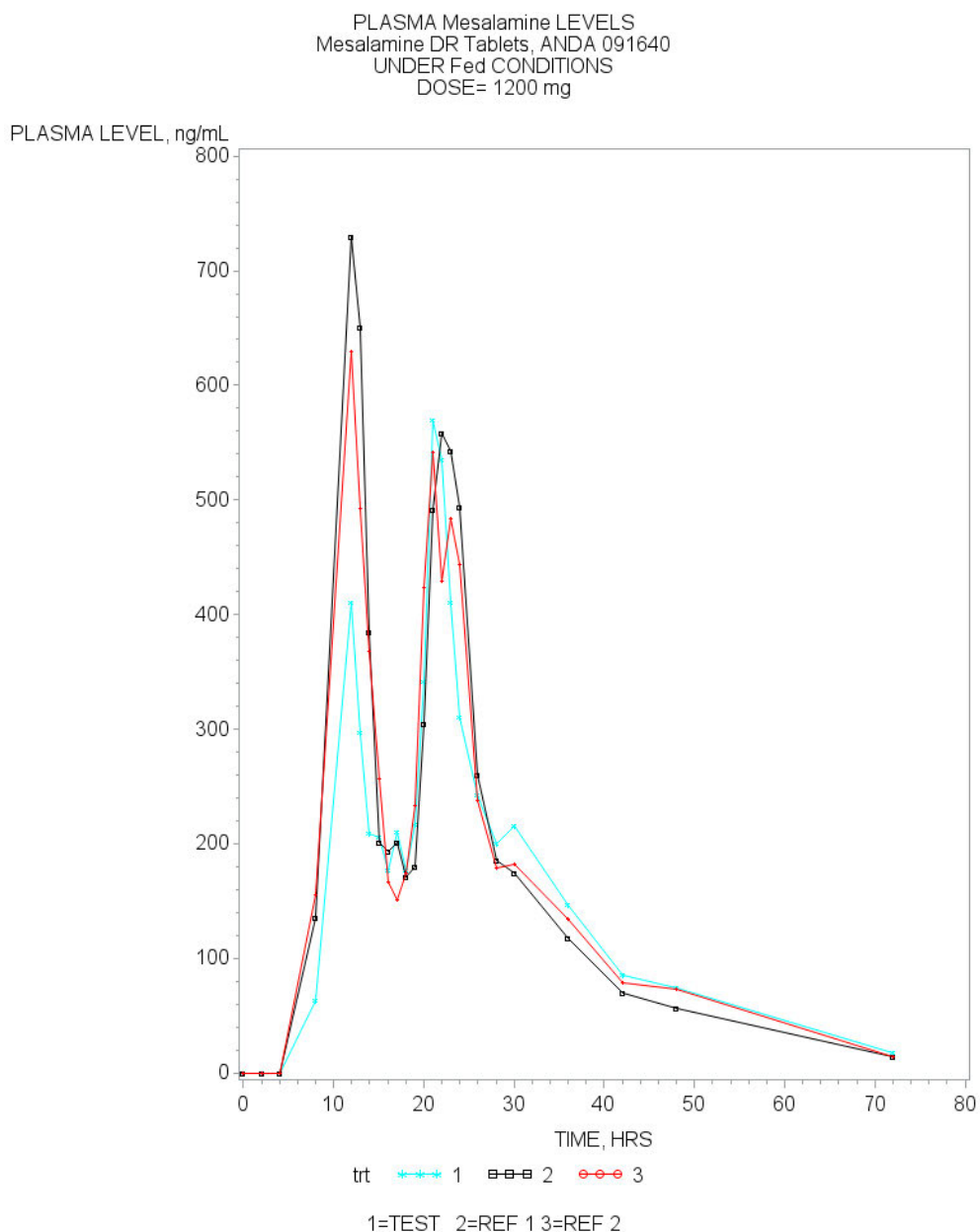
The fed study met the BE acceptance criteria of reference scaled analysis for log-transformed AUC_{0-t}, AUC₈₋₄₈ and C_{max} of Mesalamine Delayed Release Tablets. The fed study is acceptable.

²² Subject (b) (6) has reported pre-dose value in Period 2, which was less than 5% of C_{max} for the corresponding period and thus was included in the statistical analysis.

Table 39. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Test 1 (n=58)			Reference 1 (n=58)		Reference 2 (n=58)		RatioT1R1	RatioT1R2	RatioR1R2
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T1/R1)	(T1/R2)	(R1/R2)
0.00	0.08	761.58	0.00	.	0.00	.	.	.	.
2.00	0.06	761.58	0.00	.	0.00	.	.	.	.
4.00	0.06	761.58	0.00	.	0.00	.	.	.	.
8.00	63.21	624.53	135.45	449.96	154.93	334.95	0.47	0.41	0.87
12.00	410.47	221.84	729.09	181.40	629.09	203.72	0.56	0.65	1.16
13.00	296.89	219.45	650.76	194.87	492.51	195.02	0.46	0.60	1.32
14.00	208.98	279.35	384.93	215.76	368.43	208.16	0.54	0.57	1.04
15.00	205.57	350.12	200.75	162.28	256.55	213.99	1.02	0.80	0.78
16.00	176.49	393.26	193.62	178.34	167.09	169.82	0.91	1.06	1.16
17.00	210.12	297.23	200.77	240.01	150.63	144.29	1.05	1.39	1.33
18.00	176.20	233.31	171.38	148.97	174.75	148.14	1.03	1.01	0.98
19.00	216.43	215.38	180.05	130.17	233.56	191.96	1.20	0.93	0.77
20.00	341.24	211.48	304.60	145.89	423.79	200.23	1.12	0.81	0.72
21.00	569.43	171.92	491.32	181.30	541.95	219.36	1.16	1.05	0.91
22.00	534.55	201.35	558.60	161.95	428.66	200.58	0.96	1.25	1.30
23.00	410.20	166.98	542.28	154.38	483.36	207.35	0.76	0.85	1.12
24.00	309.67	147.70	494.06	224.01	443.59	193.21	0.63	0.70	1.11
26.00	242.42	118.42	260.35	173.03	238.36	94.56	0.93	1.02	1.09
28.00	199.58	87.00	185.39	97.70	179.25	88.19	1.08	1.11	1.03
30.00	215.92	72.17	174.15	84.75	182.29	75.07	1.24	1.18	0.96
36.00	146.43	80.31	118.02	84.67	134.72	78.95	1.24	1.09	0.88
42.00	85.27	88.96	69.70	94.32	78.34	74.58	1.22	1.09	0.89
48.00	74.61	125.34	56.90	109.76	72.73	106.05	1.31	1.03	0.78
72.00	17.38	221.96	14.05	246.28	14.47	206.72	1.24	1.20	0.97

Figure 2. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



4.1.2.5 $T_{\max}$ Analysis

Since the traditional DB statistical analysis shows significant $T_{\max}$ difference (around 4 hrs) between the Test and Reference products ($T_{\max \text{ test}}=21$ hr, $T_{\max \text{ RLD1}}=17.058$, $T_{\max \text{ RLD2}}=17.5$, and $T_{\max \text{ RLD combined}}=17.279$), the reviewer conducted further $T_{\max}$ analysis on the dual peaks in the PK profiles.

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Individual T_{max} in the Fed Study (Single T_{max} vs. Dual Peak T_{max})

Subject #	T _{max} (hr)			Test		RLD ₁		RLD ₂	
	Test	RLD 1	RLD 2	T _{max} 1	T _{max} 2	T _{max} 1	T _{max} 2	T _{max} 1	T _{max} 2
(b) (6)	30	12	14	15	30	12	24	14	24
	26	8	12	13	26	8	26	12	26
	8	24	24	8	21	N/A	24	N/A	24
	17	28	8	17	28	12	28	8	26
	30	15	28	24	30	15	19	23	28
	21	8	12	21	30	8	17	12	26
	22	24	24	15	22	12	24	24	N/A
	12	26	8	12	24	12	26	8	30
	22	23	12	22	30	20	23	12	24
	21	14	17	21	28	14	26	17	30
	21	16	17	21	36	16	26	17	28
	17	20	26	17	30	20	26	26	48
	26	23	24	26	48	23	42	24	36
	24	19	8	18	24	19	28	8	20
	16	14	12	12	16	14	26	12	24
	21	8	18	21	26	8	26	18	26
	24	23	23	24	30	23	30	23	30
	21	12	24	21	26	12	26	24	48
	21	17	13	21	30	17	24	13	26
	36	21	22	36	.	21	36	22	30
	23	12	13	23	42	12	26	14	28
	18	24	12	18	26	22	24	12	24
	22	22	20	22	30	22	24	20	26
	26	28	28	26	.	28	48	28	48
	23	22	23	23	30	22	30	23	30
	21	13	14	21	36	13	30	14	28
	13	13	13	13	26	13	26	13	26
	20	23	23	20	26	23	30	23	36
	23	22	48	23	30	22	30	22	48
	12	12	12	12	18	12	17	12	28
	30	23	12	22	30	23	36	12	30
	12	12	20	12	26	12	22	20	36
	23	22	21	23	36	22	30	21	36
	17	13	12	17	24	13	.	12	n/a
	12	18	12	12	28	18	28	12	18
	8	22	8	8	23	22	.	8	26
	12	20	12	12	18	20	26	12	18
	26	12	30	26	.	12	26	22	30

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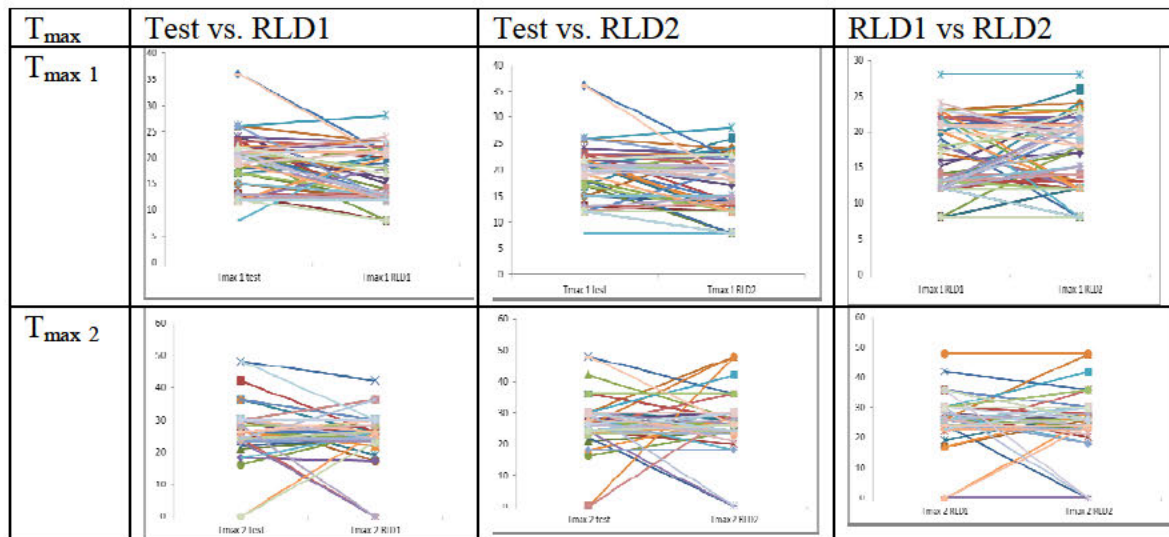
Subject #	T _{max} (hr)			Test		RLD ₁		RLD ₂	
	Test	RLD 1	RLD 2	T _{max 1}	T _{max 2}	T _{max 1}	T _{max 2}	T _{max 1}	T _{max 2}
(b) (6)	12	14	24	12	23	14	24	14	24
	21	18	20	21	30	18	36	20	26
	19	13	21	19	30	13	26	21	30
	15	13	15	15	24	13	23	15	23
	19	12	12	19	24	12	24	12	23
	12	12	12	12	24	12	24	12	26
	12	13	14	12	24	13	24	14	26
	12	12	12	12	24	12	26	12	28
	13	12	15	13	24	12	26	15	30
	21	21	19	21	28	21	.	19	24
	21	21	21	21	30	21	30	21	n/a
	20	13	21	20	30	13	26	18	21
	21	36	18	21	24	24	36	18	26
	12	8	8	12	26	8	28	8	24
	21	12	21	21	.	12	23	21	30
	12	12	8	12	30	12	24	8	24
	36	20	36	36	48	20	30	18	26
	36	23	30	20	26	23	30	20	30
	19	21	20	19	30	21	30	20	30
	22	17	23	22	n/a	17	36	23	n/a
Median	21	17	17.5	20	28	14	26	17	26
mean	19.88	17.43	18.09	18.59	27.98	16.28	27.38	16.60	28.54
min	8	8	8	8	16	8	17	8	18
max	36	36	48	36	48	28	48	28	48

1. 50 out of 57 individual profile of Test product had C_{max} at T_{max1}, while reference product showed 52 out of 58 for T_{max1} of RLD₁ and 50 out of 57 for T_{max1} of RLD₂. Thus, most individual profiles showed C_{max} at the earlier T_{max} for both products.
2. The difference observed on median T_{max} is further compared with T_{max1} and T_{max} in mean and %CV. As shown in the table below, both products were highly variable for Parameters T_{max} and T_{max1}, which was also observed in NDA study's plasma concentration profiles²³. Due to the study product's prolonged absorption process, the reviewer compared T_{max} values between Test and Reference product by ratio instead of difference. The ratio of T_{max} mean is around 110% while the median around 120%, i.e. the ratio is close to 1. The range of T_{max} in the current fed study is similar, i.e. 8-36 for test product and 8-36 or 8-48 for the reference product.

²³ DARRTS: REV-CLINPHARM-01 (General Review), dated 12/21/2006

Product	Mean (%CV)			Median		
	T _{max}	T _{max1}	T _{max2}	T _{max}	T _{max1}	T _{max2}
Test Product	19.88 (32.72%)	18.59 (31.19%)	27.98 (21.78%)	21	20	28
Reference Product 1	17.43 (33.75%)	16.28 (30.48%)	27.38 (20.23%)	17	14	26
Reference Product 2	18.09 (42.76%)	16.60 (32.58%)	28.54 (24.14%)	17.5	17	26
Ratio (Test/Ref1)	114.06%	114.19%	102.19%	123.53%	142.86%	107.69%
Ratio (Test/Ref2)	109.89%	111.99%	98.04%	120.00%	117.65%	107.69%
Ratio(Ref1/Ref2)	96.35%	98.07%	95.94%	97.14%	82.35%	100.00%

3. The stick plots below show that the observed within subject difference of T_{max2} between the test and RLD product is also shown when compared between the RLD treatments. However, for T_{max1}, test and RLD products are comparable except two subjects (b) (6) which had significant late peak (at 36 hrs) for the test product. In NDA 022000's single dose PK study under fasting condition²³, it is reported that some subject had a very late peak around 30 hours (Reported T_{max} range 4-32.1 hr). There is no validated Fed study conducted on 1.2 g in NDA 02200, but on 2.4 g (The T_{max} reported in the study was in range of 4 to 48 hours). Thus, the observed significant late peak of 36 hours is acceptable and T_{max1} of both products are comparable.



4. As indicated in dissolution section as well as in pilot study section, the RLD shows high variability from batch to batch. The variability showed not only in different dissolution rate but also in different T_{max}. Although the T_{max} of the test product in pivotal fed study is slightly different from that of the RLD, it is still similar to the T_{max} of the RLD (22 hours) from different batch (Batch LC089A) used in failed study (MSN-P2-602) of the current ANDA (see discussion in failed study, section 4.1.4.4). Furthermore, the T_{max} of the test product (21

hours) of the current ANDA is also comparable to the T_{max} of the RLDs under fed condition in (b) (4). Therefore, the difference of T_{max} between the test and the reference product is considered small and within the variability range of the reference product.

5. The PK parameters of the fasting study are comparable to the fasting study on 1.2 g in NDA 022000 (see section 4.1.1.4). The profiles in the innovator's fasting study on health subjects revealed two peaks at around 6 hours and 12 hours post dose (see figure below), which matches the Fasting study in the current application.

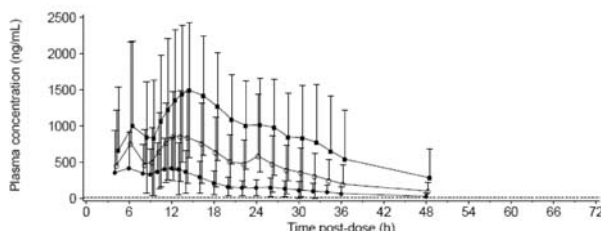
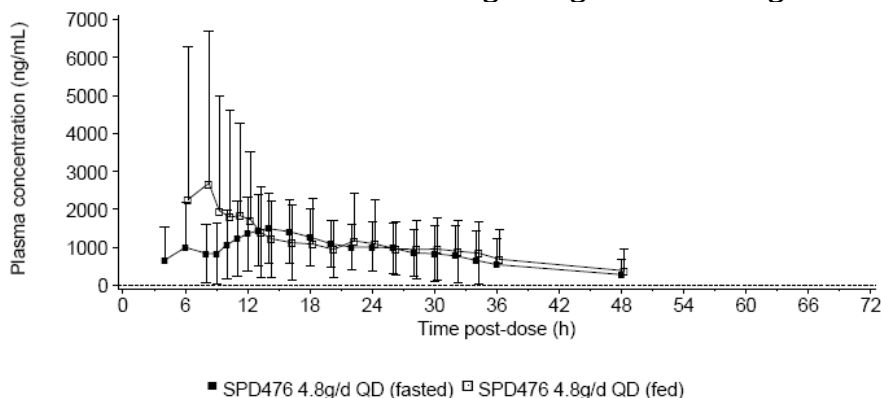


Figure 6: Arithmetic Mean ($\pm$ SD) Plasma Concentration-Time Profiles of 5-ASA Following a Single Oral Dose of 1.2g, 2.4g and 4.8g SPD476 (Fasted)

The reviewer could not locate any PK parameters for single dose of 1.2 g under fed condition in the NDA submission, but the Lialda® label states that high fat meal resulted in further delay in absorption. From the innovator's study SPD476-106 (4.8 g dose), it showed that subjects generally showed two or more peaks and the initial sharp peak under fed condition occurred slightly later (at 8 hours) and more protracted peak was also delayed (at 24 hours). The observed median t_{max} for the SPD476-106 was 10 hrs (range of 4 to 48 hours).

Mean Plasma concentration following a single dose of 4.8 g Lialda®



Based on the above reasons, the small difference in T_{max} between the test and reference products are considered within the variability range of the reference product and should not cause difference of the drug amount delivered to the site of action in health subjects.

4.1.3 Single-dose Pilot Fed Bioequivalence Study

During the course of bioequivalence evaluation, the firm conducted two pilot fed studies (MSN-P2-481 and MSN-P2- 602). The study design for both pilot studies is the same as the pivotal study MSNP3- 482 in section 4.1.2, except that the plasma sampling time points were somewhat different among the three fed studies and that sampling duration was only up to 48 hrs post dose in Study MSN-P2-602. The summary of clinical study reports for the pilot Studies MSN-P2-481 and MSN-P2- 602 are attached below.

The Test Product used in the two pilot fed BE studies is the same product batch (Batch No. EMM196) as that in the pivotal fed BE study (MSN-P3-482). The Reference Product used in Study MSN-P2- 481 was also the same batch (Batch No. FC207A) as that in the pivotal fed BE study. However, the Reference product in Study MSN-P2-602 was from a different batch (Batch No. LC089A).

4.1.3.1 Study Design

Table 40. Study Information

Study Number	MSN-P2-481
Study Title	Single Dose, Partial Replicate, Crossover Comparative Bioavailability Study of Mesalamine 1.2 g Delayed-Release Tablets in Healthy Male and Female Volunteers / Fed State
Clinical Site (Name & Address)	Algorithme Pharma Inc. 1200 Beaumont Ave. Mount-Royal, Quebec, Canada H3P 3P1 Telephone: (514) 858-6077 Fax: (514) 380-5261
Principal Investigator	Eric Sicard, M.D. esicard@algopharm.com
Dosing Dates	Period 1: 2012/05/10 Period 2: 2012/05/17 Period 3: 2012/05/24
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	2012/05/31 to 2012/06/19
Analytical Director	(b) (4)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	a) 40 days b) -80°C ± 20°C nominal

Table 41. Product Information

Product	Test	Reference
Treatment ID	A	B
Product Name	Mesalamine	Lialda™
Manufacturer	Cadila Healthcare Limited, India	Giullani S.p.A., Italy for Shire US Inc., USA
Batch/Lot No.	EMM196	FC207A
Manufacture Date	03/2012	N/A
Expiration Date	N/A	03/2014
Strength	1.2 g	1.2 g
Dosage Form	delayed-release tablet	delayed-release tablet
Bio-Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency (Assay)	102.2% of label claim	99.5% of label claim
Content Uniformity (mean, %CV)	Acceptance value : 2.9	Acceptance value : 1.9
Dose Administered	1.2 g	1.2 g
Route of Administration	Oral	Oral

Table 42. Study Design, Single-Dose Fed Bioequivalence Study

No. of Subjects	66 dosed and 61 completed and 60 ²⁴ included in the statistical analysis
No. of Sequences	3
No. of Periods	3
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	SUS:1, 5, 9, 12, 13, 18, 20, 23, 27, 30, 32, 34, 38, 40, 43, 48, 50, 54, 56, 58, 63, 64 USS:2, 4, 7, 10, 15, 17, 21, 22, 25, 28, 33, 36, 39, 42, 45, 47, 51, 52, 57, 59, 62, 66 SSU:3, 6, 8, 11, 14, 16, 19, 24, 26, 29, 31, 35, 37, 41, 44, 46, 49, 53, 55, 60, 61, 65
Blood Sampling Times	0.0 (Pre-dose), 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 20, 22, 24, 26, 28, 30, 36, 42, 48 and 72 hours post dose
Blood Volume Collected/Sample	4 mL in K ₂ EDTA vacutainers

²⁴ Subject (b) (6) completed all periods of the study but was removed from the pharmacokinetic and statistical analysis after bioanalysis due to positive pre-dose mesalamine concentration greater than 5% of the C_{max}.

Blood Sample Processing/Storage	Blood samples will be centrifuged at 4°C nominal (approximately 1500g for 10 minutes) as soon as possible after blood collection. The plasma obtained will be transferred in polypropylene culture tubes. When feasible, the plasma will be separated into duplicate tubes. All samples will be frozen in an upright position and stored at -80°C nominal until assayed. Samples will be shipped on dry ice to the analytical facility. The time from blood samples collection to plasma aliquot storage should be within 90 minutes. The tubes will be labeled according to clinical SOP.
IRB Approval	Yes (April 12, 2012)
Informed Consent	Yes (April 12, 2012)
Length of Fasting Before Meal	At least 10 hours
Length of Confinement	At least 72 hours (at least 24 hours before dosing and 48 hours after dosing)
Safety Monitoring	Vital signs will be monitored if judged necessary by the physician in charge. ECG will be recorded if judged necessary by the physician in charge. No other measurements are required during this study unless judged necessary by the physician in charge.

Standard FDA Meal Used?	No
If No, then meal components and composition is listed in the tables below	

Components of Non-standard FDA Meal Used in Fed Bioequivalence Study					
Ingredients	Amount (g)	Energy (kcal)	Protein (kcal)	Fat (kcal)	Carbohydrate (kcal)
240 mL Whole Milk (3.25%)	29	156	36	72	48
2 Large Eggs	24	146	48	90	8
4 oz Hash Brown Potatoes / 2 patties	46	264	8	144	112
1 English Muffin	34	141	20	9	112
4.5 g of Butter	3.5	31.5	0	31.5	0
2 Slices of Bacon	26	199	24	171	4
TOTAL	162.5	937.5	136	517.5	284
PERCENTAGE	--	--	14.5%	55.2%	30.3%

4.1.3.2 Clinical Results

Table 43. Demographics Profile of Subjects Completing the Bioequivalence Study

Study No. MSN-P2-481				
		Treatment Groups		
		Test Product N =60	Reference Product N =60	
Age (years)	Mean ± SD	39 ± 13	39 ± 13	
	Range	18 - 70	18 - 70	
Age	< 18	0	0	

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Groups	18 – 40	31 (51.7%)	31 (51.7%)
	41 – 64	28 (46.7%)	28 (46.7%)
	65 – 75	1 (1.7%)	1 (1.7%)
	> 75	0	0
Sex	Male	30 (50.0%)	30 (50.0%)
	Female	30 (50.0%)	30 (50.0%)
Race	White	52 (86.7%)	52 (86.7%)
	Black	5 (8.3%)	5 (8.3%)
	Asian	1 (1.7%)	1 (1.7%)
	American Native or Alaska Native	1 (1.7%)	1 (1.7%)
	Pacific Islander	1 (1.7%)	1 (1.7%)
	Others	0	0
BMI (kg/m ²)	Mean ± SD	25.01 ± 2.76	25.01 ± 2.76
	Range	19.90 – 29.48	19.90 – 29.48
Other Factors		NA	NA

Table 44. Dropout Information, Fed Bioequivalence Study

Study No. MSN-P2-481				
Subject No (b) (6)	Reason for dropout/replacement	Period	Replaced?	Replaced with
	Withdrawn during period 2 by the sponsor due to missing the 72-hr blood sampling in period 1.	1, 2, 3	No	NA
	Withdrawn after dosing of period 1 due to a skin reaction (scabies).	2, 3	No	NA
	Completed all periods of the study but was removed from the pharmacokinetic and statistical analysis after bioanalysis due to positive pre-dose mesalamine concentration greater than 5% of the C _{max} .	2	No	NA
	Withdrawn prior to dosing of period 2 due to a protocol violation (positive urine tested for cocaine).	2, 3	No	NA
	Withdrawn after dosing of period 1 by the physician due to clinical event (headache).	2, 3	No	NA
	Withdrawn before dosing of period 2 due to elevated hCG (pregnancy).	2, 3	No	NA

Table 45. Study Adverse Events, Fed Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fed Bioequivalence Study Study No. MSN-P2-481	
	Test	Reference

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GASTROINTESTINAL DISORDERS [n(%)]	4 (6.3)	6 (4.8)
Constipation [n(%)]	1 (1.6)	3 (2.4)
Abdominal Pain Upper [n(%)]	2 (3.2)	1 (0.8)
Diarrhoea [n(%)]	1 (1.6)	1 (0.8)
Gastrooesophageal Reflux Disease [n(%)]	1 (1.6)	1 (0.8)
Nausea [n(%)]	1 (1.6)	1 (0.8)
Abdominal Distension [n(%)]	1 (1.6)	0
Abdominal Pain [n(%)]	0	1 (0.8)
Abnormal Faeces [n(%)]	1 (1.6)	0
Eructation [n(%)]	1 (1.6)	0
Flatulence [n(%)]	1 (1.6)	0
NERVOUS SYSTEM DISORDERS [n(%)]	2 (3.2)	5 (4.0)
Headache [n(%)]	1 (1.6)	3 (2.4)
Somnolence [n(%)]	1 (1.6)	2 (1.6)
Dizziness [n(%)]	0	1 (0.8)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS [n(%)]	1 (1.6)	5 (4.0)
Vessel Puncture Site Haematoma [n(%)]	1 (1.6)	2 (1.6)
Vessel Puncture Site Pain [n(%)]	0	2 (1.6)
Injury [n(%)]	0	1 (0.8)
Procedural Dizziness [n(%)]	0	1 (0.8)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS [n(%)]	1 (1.6)	1 (0.8)
Fatigue [n(%)]	1 (1.6)	0
Feeling Cold [n(%)]	0	1 (0.8)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS [n(%)]	2 (3.2)	0
Back Pain [n(%)]	1 (1.6)	0
Pain In Extremity [n(%)]	1 (1.6)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS [n(%)]	0	2 (1.6)
Nasal Congestion [n(%)]	0	2 (1.6)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS [n(%)]	0	2 (1.6)
Acarodermatitis [n(%)]	0	1 (0.8)
Rash Generalised [n(%)]	0	1 (0.8)
INFECTIONS AND INFESTATIONS [n(%)]	0	1 (0.8)
Oral Herpes [n(%)]	0	1 (0.8)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS [n(%)]	0	1 (0.8)
Dysmenorrhoea [n(%)]	0	1 (0.8)
Total	9 (14.3)	20 (15.9)

Note: Population is the sum of all drug administrations.
Each adverse event is counted only once for each subject per drug administration within each System Organ Class and Preferred Term.

Note:

Twenty two (22) (33.3%) of the 66 subjects included in this study experienced a total of 46 adverse events.

Nine (9) subjects (14.3%) reported 18 adverse events (5 different System Organ Classes and 15 different Preferred Terms) were reported after the administration of the Test product and twenty (20) subjects (15.9%) reported 28 adverse events (8 different System Organ Classes and 19 different Preferred Terms) were reported after the administration of the Reference product.

The severity of adverse events ranged from mild to severe. Two (2) severe adverse events (Test: constipation, reasonable possibility related; Reference: diarrhea, not reasonable possibility related) were observed during the study.

Table 46. Protocol Deviations, Fed Bioequivalence Study

Study No. MSN-P2-481		
Type	Subjects # (Test)	Subjects # (Ref.)
Blood sampling time deviations	(b) (6)	
Collection time not recorded		
Collection time incorrectly recorded		
Subject was not at clinical site up for at least 24 hours prior to drug administration.		

* Subject had deviation for both administrations of the same treatment.

4.1.3.3 Bioanalytical Results

Table 47. Assay Validation – Within the Fed Bioequivalence Study

Bioequivalence Study No. MSN-P2-481 Mesalamine											
Parameter	Standard Curve Samples										
Conc. (ng/mL)	2.60	5.00	10.00	30.00	75.00	225.00	375.00	600.00	1050.00	1275.00	1500.00
Inter day Precision (%CV)	3.2	5.6	6.6	4.4	3.2	3.7	4.0	4.1	4.2	3.4	3.8
Inter day Accuracy	98.7	102.1	99.7	102.6	102.2	100.5	99.9	102.0	97.1	96.9	98.5

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(%Actual)											
Linearity	0.9929 to 0.9996										
Linearity Range (ng/mL)	2.60 to 1500.00										
Sensitivity/LOQ (ng/mL)	2.60										

Bioequivalence Study No. MSN-P2-481 Mesalamine				
Parameter	Quality Control Samples			
Concentration (ng/mL)	7.60	150.00	750.00	1100.00
Inter day Precision (%CV)	6.8	4.9	4.8	4.4
Inter day Accuracy (%Actual)	106.7	106.9	102.5	99.6

Table 48. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
	(b) (4)	Sample Coding and Re-assay

4.1.3.4 Pharmacokinetic Results

Table 49. Geometric Means and 90% Confidence Intervals - Firm Calculated

Mesalamine Delayed Release Tablets, 1 × 1200 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study, Study No. MSN-P2-481				
Parameter (units)	Ratio of Least Square Means %	s ² wr	sWR	Criteria Bound
LAUC _{0-t}	84.83	0.14903	0.38604	-0.03952
LAUC ₈₋₄₈	83.98	0.18235	0.42702	-0.05678
LC _{max}	76.42	0.67710	0.82286	-0.28037

Table 50. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Mesalamine Delayed Release Tablets, 1 × 1200 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals								
Fed Bioequivalence Study, Study No. MSN-P2-481								
SUMMARY OF STATISTICAL ANALYSIS – UNSCALED DATA								
Parameter (units)	Test	Reference	Ratio	90% C.I.				
AUC _{8-48 hr} (hr *ng/ml)	6839.60	8064.36	0.85	76.40	94.16			
AUC _{0-t} (hr *ng/ml)	7593.63	8898.84	0.85	76.99	94.57			
C _{max} (ng/ml)	1085.51	1420.24	0.76	62.91	92.86			
SUMMARY OF STATISTICAL ANALYSIS – SCALED DATA								
Parameter (units)	T/R Ratio	Lower 90%	Upper 90%	s2wr	sWR [#]	Criteria Bound	Method Used	OUTCOME

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		CI	CI					
AUC_{8-48 hr} (hr *ng/ml)	0.85	76.40	94.16	0.18234 52	0.42701 9	-0.060848	Scaled/P E	PASS
AUC_{0-t} (hr *ng/ml)	0.85	76.99	94.57	0.14902 44	0.38603 68	-0.041525	Scaled/P E	PASS
C_{max} (ng/ml)	0.77	62.91	92.86	0.67709 06	0.82285 51	-0.277774	Scaled/P E	FAIL

4.1.4 Single-dose Fed Bioequivalence Study

4.1.4.1 Study Design

Table 51. Study Information

Study Number	MSN-P2-602
Study Title	Single Dose, Partial Replicate, Crossover Comparative Bioavailability Study of Mesalamine 1.2 g Delayed-Release Tablets in Healthy Male and Female Volunteers / Fed State
Clinical Site (Name & Address)	Algorithme Pharma Inc. 1200 Beaumont Ave. Mount-Royal, Quebec, Canada H3P 3P1 Telephone: (514) 858-6077 Fax: (514) 380-5261
Principal Investigator	Eric Sicard, M.D. esicard@algopharm.com
Dosing Dates	Period 1: 2012/09/05 Period 2: 2012/09/12 Period 3: 2012/09/19
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	2012/10/01 to 2012/10/24
Analytical Director	(b) (4)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	a) 49 days b) -80°C ± 20°C nominal

Table 52. Product Information

Product	Test	Reference
Treatment ID	A	B
Product Name	Mesalamine	Lialda™
Manufacturer	Cadila Healthcare Limited, India	Cosmo S.p.A., Milan, Italy for Shire US Inc., USA
Batch/Lot No.	EMM196	LC089A
Manufacture Date	03/2012	N/A
Expiration Date	N/A	07/2014
Strength	1.2 g	1.2 g

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Dosage Form	delayed-release tablet	delayed-release tablet
Bio-Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency (Assay)	102.2% of label claim	103.4% of label claim
Content Uniformity (mean, %CV)	Acceptance value : 2.9	Acceptance value : 3.8
Dose Administered	1.2 g	1.2 g
Route of Administration	Oral	Oral

Table 53. Study Design, Single-Dose Fed Bioequivalence Study

No. of Subjects	66 dosed and 60 completed and 56 ²⁵ included in the statistical analysis
No. of Sequences	3
No. of Periods	3
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	
Blood Sampling Times	post dose
Blood Volume Collected/Sample	4 mL in K ₂ EDTA vacutainers
Blood Sample Processing/Storage	Blood samples will be centrifuged at 4°C nominal (approximately 1500g for 10 minutes) as soon as possible after blood collection. The plasma obtained will be transferred in polypropylene culture tubes. When feasible, the plasma will be separated into duplicate tubes. All samples will be frozen in an upright position and stored at -80°C nominal until assayed. Samples will be shipped on dry ice to the analytical facility. The time from blood samples collection to plasma aliquot storage should be within 90 minutes. The tubes will be labeled according to clinical SOP.
IRB Approval	Yes (April 4, 2013)
Informed Consent	Yes (April 4, 2013)
Length of Fasting Before Meal	At least 10 hours
Length of Confinement	At least 72 hours (at least 24 hours before dosing and 48 hours after dosing)
Safety Monitoring	Vital signs will be monitored if judged necessary by the physician in charge. ECG will be recorded if judged necessary by the physician in charge. No other measurements are required during this study unless judged necessary by the physician in charge.

²⁵ subjects (b) (6) did not have at least three consecutive mesalamine samples with levels above the lower limit of quantification (LLOQ) in one period. Also, subject (b) (6) had no detectable mesalamine concentrations for all samples in one period (below the limit of quantitation (BLQ)). These periods were judged non-evaluable and as a result, all samples for subjects (b) (6) were excluded from the pharmacokinetic and statistical analyses

Standard FDA Meal Used?	No
If No, then meal components and composition is listed in the tables below	

Components of Non-standard FDA Meal Used in Fed Bioequivalence Study					
Ingredients	Amount (g)	Energy (kcal)	Protein (kcal)	Fat (kcal)	Carbohydrate (kcal)
240 mL Whole Milk (3.25%)	29	156	36	72	48
2 Large Eggs	24	146	48	90	8
4 oz Hash Brown Potatoes / 2 patties	46	264	8	144	112
1 English Muffin	34	141	20	9	112
4.5 g of Butter	3.5	31.5	0	31.5	0
2 Slices of Bacon	26	199	24	171	4
TOTAL	162.5	937.5	136	517.5	284
PERCENTAGE	--	--	14.5%	55.2%	30.3%

4.1.4.2 Clinical Results

Table 54. Demographics Profile of Subjects Completing the Bioequivalence Study

Study No. MSN-P2-602			
		Treatment Groups	
		Test Product N = 56	Reference Product N = 56
Age (years)	Mean ± SD Range	40 ± 11 19 - 65	40 ± 11 19 - 65
Age Groups	< 18 18 – 39 40 – 64 65 – 75 > 75	0 29 (51.8%) 26 (46.4%) 1 (1.8%) 0	0 29 (51.8%) 26 (46.4%) 1 (1.8%) 0
Sex	Male Female	27 (48.2%) 29 (51.8%)	27 (48.2%) 29 (51.8%)
Race	White Black Asian American Native or Alaska Native Pacific Islander Others	44 (78.6%) 9 (16.1%) 3 (5.4%) 0 0 0	44 (78.6%) 9 (16.1%) 3 (5.4%) 0 0 0
BMI (kg/m ²)	Mean ± SD Range	24.65 ± 2.79 19.31 – 29.97	24.65 ± 2.79 19.31 – 29.97
Other Factors		NA	NA

Table 55. Dropout Information, Fed Bioequivalence Study

Subject No.	Reason	Period	Replaced?
(b) (6)	Withdrawn from the study by the Sponsor after dosing of period 1. This subject experienced a gastrointestinal adverse event within the restriction period (abnormal faeces of mild intensity) that could have an impact on his pharmacokinetic profile.	2, 3	No
	Withdrawn from the study by the Sponsor after dosing of period 1 due to a meal deviation (critical lunch was not entirely eaten).	2, 3	No
	Withdrew consent from the study before dosing of period 3 for personal reasons (not related to clinical event(s)).	3	No
	Withdrawn from the study after sample analysis for not having at least three consecutive mesalamine samples with levels above the lower limit of quantification (LLOQ) in one period.	3	No
	Withdrawn after sample analysis for not having at least three consecutive mesalamine samples with levels above the lower limit of quantification (LLOQ) in one period.	3	No
	Withdrawn after sample analysis due to no detectable mesalamine concentrations for all samples in one period (below the limit of quantitation (BLQ)).	2	No
	Withdrawn before dosing of period 3 for safety reasons (Investigator's decision; tonsillitis of moderate intensity).	3	No
	Withdrawn after sample analysis for not having at least three consecutive mesalamine samples with levels above the lower limit of quantification (LLOQ) in one period.	2	No
	Withdrawn before dosing of period 3 for safety reasons (Investigator's decision; metrorrhagia of mild intensity).	3	No
	Withdrew consent before dosing of period 3 for personal reasons (not related to clinical event(s)).	3	No

Table 56. Study Adverse Events, Fed Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fed Bioequivalence Study Study No. MSN-P2-602	
	Test	Reference
NERVOUS SYSTEM DISORDERS [n(%)]	3 (4.8)	14 (11.0)
Headache [n(%)]	2 (3.2)	9 (7.1)
Somnolence [n(%)]	1 (1.6)	5 (3.9)
Dizziness [n(%)]	0	3 (2.4)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS [n(%)]	4 (6.3)	7 (5.5)
Vessel Puncture Site Haematoma [n(%)]	2 (3.2)	4 (3.1)
Vessel Puncture Site Reaction [n(%)]	0	2 (1.6)
Injury [n(%)]	1 (1.6)	0
Scratch [n(%)]	1 (1.6)	0
Vessel Puncture Site Pain [n(%)]	0	1 (0.8)

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GASTROINTESTINAL DISORDERS [n(%)]	2 (3.2)	5 (3.9)
Abdominal Pain [n(%)]	1 (1.6)	1 (0.8)
Diarrhoea [n(%)]	1 (1.6)	1 (0.8)
Nausea [n(%)]	0	2 (1.6)
Abnormal Faeces [n(%)]	1 (1.6)	0
Constipation [n(%)]	0	1 (0.8)
Dyspepsia [n(%)]	0	1 (0.8)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS [n(%)]	1 (1.6)	5 (3.9)
Cough [n(%)]	1 (1.6)	2 (1.6)
Nasal Congestion [n(%)]	0	2 (1.6)
Oropharyngeal Pain [n(%)]	0	2 (1.6)
Dry Throat [n(%)]	0	1 (0.8)
Dysphonia [n(%)]	1 (1.6)	0
Rhinorrhoea [n(%)]	0	1 (0.8)
RENAL AND URINARY DISORDERS [n(%)]	1 (1.6)	2 (1.6)
Pollakiuria [n(%)]	1 (1.6)	1 (0.8)
Dysuria [n(%)]	0	1 (0.8)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS [n(%)]	0	2 (1.6)
Arthralgia [n(%)]	0	1 (0.8)
Musculoskeletal Pain [n(%)]	0	1 (0.8)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS [n(%)]	0	2 (1.6)
Menstruation Delayed [n(%)]	0	1 (0.8)
Metrorrhagia [n(%)]	0	1 (0.8)
EAR AND LABYRINTH DISORDERS [n(%)]	1 (1.6)	0
Ear Pain [n(%)]	1 (1.6)	0
INFECTIONS AND INFESTATIONS [n(%)]	0	1 (0.8)
Tonsillitis [n(%)]	0	1 (0.8)
Total	11 (17.5)	29 (22.8)
Note: Population is the sum of all drug administrations. Each adverse event is counted only once for each subject per drug administration within each System Organ Class and Preferred Term.		

Note:

Fourteen (14) adverse events (6 different System Organ Classes and 12 different Preferred Terms) were reported after the administration of the Test product and 47 adverse events (8 different System Organ Classes and 23 different Preferred Terms) were reported after the administration of the Reference product.

The severity of adverse events was mild or moderate. No severe adverse events were observed during the study.

Table 57. Protocol Deviations, Fed Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
Blood sampling time deviations	(b) (6)	
Blood sampling collection time incorrectly recorded		
Blood sampling collection time not recorded		
The centrifuge display showed temperatures ranging from 2°C to 20°C for approximately 70 seconds during centrifugation of Sample 01.		
Clinical events were recorded 1 and 3 days after the collection of the last blood draw of the study.		

* Subject had deviation for both administrations of the same treatment.

4.1.4.3 Bioanalytical Results

Table 58. Assay Validation – Within the Fed Bioequivalence Study

Bioequivalence Study No. MSN-P2-602 Mesalamine											
Parameter	Standard Curve Samples										
Conc. (ng/mL)	2.60	5.00	10.00	30.00	75.00	225.00	375.00	600.00	1050.00	1275.00	1500.00
Inter day Precision (%CV)	3.2	5.8	5.0	3.6	3.7	4.1	2.4	3.7	3.1	2.8	3.6
Inter day Accuracy (%Actual)	99.4	102.5	97.9	96.4	101.0	103.4	101.8	101.8	94.8	100.9	100.1
Linearity	0.9946 – 0.9995										
Linearity Range (ng/mL)	2.60 to 1500.00										
Sensitivity/LOQ (ng/mL)	2.60										

Bioequivalence Study No. MSN-P2-602 Mesalamine					
Parameter	Quality Control Samples				
Concentration (ng/mL)	7.60	100.00	150.00	750.00	1100.00
Inter day Precision (%CV)	8.4	5.4	4.4	4.4	4.3
Inter day Accuracy (%Actual)	95.5	104.1	101.9	102.5	100.0

Table 59. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
	(b) (4)	Sample Coding and Re-assay

4.1.4.4 Pharmacokinetic Results

Table 60. Geometric Means and 90% Confidence Intervals - Firm Calculated

Mesalamine Delayed Release Tablets, 1 × 1200 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study, Study No. MSN-P2-602				
Parameter (units)	Ratio of Least Square Means %	s ² wr	sWR	Criteria Bound
LAUC _{0-t}	81.58	0.44091	0.66401	-0.17247
LAUC ₈₋₄₈	83.31	0.42038	0.64837	-0.17285
LC _{max}	72.69	0.81169	0.90094	-0.28681

Table 61. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Mesalamine Delayed Release Tablets, 1 × 1200 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals								
Fed Bioequivalence Study, Study No. MSN-P2-602								
SUMMARY OF STATISTICAL ANALYSIS – UNSCALED DATA								
Parameter (units)	Test	Reference	Ratio	90% C.I.				
AUC _{8-48 hr} (hr *ng/ml)	4532.05	5451.78	0.83	69.26	99.78			
AUC _{0-t} (hr *ng/ml)	4560.34	5595.02	0.82	67.91	97.82			
C _{max} (ng/ml)	562.64	777.54	0.72	57.31	91.36			
SUMMARY OF STATISTICAL ANALYSIS –SCALED DATA								
Parameter (units)	T/R Ratio	Lower90% CI	Upper90% CI	s2wr	sWR [#]	Criteria Bound	Method Used	OUTCOME
AUC _{8-48 hr} (hr *ng/ml)	0.83	69.26	99.78	0.4203847	0.6483708	- 0.172854	Scaled/PE	PASS
AUC _{0-t} (hr *ng/ml)	0.82	67.91	97.82	0.4409142	0.6640137	- 0.172473	Scaled/PE	PASS
C _{max} (ng/ml)	0.73	57.31	91.36	0.8116948	0.900941	- 0.286806	Scaled/PE	FAIL

Summary/Conclusions, Single-Dose failed pilot Fed Bioequivalence Studies:

In each pilot fed BE study, the within-subject variability (standard deviation) for the Reference product, SWR, was > 0.294 for all PK parameters of mesalamine. Thus, the reference-scaled average bioequivalence approach was applied to the statistical analysis of AUC_{0-t}, AUC_{8-48 hr} and C_{max}. The results of statistical analysis of each PK parameter

in the pilot fed BE studies (MSN-P2-481 and MSN-P2-602) are summarized in section [4.1.3.4](#) and [4.1.4.4](#), respectively.

The statistical analysis results indicate that the Test Product, Zydus's Mesalamine Delayed-Release Tablets 1.2 g is bioequivalent to the Reference product (RLD), LIALDA[®] (Mesalamine) Delayed-Release Tablets 1.2 g, in both fed studies, in terms of AUC_{0-t} and AUC_{8-48hr} of mesalamine, but not for C_{max}. The firm states that the primary reason for C_{max} of the Test Product not being bioequivalent to that of the Reference product in both pilot fed studies is due to the plasma sampling time not being optimal to accurately capture the peak time (T_{max}) for the Test Product, and thus C_{max} was underestimated for the Test Product in both pilot fed studies. The reviewer summarized the comparison of the three fed studies along with the T_{max} data below:

Application #		ANDA 091640			ANDA 203574	NDA 022000
Fed Study #		MSN-P2-481 (Pilot, 1.2 g)	MSN-P2-602 (Pilot, 1.2 g)	MSN-P3-482 (Pivotal, 1.2 g)	MES/2010/616 (Pivotal, 2.4 g)	476-105 (2.4 g)
# of Plasma Time Points Sampling		26	22	24	24	28
Time Points		0, 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 20, 22, 24, 26, 28, 30, 36, 42, 48, 72	0, 2, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 36, 42, 48	0, 2, 4, 8, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, 28, 30, 36, 42, 48, 72	0.0 4.0 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 11.0, 12.0, 13.0, 14.0, 15.0, 16.0, 17.0, 18.0, 19.0, 20.0, 22.0, 24.0, 30.0, 36.0, 48.0, 72.0	0, 1, 2, 4, 6, 8, 9, 10, 11, 12, 13, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 48, 60, 72, 96, 120
T _{max} , Medium (Range)	Test	24 hr (8-42 hr)	24 hr (7-48 hr)	21 hr (8-36 hr)	16 hr (6-36 hr)	N/A
	RLD	14 hr (8-42 hr)	22 hr (7-48 hr)	17 hr (8-48 hr)	16.5 hr (6-36 hr)	8.04 (4-48 hr)
Geometric Mean of C _{max} (ng/ml)	Test	1085.51	562.64	1123.93	See comment below*	
	RLD	1420.24	777.54	1234.23		
	point estimate	0.77	0.73	0.91		

* In theory, the more accurate the C_{max} is, the higher values it would be. Thus, one would expect the C_{max} in study MSN-P3-482 (which have more sampling points) is higher than those in MSN-P2-481 and MSN-P2-602 (which have less sampling points). However, due to the inter- and intra-subject variability, such comparison is not practical. This is supported by the values of C_{max} for MSN-P2-481, MSN-P2-602 and MSN-P2-482 in the above table.

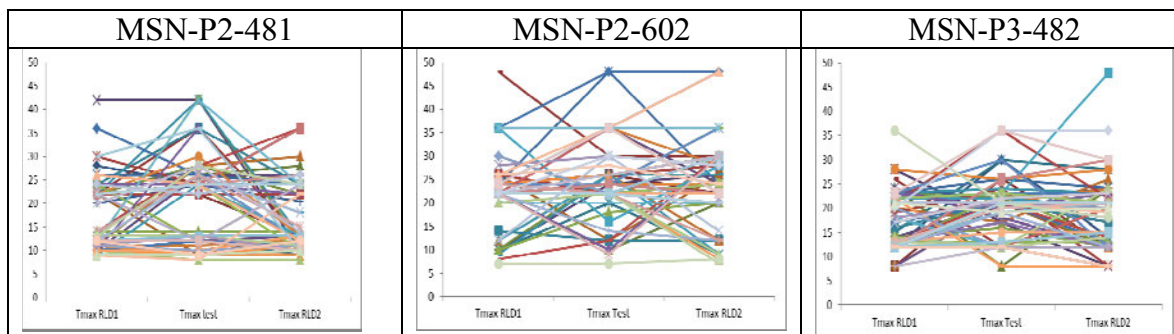
The firm stated that “The first fed study MSN-P2-481 was carried out without knowledge of the in vivo pharmacokinetic behavior of the Reference product. It was thought that mesalamine C_{max} for the Test product did not meet BE criteria in this first fed study possibly because the Reference product (Batch FC207A) did not perform as expected in vivo. Thus, another fed BE study (MSN-P2-602) was carried out using a different batch of Reference product (Batch LC089A) to explore the impact of different batches of Reference product in a pilot/streamlined fashion. Unfortunately, the shorter sampling

time in the exploratory/pilot Study MSN-P2-602 appeared to have compromised the assessment of C_{max} , since in some subjects, T_{max} occurred at the very last sampling time, 48 hrs. In addition, there was less frequent sampling time over the 10 to 16 hours post-dose period in Study MSN-P2-602, which could also compromise C_{max} assessment.”

It seems that after the 1st pilot study failed, the firm tried to re-conduct the BE study using different batch of RLD product (LC089A), which showed slower release in the in vitro BE dissolution testing (in [section 3.9](#)). However, the 2nd study MSN-P2-602 still failed on C_{max} , which indicate the reference variability (showed in in vitro dissolution) is not the key reason for the failure of bioequivalence of C_{max} (The insufficient sampling time is the reason). In addition, the pilot study MSN-P2-602 had sampling time points up to 48 hours, which did not meet the recommendations of 72 hours in DB Draft Guidance on Mesalamine.

It is very interesting that although 2nd study MSN-P2-602 failed the 90% CI for C_{max} , it showed a more similar T_{max} (24 hours) to that of reference (22 hours). The reviewer also noticed that comparing to Batch FC207A (used in pivotal fed study), Batch LC089A (used in MSN-P2-602) has a more similar dissolution release profile as the test product, i.e. both of them showed slower release.

The reviewer, thus, compared the observed T_{max} in these three studies for both test and reference product in stick plots in the same time scale for T_{max} (0-50 hrs), shown below:



As shown above, pilot study MSN-P2-481 had big gap for observed T_{max} between 14 to 20 hours for both test and reference product. Due to the dual peak profiles for the study product, without dense timing sampling at Peak 1 period (5 time points)²⁶, the observed T_{max} might be reported by the 2nd Peak T_{max} . Thus, from the observed T_{max} in Pivotal Fed study MSN-P3-482, the reviewer agrees with the firm's statement that insufficient sampling frequency around the T_{max} caused the failure of C_{max} estimation. Similar gap of T_{max} was also observed in pilot study MSN-P2-602, which had only time points 4 time points between 14-20 hours. This conclusion is further supported by the fact the T_{max} of 21 hours for the test and 17 hours for the reference products are right at two new sampling points which were added in the pivotal study MSN-P3-482.

²⁶ As per Lialda® label, plasma concentrations of mesalamine reached a maximum by 9-12 hours on average for the doses studied.

The firm states that “*The Reference Batch FC207A showed much more rapid dissolution at pH 6.5 and pH 6.8 than the Test Batch EMM196. This may explain the early absorption of mesalamine (in the proximal small intestine) and greater subjects with much earlier T_{max} associated with the Reference product in Study MSNP2- 481.*” The reviewer summarized T_{max} results of the RLD from some Fed studies from the in-house ANDAs. It seems the slower release of RLD product also had later T_{max} median in BE study under Fed condition. However, it should be noted that T_{max} results might also be impacted by food interaction from the given breakfast, study subject GI condition, firm’s analytical method, BE study sampling time points, etc. In addition, different analytical lab’s practice on dissolution might also impact the dissolution result.

Observed T_{max} from in-house ANDAs Fed Studies

In vitro BE dissolution at pH 6.8	ANDA # (Dose)	Observed T_{max} (Median, hr)
(b) (4)	203574 (2.4 g)	16.50
	91640 (1.2 g, FC207A)	14/17.279
	91640 (1.2 g, LC089A)	22
(b) (4)		

In Summary, based on the above discussion, the two pilot BE studies failed 90% CI for C_{max} due to insufficient sampling time points to estimate the C_{max} .

²⁷ The application is pending DB review.

²⁸ The application is currently refused to file as the firm did not include all the completed subjects in its statistical analysis.

4.2 Dissolution Data

Dissolution Review Path	DARRTS: REV-BIOEQ-02 (Dissolution Review), final date 07/28/2010 DARRTS: REV-BIOEQ-01 (General Review), final date 02/23/2012
--------------------------------	--

Table 62. Dissolution Data

(b) (4)



²⁹ Large variability of RLD at hours was also observed in ANDA 203574 (DARRTS: REV-BIOEQ-21 (Primary Review), final date 09/19/2013)

APPEARS THIS WAY ON ORIGINAL

4.3 In vitro BE dissolution study data

4.3.1 0.1 N HCl and pH 6.4

**Table 1 Pretreatment Stage 1: 2 hours in 0.1 N HCl at 100 rpm (750 mL)
Pretreatment Stage 2: 1 hour in pH 6.4 Phosphate buffer at 100 rpm (950 mL)**

Product Name	Mesalamine Tablets, 1.2 g	Delayed-Release	LIALDA® (Mesalamine) Release Tablets, 1.2 g	Delayed-
Batch No.	Lot No.: EMM 196 Mfg date: March, 2012		Lot No.: FC207A (Unit 1-12), LC089A (Unit 13-24) Expiry date: FC207A -March, 2014 LC089A-July, 2014	
Manufacturer:	Cadila Healthcare Limited, India		Cosmo S.p.A. for Shire US Inc., USA	
Time point	% Dissolved		% Dissolved	
	2 hours in 0.1 N HCl	1 hour in pH 6.4 Phosphate buffer	2 hours in 0.1 N HCl	1 hour in pH 6.4 Phosphate buffer
Unit-1	(b) (4)			
Unit-2				
Unit-3				
Unit-4				
Unit-5				
Unit-6				
Unit-7				
Unit-8				
Unit-9				
Unit-10				
Unit-11				
Unit-12				
Unit-13				
Unit-14				
Unit-15				
Unit-16				
Unit-17				
Unit-18				
Unit-19				
Unit-20				
Unit-21				
Unit-22				
Unit-23				
Unit-24				
Mean	0.0	0.0	0.0	0.0
Min	(b) (4)			
Max	(b) (4)			
% RSD	176.9	38.6	159.2	94.0
Date of analysis:	April 7, 2012 (1-12 units) April 13, 2012 (13-24 units)		March 25, 2012 (1-12 units) March 27, 2012 (13-18 units) April 2, 2012 (19-24 units)	

4.3.2 pH 6.5

Table 2 Evaluation Stage: pH 6.5 Phosphate buffer at 100 rpm

Product Name	Mesalamine Delayed-Release Tablets, 1.2 g						LIALDA® (Mesalamine) Delayed-Release Tablets, 1.2 g					
Batch No.	Lot No.: EMM 196 Mfg date: March, 2012						Lot No.: FC207A (Unit 1-12), LC089A (Unit 13-24) Expiry date: FC207A -March, 2014 LC089A-July, 2014					
Manufacturer	Cadila Healthcare Limited, India						Cosmo S.p.A. for Shire US Inc., USA					
Time point	% Dissolved in Hours						% Dissolved in Hours					
	1	2	4	6	8	10	1	2	4	6	8	10
Unit-1	(b) (4)											
Unit-2												
Unit-3												
Unit-4												
Unit-5												
Unit-6												
Unit-7												
Unit-8												
Unit-9												
Unit-10												
Unit-11												
Unit-12												
Unit-13												
Unit-14												
Unit-15												
Unit-16												
Unit-17												
Unit-18												
Unit-19												
Unit-20												
Unit-21												
Unit-22												
Unit-23												
Unit-24												
Mean	0.4	0.3	0.3	0.8	1.2	2.6	0.7	2.1	13.6	32.5	65.3	87.2
Min	(b) (4)											
Max												
% RSD	64.7	197.9	114.4	84.1	102.2	95.7	84.7	56.8	51.4	45.6	42.0	23.8
Date of analysis:	April 7, 2012 (1-12 units) April 12, 2012 (13-24 units)						March 25, 2012 (1-6 units) March 27, 2012 (7-12 units) April 2, 2012 (13-18 units) April 12, 2012 (19-24 units)					

4.3.3 pH 6.8

Table 3 Evaluation Stage: pH 6.8 Phosphate buffer at 100 rpm

Product Name	Mesalamine Delayed-Release Tablets, 1.2 g					LIALDA [®] (Mesalamine) Delayed-Release Tablets, 1.2 g				
Batch No.	Lot No.: EMM 196 Mfg date: March, 2012					Lot No.: FC207A (Unit 1-12), LC089A (Unit 13-24) Expiry date: FC207A -March, 2014 LC089A-July, 2014				
Manufacture	Cadila Healthcare Limited, India					Cosmo S.p.A. for Shire US Inc., USA				
Time point	% Dissolved in Hours					% Dissolved in Hours				
	1	2	4	6	8	1	2	4	6	8
Unit-1	(b) (4)									
Unit-2										
Unit-3										
Unit-4										
Unit-5										
Unit-6										
Unit-7										
Unit-8										
Unit-9										
Unit-10										
Unit-11										
Unit-12										
Unit-13										
Unit-14										
Unit-15										
Unit-16										
Unit-17										
Unit-18										
Unit-19										
Unit-20										
Unit-21										
Unit-22										
Unit-23										
Unit-24										
Mean	2.7	5.1	28.4	70.9	98.2	4.5	17.5	61.6	91.9	102.8
Min	(b) (4)									
Max										
% RSD	87.1	71.7	62.1	24.1	5.4	112.9	54.9	31.3	13.9	2.9
Date of analysis:	April 7, 2012 (1-12 units) April 9, 2012 (13-18 units) April 12, 2012 (19-24 units)					March 25, 2012 (1-6 units) March 27, 2012 (7-12 units) April 2, 2012 (13-18 units) April 12, 2012 (19-24 units)				

4.3.4 pH 7.2

Table 4 Evaluation Stage: pH 7.2 Phosphate buffer at 100 rpm

Product Name	Mesalamine Delayed-Release Tablets, 1.2 g					LIALDA [®] (Mesalamine) Delayed-Release Tablets, 1.2 g				
Batch No.	Lot No.: EMM 196 Mfg date: March, 2012					Lot No.: FC207A (Unit 1-12), LC089A (Unit 13-24) Expiry date: FC207A -March, 2014 LC089A-July, 2014				
Manufactured By:	Cadila Healthcare Limited, India					Cosmo S.p.A. for Shire US Inc., USA				
Time point	% Dissolution in Hours					% Dissolution in Hours				
	1	2	4	6	8	1	2	4	6	8
Unit-1	(b) (4)									
Unit-2										
Unit-3										
Unit-4										
Unit-5										
Unit-6										
Unit-7										
Unit-8										
Unit-9										
Unit-10										
Unit-11										
Unit-12										
Unit-13										
Unit-14										
Unit-15										
Unit-16										
Unit-17										
Unit-18										
Unit-19										
Unit-20										
Unit-21										
Unit-22										
Unit-23										
Unit-24										
Mean	10.6	31.7	73.2	100.1	102.8	9.6	26.7	68.5	96.0	104.6
Min	(b) (4)									
Max										
% RSD	15.5	9.0	4.9	2.7	2.4	35.6	32.1	28.1	12.8	3.7
Date of analysis:	April 13, 2012 (1-12 units) April 11, 2012 (13-24 units)					March 25, 2012 (1-6 units) March 27, 2012 (7-12 units) April 2, 2012 (13-18 units) April 11, 2012 (19-24 units)				

4.3.5 pH 7.5

Table 5 Evaluation Stage: pH 7.5 Phosphate buffer at 100 rpm

Product Name	Mesalamine Delayed-Release Tablets, 1.2 g					LIALDA® (Mesalamine) Delayed-Release Tablets, 1.2 g				
Batch No.	Lot No.: EMM 196 Mfg date: March, 2012					Lot No.: FC207A (Unit 1-12), LC089A (Unit 13-24) Expiry date: FC207A -March, 2014 LC089A-July, 2014				
Manufactured By:	Cadila Healthcare Limited, India					Cosmo S.p.A. for Shire US Inc., USA				
Time point	% Dissolution in Hours					% Dissolution in Hours				
	1	2	4	6	8	1	2	4	6	8
Unit-1	(b) (4)									
Unit-2										
Unit-3										
Unit-4										
Unit-5										
Unit-6										
Unit-7										
Unit-8										
Unit-9										
Unit-10										
Unit-11										
Unit-12										
Unit-13										
Unit-14										
Unit-15										
Unit-16										
Unit-17										
Unit-18										
Unit-19										
Unit-20										
Unit-21										
Unit-22										
Unit-23										
Unit-24										
Mean	9.7	30.3	72.7	99.1	102.8	11.0	28.7	70.1	94.8	103.4
Min	(b) (4)									
Max										
% RSD	25.3	11.9	8.0	3.9	2.0	33.1	34.5	32.1	15.1	3.6
Date of analysis:	April 08, 2012 (1-12 units) April 11, 2012 (13-24 units)					March 26, 2012 (1-6 units) March 27, 2012 (7-12 units) April 2, 2012 (13-18 units) April 11, 2012 (19-24 units)				

4.4 Detailed Regulatory History

1. The OB lists the following Mesalamine modified release products as currently marketed products:

Application No	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant	Approval date
N022000	Yes	Mesalamine	Tablet, Delayed Release; Oral	1.2 g	Lialda®	Shire	Jan 16, 2007
N019651	Yes	Mesalamine	Tablet, Delayed Release; Oral	400 mg	Asacol®	Warner Chilcott Llc	Jan 31, 1992
N021830	Yes	Mesalamine	Tablet, Delayed Release; Oral	800 mg	Asacol HD®	Warner Chilcott Llc	May 29, 2008
N204412	Yes	Mesalamine	Capsule, Delayed release; Oral	400 mg	DELZICOL	Warner Chilcott Llc	Feb 1, 2013
N 020049	Yes	Mesalamine	Capsule, extended release; Oral	500mg (also 250 mg)	Pentasa	Shire	Jul 8, 2004 (May 10, 1993)
N022301	Yes	Mesalamine	Capsule, extended release; Oral	375 mg	APRISO	SALIX PHARMS	Oct 31, 2008

Asacol (delayed-release tablet) was the first mesalamine oral product approved on June 31, 1992 for the treatment of mildly to moderately active ulcerative colitis (UC) and for the maintenance of remission of UC. Soon after that, Pentasa (extended-release capsule, 250 mg) was approved on May 10, 1993 for the induction of remission and for the treatment of patients with mildly to moderately active UC. Pentasa 500 mg strength was approved on July 8, 2004 (NDA 20-049/SCS-015) based on formulation proportionality and an in vivo-in vitro correlation, which has been established for the 250 mg strength (NDA 20-049/SCS-013)³⁰. Four newer RLDs were approved recently, namely Lialda (January 16, 2007), Asacol HD (May 29, 2008), Apriso (October 31, 2008) and Delzicol (Feb. 2013), all based on clinical trials.

For Asacol, **prior** to 2010, OGD recommended (1) a parallel design, three arm (test, reference and placebo) bioequivalence study with clinical endpoints in patients with ulcerative colitis (male and female); (2) comparative dissolution studies with the evaluation stage covering a range of pH values (pH of 6.0, 6.5, 6.8, 7.2, and 7.5) representative of the GI tract. The above recommendations have been sent to several firms in control correspondences

2. Shire Pharmaceuticals (the Pentasa sponsor) filed a Citizen Petition (CP, No. FDA-2008-P-0507) on September 10, 2008, and Warner Chilcott Company (the Asacol and Asacol HD sponsor) filed a CP Docket No. FDA-2010-P-0111) on February 22, 2010. The FDA issued the response to both citizen petitions on August 20, 2010. In the CP response, FDA concluded that 'bioequivalence of mesalamine delayed release tablets (RLD: Asacol and Asacol HD) is recommended to be demonstrated by equivalence of pharmacokinetic profiles

³⁰ \\cdsnas\OGDS6\CONTROLS\2004-docs\04-293.pdf.

and equivalent in vitro drug release (dissolution) under multiple conditions representative of the conditions in the GI tract.’³¹. FDA also concluded that ‘the decision about generic products referencing Asacol should also apply to generic products referencing Pentasa and other mesalamine modified release products (Apriso and Lialda)’³².

The Agency response to the Asacol and Pentasa petitions did not describe the appropriate PK metrics and the comparative dissolution test conditions. The OGD later summarized the appropriate PK metrics and the comparative BE dissolution test conditions recommended for five mesalamine oral products as follows:

In Vitro BE studies

Table 1: Recommendations for comparative dissolution testing (Note PB is Phosphate Buffer)

Product	Strength (mg)	Apparatus	Speed (rpm)	Pretreatment Stage	Evaluation Stage	Volume (mL)	Sampling
Asacol Asacol HD	400 800	II (paddle)	100 rpm for pretreatment stage; 50 rpm for evaluation stage.	2 hours in 0.1 N HCl (500 mL)	Each of (1) pH 4.5 Acetate buffer (2) pH 6.0 PB (3) pH 6.5 PB (4) pH 6.8 PB (5) pH 7.2 PB (6) pH 7.5 PB	900	0, 10, 20, 30, 45, 60, 75, 90, 120, 150 min or as needed for profile comparison
Lialda	1200	II (paddle)	100 rpm for pretreatment stage and buffer stages.	2 hours in 0.1 N HCl (750 mL)	Buffer stage 1: (950 mL) pH 6.4 PB for 1 hour Buffer stage 2: (960 mL) Each of (1) pH 6.5 PB (2) pH 6.8 PB (3) pH 7.2 PB (4) pH 7.5 PB		1, 2, 4, 6 and 8 hours or as needed for profile comparison
Pentasa	250 / 500	II (paddle)	100 rpm	None	Each of (1) 0.1 N HCl (2) pH 4.5 Acetate buffer (3) pH 6.0 PB (4) pH 6.5 PB (5) pH 6.8 PB (6) pH 7.2 PB (7) pH 7.5 PB	900	1, 2, 4, 6, 8, and 12 hours or as needed for profile comparison
Apriso	375	I (basket)	100 rpm for acid stage and buffer stage	2 hours in 0.1 N HCl (750 mL)	Each of (1) pH 4.5 Acetate buffer (2) pH 6.0 PB (3) pH 6.5 PB (4) pH 6.8 PB (5) pH 7.2 PB (6) pH 7.5 PB	1000	0.5, 1, 2, 4, 7 and 9 hours or as needed for profile comparison

Please note that Delzicol was approved after the CP and guidance were issued. The BE recommendation for this RLD is under review.

³¹ Asacol and Pentasa Citizen Petition Response \\cdsnas\OGDS6\CONTROLS\2008-docs\08-1019.pdf; \\cdsnas\OGDS6\CONTROLS\2010-docs\10-0151.pdf.

³² \\cdsnas\OGDS6\CONTROLS\2008-docs\08-1019.pdf ; \\cdsnas\OGDS6\CONTROLS\2010-docs\10-0151.pdf

Selection of partial AUC matrix, AUC8-48 for mesalamine DR tablet (please note this matrix does not apply to Apriso and Pentosa as they are ER capsules)³³

The original OGD recommendation for partial AUC is AUC0-Tmax and AUCtmax-24 based on simulation data. The recommendation was changed to AUC 8-48 due to the following:

The NDA sponsor was requested to reformulate Asacol 400 mg tablets due to the existence of dibutyl phthalate (DBP). DBP serves as a plasticizer in the Asacol formulation and is believed to have adverse reproductive and developmental effects based on recently publication in animal studies. Warner Chilcott submitted an IND 026093 on 12/29/2010 which included study protocol, PR-08210. In the OCP response, AUC₈₋₄₈ was recommended as opposed to the (b) (4) because it's more clinically relevant. Additional exploratory parameters, such as those the sponsor proposed (0-12 and 12-48 hours, etc.) may be included as secondary endpoints and would be helpful in evaluating partial AUC (pAUC) as an PK parameter for future studies.

On October 28, 2011, a meeting was held among OGD, OCP, ONDQA, and ORP to discuss the differences in Asacol BE recommendation. OGD agreed with OND on the partial AUC₈₋₄₈ based on the following reasons: (1) AUC₈₋₄₈ reflects the absorption in the colon, which is the site of action; (2) the variability of (b) (4) AUC₈₋₄₈ is highly correlated with AUC_t. However, since Asacol and other mesalamine oral products are locally acting, it is important to have profile similarity between the reference product and the generic product to ensure they have similar delivery in the gastrointestinal tract. Thus OGD may evaluate other pAUCs during the review process as supportive information. To aid this evaluation and to ensure the best possible characterization of drug absorption by AUC8-48, OGD recommends dense sampling in the time between Tmax and 24 hours.

3. Warner Chilcott Company filed another Citizen Petition (Docket No. FDA-2012-P-1087) on October 14, 2012 requesting changes to the pAUC time interval from AUC8-48 to AUC0-12 and AUC12-48 existing guidance. In the FDA's response issued Mar., 2013, the FDA stated that it *"denies your specific requests that we change our bioequivalence recommendations, though we grant your request that FDA clarify its position on the within-subject variability of Asacol and Asacol HD and the relevance of that variability to use of the reference-scaled approach for demonstrating bioequivalence in highly-variable drug products"*.³⁴ Therefore, the FDA continues to recommend AUC8-48.

4. Rationale for Lialda BE recommendations:

Lialda is similar to three other modified release mesalamine products: Asacol and Asacol HD. Thus the framework from the 2010 Citizen Petition response should also apply to Lialda. For all mesalamine products, OGD will ask for PK studies and comparative dissolution studies in

³³ The draft pAUC matrix for Apriso and Pentosa are AUC0-3 and AUC3-t. They are under review pending CP#FDA-2013-P-0470

³⁴ Dockets Search at regulations.gov (<http://www.regulations.gov/#!home>); Search: FDA-2012-P-1087; see FDA/CDER to Warner Chilcott, LLC – Petition Partial Approval and Denial and Acknowledgement Letter to Alvin Howard (Warner Chilcott Company, LLC); Last Accessed Date: 04/03/2013

multiple pH media to demonstrate bioequivalence. The recommendation of the partial AUC of 8-48 is consistent with recommendations provided for the other enteric coated mesalamine tablets (Asacol and Asacol HD) and consistent with recommendations from OND to NDA sponsors.

Both fed and fasted studies are recommended because this is the general OGD policy for modified release dosage forms. Pharmacokinetics of mesalamine from Lialda has been observed to be highly variable and thus a scaled average bioequivalence approach is recommended. Within subject CV% for AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} were estimated as 50.1%, 45.5% and 90.7% in study SPD476-106. Part of the high variability in C_{max} arises because most subjects have two widely separated peaks in the plasma concentration profile.

The recommended dose of 1200 mg is one tablet. The results of study SPD476-106 indicate proportionality between 1200 mg and 2400 mg doses. There are no safety concerns with exposure to healthy subjects to a dose of 1200 mg of mesalamine.

Mesalamine has one significant pre-systemic metabolite (5-Ac-ASA) that was measured in most pharmacokinetic studies for the Lialda NDA. For other mesalamine products, OGD has determined that this metabolite does not contribute significantly to safety or efficacy and therefore does not recommend that it be measured in bioequivalence studies.

(b) (4)

Any generic product should have equivalent performance as the RLD. The requirement that ANDA products be equivalent in dissolution to Lialda ensures that dissolution will distinguish the many different products on the market and makes it clear to the ANDA sponsors that they should develop (b) (4) product with the same extended release performance as the RLD.

4.5 Consult Reviews

From: Cui, Minglei
Sent: Sunday, February 09, 2014 3:14 PM
To: Lionberger, Robert; Zhao, Joan
Cc: Jiang, Xiaojian; Stier, Ethan; Zhang, Xinyuan; Cui, Minglei
Subject: RE: Help on Comparative Dissolution Testing for Lialda

Dear Rob and Susie,

Thank you very much for the prompt response and your expert opinion on the issue. We really appreciate your extensive analysis and relevant references.

I agree with you that we should be cautious for dissolution difference at pH 6.8. As a matter of fact, other firm is able to establish the dissolution similarity for this pH. In my review 203574, although the firm failed f2 acceptance criteria for pH 6.5 due to high variability (around “critical point”), it passed f2 acceptance criteria for pH 6.8. Thus, if the failure of meeting f2 criteria at pH 6.5 is due to high variability, the different dissolution at pH 6.8 could be the result of formulation difference. We will discuss this issue further and incorporate your opinion into our review.

Thanks again for your help,

Minglei

From: Lionberger, Robert
Sent: Sunday, February 09, 2014 1:39 PM
To: Cui, Minglei; Zhao, Joan
Cc: Jiang, Xiaojian; Stier, Ethan; Zhang, Xinyuan
Subject: RE: Help on Comparative Dissolution Testing for Lialda

Hi Joan and Minglei

Here are our thoughts (Susie did all the analysis)

We think it is okay not to have f2>50 criterion for the pH 6.5 and pH 6.8 condition because the RLD, Lialda, is designed to release when pH>7.

However, we think some evaluation should be applied to the test product because the RLD starts to release after 4 hours in pH 6.5, and after 3 hours in pH 6.8.

The data for this test product seem to show that it is more resistant to release than the RLD under these conditions.

The concern is that if a patient has constantly low pH across the GI tract and if the test product does not release at pH 6.5 or pH 6.8, the test product will not perform the same as the RLD. Therefore, we did literature search on the GI pH in UC patients.

Although some UC patients may have very low pH in the colon (see attached reference), it might be okay for this specific product because the peak pH in distal small bowel is still higher than 6.5 (see attached references) for every patient measured. If the test product stays long enough in the peak pH, the polymer is being destroyed, the test product should continuously release even when the pH drops in the colon

At pH 6.5, it is okay to have minimum release criteria, the goal of the products is not to release at this pH. (test product is acceptable if it has minimal release for four hours like the RLD)

However, I would be careful if they do not release similarly in pH 6.8 because we don't have dissolution profiles between pH 6.8 and 7.2 and some patients may have low pH in the distal small bowel (see attached reference, table 3 of 'Inflammatory Bowel disease pH_drug deliver 2011.pdf, in which some patients may have as low as pH 6.9 in distal small bowel). An alternative to the f2 and considering the variability of the RLD, would be if the mean of the RLD is within the range of the RLD data at pH 6.8 over the 2-8 hour range.

Rob

From: Cui, Minglei

Sent: Wednesday, February 05, 2014 8:44 PM

To: Lionberger, Robert; Zhang, Xinyuan

Cc: Zhao, Joan; Jiang, Xiaojian; Stier, Ethan

Subject: RE: Help on Comparative Dissolution Testing for Lialda

Thank you very much, Rob. We are looking forward to hearing from you.

Minglei

From: Lionberger, Robert

Sent: Wednesday, February 05, 2014 6:48 PM

To: Cui, Minglei; Zhang, Xinyuan

Cc: Zhao, Joan; Jiang, Xiaojian; Stier, Ethan

Subject: Re: Help on Comparative Dissolution Testing for Lialda

We can discuss and give you a reply on friday

Rob

From: Cui, Minglei

Sent: Wednesday, February 05, 2014 03:47 PM

To: Lionberger, Robert; Zhang, Xinyuan

Cc: Zhao, Joan; Jiang, Xiaojian; Cui, Minglei; Stier, Ethan

Subject: RE: Help on Comparative Dissolution Testing for Lialda

Dear Rob and Susie,

Would you please help us on the issue mentioned in Zhao's email below? I would like to have your advice on whether it is OK if we do not apply f2 acceptance criteria (i.e. have to >50) to the pH 6.5 and pH 6.8 data. The RLD is Lialda. The firm has acceptable in vivo BE studies (PK fasting and fed) and acceptable in vitro BE studies at the 7.2 and pH 7.5 buffer stages (f2>50). The firm also conducted clinical endpoint studies previously. Please let us know if we can use in vitro BE studies at pH 6.5 and pH 6.8 as **information only** (These two pH are very close to pH 6.4 at which no release is expected). We would appreciate a prompt response since this is a priority review and the goal date is 2/17.

Thank you very much,

Minglei

From: Zhao, Joan
Sent: Monday, February 03, 2014 1:40 PM
To: Zhang, Xinyuan
Cc: Cui, Minglei; Lionberger, Robert; Jiang, Xiaojian
Subject: Help on Comparative Dissolution Testing for Lialda

Hi Susie,

Please kindly guide us on recommendations for comparative dissolution testing at pH 6.5 and pH 6.8.

For ANDA 091640, the firm initially conduct a clinical endpoint BE study before the Agency's CP response. In the current application, the firm submitted its BE PK studies and in vitro dissolution study on its original formulation. The PK BE studies are found acceptable. However, we notice that the F2 values for firm's dissolution testing at pH 6.5 and pH 6.8 are far lower than 50 when comparing the Test and RLD products. The test product showed minimal release up to 10 hours at pH 6.5 (Mean <5%) and slower release before the 8 hour time point at pH 6.8. The difference in dissolution at lower pH is most likely due to the tablet coating composition

(b) (4) which dissolves at (b) (4)

Since the firm developed its formulation before our CP response is posted, the firm might not consider to reach the similar dissolution performance at pH 6.5 and 6.8. The formulation of Lialda® is to dissolve when it reaches the lower tract of the small bowel for delayed release. As per Lialda® label, the product should dissolve at or above pH 6.8. The firm's test product dissolution profile at pH 6.5 and 6.8 should not likely impact its in vivo performance. Therefore, should dissolution in pH 6.5 and 6.8 serve as information only in this case, which was mentioned in Dr. Lionberger's email below ? Please kindly advise?

For your information, RLD product dissolution profiles at pH 6.5 and pH 6.8 in our current in house ANDAs were summarized below:

0.1N HCl Followed by pH 6.4 Phosphate Buffer and pH 6.5 Phosphate Buffer

ANDA #	Product (unit #)	Testing Date	Exp Date		Collection Times (hr)											
					1	2	3	4	5	6	8	10	12			

(b) (4)

(b) (4)

203574	RLD (24)	7/20/2012	9/2014	Mean	2	3	12	31		78	100	103	104
				% CV	50	42.8	17.7	14.9		10.8	3.1	1.4	1
091640	RLD (24)	3/25/2012 3/27/2012 4/2/2012 4/12/2012	3/2014 7/2014	Mean	0.7	2.1		13.6		32.5	65.3	87.2	
				% CV	84.7	56.8		51.4		45.6	42.0	23.8	
	Test (24)	4/7/2012 4/12/2012	N/A	Mean	0.4	0.3		0.3		0.8	1.2	2.6	
				% CV	64.7	197.9		114.4		84.1	102.2	95.7	

0.1N HCl Followed by pH 6.4 Phosphate Buffer and pH 6.8 Phosphate Buffer

ANDA #	Product (unit #)	Testing Date	Exp Date		Collection Times (hr)								
					1	2	3	4	5	6	8	10	12
(b) (4)													
203574	RLD (24)	7/20/12 7/21/12	9/2014	Mean	16	30	54	82		103	105		
				% CV	12.5	7.8	5.6	3.2		2.5	1.2		
091640	RLD (24)	3/25/2012	3/2014	Mean	4.5	17.5		61.6		91.9	102.8		
		3/27/2012		%	112.9	54.9		31.3		13.9	2.9		
	4/2/2012	7/2014	CV										
	4/12/2012												
	Test (24)	4/7/2012	N/A	Mean	2.7	5.1		28.4		70.9	98.2		
		4/12/2012		% CV	87.1	71.7		62.1		24.1	5.4		

Thank you!

Zhuojun Joan Zhao, Ph.D.
Division of Bioequivalence II
Office of Generic Drugs
FDA/CDER/OPS
Office (240)-402-3936
Joan.zhao@fda.hhs.gov

³⁵ The application has not been reviewed by DB and the data is sourced from EDR.

Office (240)-276-8770

Fax (240)-276-8766

Joan.zhao@fda.hhs.gov

4.6 Internal Meeting on 2/25/2014

Meeting Date: February 25, 2014
Meeting Time: 10:00 AM – 11:00 PM
Meeting Location: MM2 Conference Room 373

Attendees: Ethan Stier, Xiaojian Jiang, Minglei Cui, and Zhuojun Zhao

ANDA No.	091640
Drug Product Name	Mesalamine Delayed-release Tablets
Strength(s)	1200 mg
Applicant Name	Zydus Pharmaceuticals USA Inc.
First Generic	Yes

Summary

Initially Zydus Pharmaceuticals USA Inc. conducted a clinical endpoint BE study and the application was received on December 12, 2009. However, in the Agency's response to the Citizen's Petitions (CPs) FDA-2010-P-0111 and FDA-2008-P-0507, the BE study with clinical endpoints is no longer considered to be sufficiently sensitive to establish BE of this product. Therefore, in the current amendment, the firm provided the results of its one fasting and three fed bioequivalence (BE) studies and in vitro BE dissolution testing. The tablet formulation composition used in the BE studies is identical to the original ANDA exhibit batch.

The purpose of this meeting is to discuss several issues we identified in the review as shown in brief below:

- 1) *in vitro* BE dissolution data at pH 6.8
- 2) T_{max} difference in *Fed* study
- 3) Failed pilot *Fed studies*

Formulation

RLD Formulation

Lialda® is a multi-matrix formulation containing 1.2 g of mesalamine per tablet. Mesalamine is incorporated into a lipophilic matrix, which is in turn dispersed within a hydrophilic matrix. This modified matrix system is coated with a polymer film that breaks down at or above 6.8, at which point the lipophilic/hydrophilic matrix begins to swell and erode and the active ingredient, 5-ASA, is gradually released.

Ingredient	Amount (mg)	Function	Reference to Standards
Drug substance(s) Mesalazine	1200.0	Active ingredient	EP and USP/NF
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sodium Carboxymethylcellulose	(b) (4)	(b) (4)	EP + USP/NF
Colony Wax	(b) (4)	(b) (4)	EP + USP/NF
Stearic Acid	(b) (4)	(b) (4)	EP + USP/NF
Silica, Colloidal Hydrated	(b) (4)	(b) (4)	EP + USP/NF
Sodium Starch Glycolate (Type A)	(b) (4)	(b) (4)	EP + USP/NF
Talc	(b) (4)	(b) (4)	EP + USP/NF
Magnesium Stearate	(b) (4)	(b) (4)	EP + USP/NF
(b) (4)	(b) (4)	(b) (4)	EP + USP/NF
Talc ²	(b) (4)	(b) (4)	EP + USP/NF
Methacrylic Acid Copolymer, Type A ²	(b) (4)	(b) (4)	EP + USP/NF
Methacrylic Acid Copolymer, Type B ²	(b) (4)	(b) (4)	EP + USP/NF
Triethylcitrate ²	(b) (4)	(b) (4)	EP + USP/NF
Titanium Dioxide ²	(b) (4)	(b) (4)	EP + USP/NF
Red Ferric Oxide	(b) (4)	(b) (4)	USP/NF
Polyethylene glycol 6000 ²	(b) (4)	(b) (4)	EP and USP
(b) (4)	(b) (4)	(b) (4)	EP and USP
(b) (4)	(b) (4)	(b) (4)	EP and USP
Total	1385.0		

Test Formulation

Ingredient (s)	Mesalamine Delayed-release Tablets, 1.2 g	
	Unit Composition (mg/tablet)	% w/wS
(b) (4)	(b) (4)	(b) (4)
Mesalamine (b) (4) USP	1200.000	(b) (4)
Colloidal Silicon Dioxide (b) (4) NF	(b) (4)	
Magnesium Stearate (b) (4) NF	(b) (4)	
(b) (4)	(b) (4)	
Carboxy methyl cellulose Sodium (b) (4) USP		
Sodium Starch Glycolate (b) (4) NF		
Hypromellose (b) (4) USP		
(b) (4)		
(b) (4)		
Microcrystalline Cellulose (b) (4) NF		
Colloidal Silicon Dioxide (b) (4) NF		
Magnesium Stearate (b) (4) NF		
(b) (4)		
Methacrylic Acid Copolymer (b) (4) NF		
(b) (4) NF		
Triethyl Citrate (b) (4) NF		
Talc (b) (4) USP		
(b) (4)		
(b) (4)		
(b) (4)		
Total (Coated Tablets)	1465.000	100.00

In vitro BE dissolution Study

The performance of the (b) (4) Lialda[®] is an essential attribute of the product. Demonstration of equivalence in multistage dissolution ensures the equivalent integrity of the (b) (4) at acidic pH and at pH 6.4-7.2. The firm was request to conduct in vitro BE studies comparing its test product to the RLD Lialda[®] tablets at pH 6.5, 6.8, 7.2 and 7.5 after pretreatments with 0.1 N HCl (2 hrs) and pH 6.4 Phosphate Buffer (1 hr).

Table 63: F2 values and 90% CI using bootstrapping method (24 units)

Bootstrapping method					
Treatment	pH	Frequent	Original	F2 bootstrap	Lower CI
					Upper CI

(# of units)			f2	mean	(Percentile)	(Percentile)
T vs. R (two lots) (24 vs. 24)	6.5	10000	17.07561	16.45597458	14.8008	17.79041
	6.8	10000	34.30761	34.55327	29.30018	40.78859
	7.2	10000	69.02809	69.55844	54.56053	85.90782
	7.5	10000	77.17999	73.83384	57.09611	89.58673
R1 vs. R2 (12 vs 12)	6.5	10000	31.41539	30.92268	27.83892	34.34846
	6.8	10000	35.47665	35.57934	31.12492	40.74375
	7.2	10000	32.69056	33.06435	29.99618	37.0998
	7.5	10000	28.66241	28.6892	26.55906	30.78745

As shown in the table above, the similarity dissolution profile for pH 7.2 and pH 7.5 is indicated by the fact that f2 are greater than 50 and the lower bound of 90% CIs for the f2 test comparing T vs. R are greater than 46. Per consult with the Science Team, F2 values might not be applied to pH 6.5 testing since the goal of this product is not to release at this pH. Instead, the dissolution profiles should be compared for the product release after 4 hours at pH 6.5. The test product should not have more release than the RLD product for 4 hours. The firm's test product had minimal release at pH 6.5 and thus the testing at pH 6.5 is deemed acceptable.

However, for pH 6.8, the f2 using mean profiles is lower than 50, and their lower bound of 90% CIs of f2 comparing test vs. RLD are less than 46³⁶. When the test product (12 units) compared with one batch of the RLD (Batch LC089A, 12 units), the F2 mean value is more than 50 and the lower bound of 90% CIs of f2 comparing test (12 unit) vs. reference 2 (Batch LC089A, 12 units) are higher than that comparing the RLD against itself under the same conditions (40.49 vs 31.12), as shown in table below:

Table 64: F2 values and 90% CI using bootstrapping method (12 units)

Bootstrapping method						
Treatment (# of units)	pH	Frequent	Original f2	F2 bootstrap mean	Lower CI	Upper CI
T vs. R1 (12 vs 12)	6.8	10000	25.91946	26.03284	21.63071	31.14643
T vs. R2 (12 vs. 12)	6.8	10000	50.22053	50.61836	40.49969	63.76074

R1: FC207A (Exp. Date: March 2014) R2: LC089A(Exp. Date: July 2014)

This result indicated that the RLD showed high variability at pH 6.8 between different batches, which is also observed in other in-house ANDAs (except ANDA 203574):

Table 65: 0.1N HCl Followed by pH 6.4 Phosphate Buffer and pH 6.8 Phosphate Buffer (RLD Products)

ANDA #	Unit #	Testing Date	Exp Date		Collection Times (hr)						
					1	2	3	4	5	6	8

(b) (4)

³⁶ As the RLD product is designed to release at pH above 6.8, F2 values might not be applied to pH 6.8 testing. However, the mean of the test product should be within the range of the RLD data at pH 6.8 over 2-8 hours range (Science team consult in section 4.5). Based on the current submission, the test product meet the requirements for all time points except for Time point at 4-hour (Mean_{test}=28.4, Range_{RLD}=34.6-95.6).

(b) (4)												
203574	24	7/20/12 7/21/12	9/2014	Mean	16	30	54	82		103	105	
				% CV	12.5	7.8	5.6	3.2		2.5	1.2	
091640	24	3/25/2012 3/27/2012 4/2/2012 4/12/2012	3/2014 7/2014	Mean	4.5	17.5		61.6		91.9	102.8	
				% CV	112.9	54.9		31.3		13.9	2.9	

Reference product release at pH 6.8 from in-house ANDAs

(b) (4)

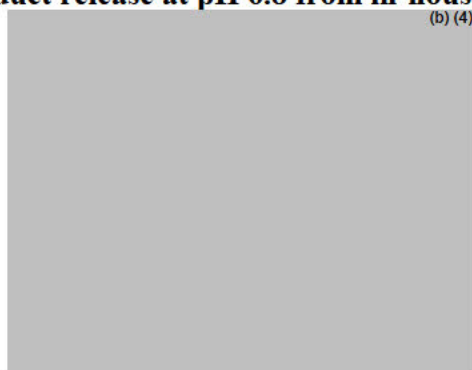
Per NDA 22000 review, there was an increase of the 2 h dissolution value with the storage time and temperature under pH 7.2. We do not have RLD dissolution profiles in the NDA 022000 submission to verify the RLD product performance at pH 6.8.

In addition, we notice significant high variability profiles of test product in pH 6.8, compared with other in-house ANDAs.

Table 66: 0.1N HCl Followed by pH 6.4 Phosphate Buffer and pH 6.8 Phosphate Buffer (Test Products)

ANDA #	unit #	Testing Date	Mfg Date		Collection Times (hr)							
					1	2	3	4	5	6	8	10
(b) (4)												
203574	24	101/12 10/2/12	8/2012	Mean	12	28	50	75		100	102	
				% CV	11.4	7.9	5.5	4.3		1.4	0.8	
091640	24	4/7/2012 4/12/2012	3/2012	Mean	2.7	5.1		28.4		70.9	98.2	
				% CV	87.1	71.7		62.1		24.1	5.4	

Test product release at pH 6.8 from in-house ANDAs



(b) (4)

It is noted the firm's dissolution testing were conducted on 2 or 3 separate dates for test product and 4 separate dates for the two lots RLD product. Day-to-Day variability is observed in the data, e.g. Test product at pH 6.8, which is much higher than the observed value for ANDA 204304 (testing were conducted on 5 separate dates).

Thus we currently could not judge the cause for such high variability on its test product. The firm should be requested to provide the method validation report, which should include precision and accuracy. In addition, to further investigate the observed high variability, the firm should also be requested to validate its method's system robustness to cover any possible deviation (e.g. buffer pH, operator, temperature, etc.). When the method is optimized, the firm should re-conduct the comparative dissolution testing on both test and RLD products at pH 6.5, 6.8, (b) (4) 7.2 and 7.5 after pretreatments with 0.1 N HCl (2 hrs) and pH 6.4 Phosphate Buffer (1 hr).

PK Parameters

Fasting Condition

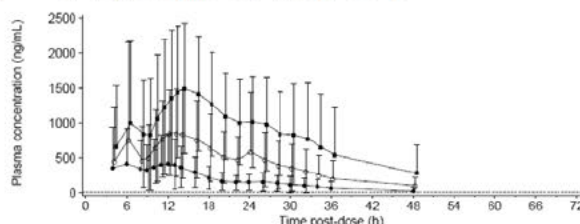
NDA 02200

Table 8: Mean (SD) PK parameters for 5-ASA following single dose administration of SPD476 under fasting conditions

Parameter ¹ of 5-ASA	SPD476 1.2g (N = 47)	SPD476 2.4g (N = 48)	SPD476 4.8g (N = 48)
AUC _{0-t} (ng.h/mL)	9039 [†] (5054)	20538 (12980)	41434 (26640)
AUC _{0-∞} (ng.h/mL)	9578 [‡] (5214)	21084 [§] (13185)	44775 [#] (30302)
Cmax (ng/mL)	857 (638)	1595 (1484)	2154 (1140)
Tmax* (h)	9.0** (4.0-32.1)	12.0 (4.0-34.1)	12.0 (4.0-34.0)
Tlag* (h)	2.0** (0-8.0)	2.0 (1.0-4.0)	2.0 (1.0-4.0)
t½ (h) (Terminal Phase)	8.56 [‡] (6.38)	7.05 [§] (5.54)	7.25 [#] (8.32)

¹Arithmetic mean of parameter values are presented except for Tmax and Tlag.

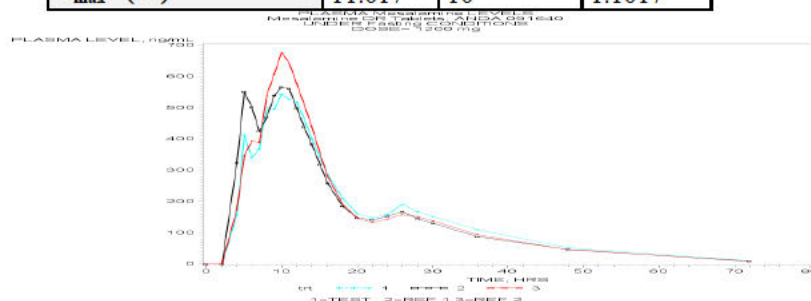
*Median (min, max); [†]N=43, [‡]N=27, [§]N=33, [#]N=36, **N=46



ANDA 091640

Fasting Bioequivalence Study, Study No. MSN-P2-480			
	Test	Reference#	Ratio T/R
AUC _{0-t} (hr *ng/ml)	9855.111	10116.06	0.974204

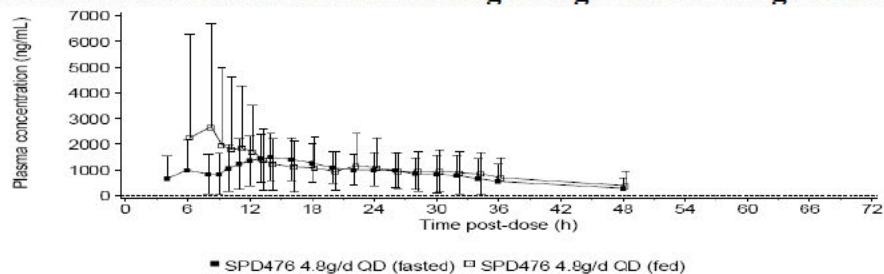
AUC _{0-48 hr} (hr *ng/ml)	7731.560	7800.737	0.991132
C _{max} (ng/ml)	1046.926	1207.07	0.867328
T _{max} * (hr)	11.017	10	1.1017



Fed Condition
NDA 02200

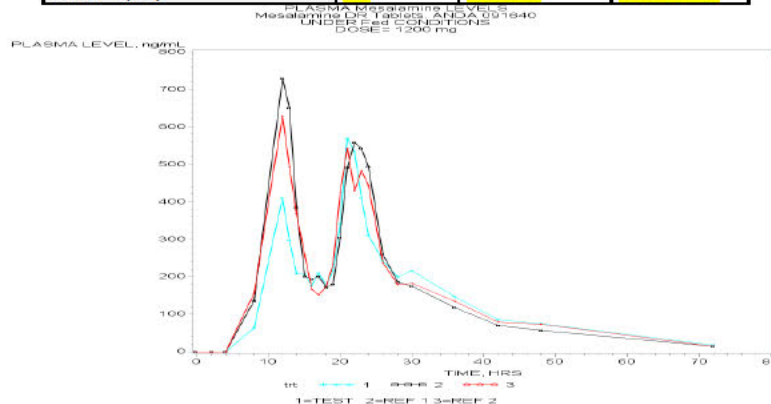
Parameter ¹ of 5-ASA (Single dose)	SPD476 2.4g (N = 28)	SPD476 4.8g (N = 28)
AUC _{0-t} (ng.h/mL)	18573 [†] (10969)	47785 (22421)
AUC _{0-∞} (ng.h/mL)	19852 [†] (11740)	48141 [#] (25627)
Cmax ² (ng/mL)	2932 (2957)	4385 (3033)
Tmax (h)	8.04 (4.00-48.0)	8.04 (6.00-32.1)
Tlag (h)	4.00 (1.99-18.0)	4.00 (2.00-16.0)
t _{1/2} (h) (Terminal Phase)	7.41 [†] (4.65)	6.28 [#] (5.31)
Σxu ³ (g)	0.0388 (0.0442)	0.156 [†] (0.121)
% Dose Absorbed ⁴	25.2 (10.4)	27.0 [†] (12.6)

Mean Plasma concentration following a single dose of 4.8 g Lialda®



ANDA 091640

Fed Bioequivalence Study, Study No. MSN-P3-482			
	Test	Reference#	Ratio T/R
AUC _{0-t} (hr *ng/ml)	9245.433	10491.365	0.881242
AUC _{0-48 hr} (hr *ng/ml)	8314.508	9454.29	0.879443
C _{max} (ng/ml)	1648.092	1890.429	0.871808
T _{max} * (hr)	21	17.279	1.215348

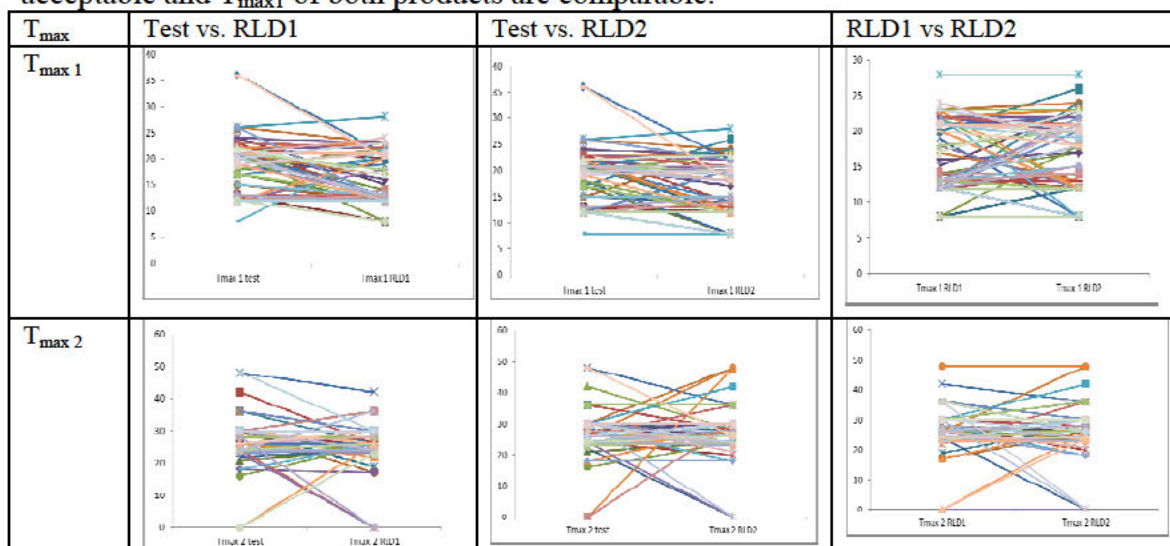


Justification for T_{max} difference:

- Most individual profiles showed C_{max} at the earlier T_{max} for both products. Thus, the difference observed on median T_{max} is further compared with T_{max1} and T_{max} in mean and %CV. As shown in the table below, both products were highly variable for Parameters T_{max} and T_{max1} , which was also observed in NDA study's plasma concentration profiles. Due to the study product's prolonged absorption process, the reviewer compared T_{max} values between Test and Reference product by ratio instead of difference.

Product	Mean (%CV)			Median		
	T_{max}	T_{max1}	T_{max2}	T_{max}	T_{max1}	T_{max2}
Test Product	19.88 (32.72%)	18.59 (31.19%)	27.98 (21.78%)	21	20	28
Reference Product 1	17.43 (33.75%)	16.28 (30.48%)	27.38 (20.23%)	17	14	26
Reference Product 2	18.09 (42.76%)	16.60 (32.58%)	28.54 (24.14%)	17.5	17	26
Ratio (Test/Ref1)	114.06%	114.19%	102.19%	123.53%	142.86%	107.69%
Ratio (Test/Ref2)	109.89%	111.99%	98.04%	120.00%	117.65%	107.69%
Ratio(Ref1/Ref2)	96.35%	98.07%	95.94%	97.14%	82.35%	100.00%

- The stick plots below show that the observed within subject difference of T_{max2} between the test and RLD product is also shown when compared between the RLD treatments. However, for T_{max1} , test and RLD products are comparable except two subjects (b) (6) and (b) (6), which had significant late peak (at 36 hrs) for the test product. In NDA 022000's single dose PK study under fasting condition, it is reported that some subject had a very late peak around 30 hours (Reported T_{max} range 4-32.1 hr). There is no validated Fed study conducted on 1.2 g in NDA 02200, but on 2.4 g (The T_{max} reported in the study was in range of 4 to 48 hours). Thus, the observed significant late peak of 36 hours is acceptable and T_{max1} of both products are comparable.



- The PK parameters of the fasting study are comparable to the fasting study on 1.2 g in NDA 022000. The reviewer could not locate any PK parameters for single dose of 1.2 g under fed condition in the NDA submission, but the Lialda® label states that high fat meal resulted in further delay in absorption. Per Lialda® Label, the recommended dosage is 2.4 g or 4.8 g given once daily.

4. We observed that the RLD seems high variable from batch to batch, not only in dissolution rate but also in T_{max} (see summary in section 5). Although the T_{max} of the test product in pivotal fed study is slightly different from that of the RLD, it is still similar to the T_{max} of the RLD from different batch (Batch LC089A) used in failed study (MSN-P2-602) of the current ANDA. Furthermore, the T_{max} of the test product (21 hours) of the current ANDA is also comparable to the T_{max} of the RLDs under fed condition in ANDA (b) (4) and (b) (4). Therefore, the difference of T_{max} between the test and the reference product is considered small and within the variability range of the reference product.

Based on the above reasons, the T_{max} difference between the test and reference products might not cause difference of the drug amount delivered to the site of action in health subjects.

Failed pilot fed studies

In each pilot fed BE study, the within-subject variability (standard deviation) for the Reference product, SWR, was > 0.294 for all PK parameters of mesalamine. The statistical analysis results indicate that the Test Product, Zydus's Mesalamine Delayed-Release Tablets 1.2 g is bioequivalent to the Reference product (RLD), LIALDA[®] (Mesalamine) Delayed-Release Tablets 1.2 g, in both fed studies, in terms of AUC_{0-t} and AUC_{8-48hr} of mesalamine, but not for C_{max} .

The reviewer summarized the comparison of the three fed studies along with the T_{max} data below:

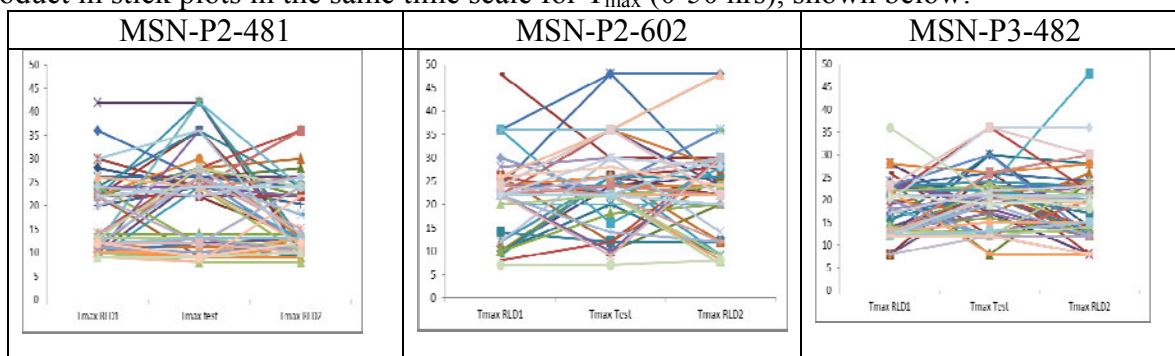
Application #		ANDA 091640			ANDA 203574	NDA 022000
Fed Study #		MSN-P2-481 (Pilot)	MSN-P2-602 (Pilot)	MSN-P3-482 (Pivotal)	MES/2010/616 (Pivotal, 2.4 g)	476-105 (2.4 g)
# of Plasma Time Points Sampling		26	22	24	24	28
Time Points		0, 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 20, 22, 24, 26, 28, 30, 36, 42, 48, 72	0, 2, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 36, 42, 48	0, 2, 4, 8, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, 28, 30, 36, 42, 48, 72	0.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 11.0, 12.0, 13.0, 14.0, 15.0, 16.0, 17.0, 18.0, 19.0, 20.0, 22.0, 24.0, 30.0, 36.0, 48.0, 72.0	0, 1, 2, 4, 6, 8, 9, 10, 11, 12, 13, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 48, 60, 72, 96, 120
T_{max} , Medium (Range)	Test	24 hr (8-42 hr)	24 hr (7-48 hr)	21 hr (8-36 hr)	16 hr (6-36 hr)	N/A
	RLD	14 hr (8-42 hr)	22 hr (7-48 hr)	17 hr (8-48 hr)	16.5 hr (6-36 hr)	8.04 (4-48 hr)

It seems that after the 1st pilot study failed, the firm tried to re-conduct the BE study using different batch of RLD product (LC089A), which showed similar slower release in its in vitro BE dissolution testing. However, the 2nd study MSN-P2-602 still failed on C_{max} , which indicate the reference variability (showed in in vitro dissolution) is not the key reason for the failure of

bioequivalence of C_{max} . **The insufficient sampling time is the reason.** In addition, the pilot study MSN-P2-602 had sampling time points up to 48 hours, which did not meet the recommendations of 72 hours in DB Draft Guidance on Mesalamine.

It is very interesting that although 2nd study MSN-P2-602 failed the 90% CI for C_{max} , it showed a more similar T_{max} (24 hours) to that of reference (22 hours). The reviewer also noticed that comparing to Batch FC207A (used in pivotal fed study), Batch LC089A (used in MSN-P2-602) has a more similar dissolution release profile as the test product, i.e. both of them showed slower release.

Thus, the reviewer compared the observed T_{max} in these three studies for both test and reference product in stick plots in the same time scale for T_{max} (0-50 hrs), shown below:



As shown above, pilot study MSN-P2-481 had big gap for observed T_{max} between 14 to 20 hours for both test and reference product. Due to the dual peak profiles for the study product, without dense timing sampling at Peak 1 period (5 time points)³⁷, the observed T_{max} might be reported by the 2nd Peak T_{max} . Thus, from the observed T_{max} in Pivotal Fed study MSN-P3-482, the reviewer agrees with the firm's statement that insufficient sampling frequency around the T_{max} caused the failure of C_{max} estimation. Similar gap of T_{max} was also observed in pilot study MSN-P2-602, which had only time points 4 time points between 14-20 hours. This conclusion is further supported by the fact the T_{max} of 21 hours (test) and 17 hours (RLD) are right at two new sampling points in the pivotal study MSN-P3-482.

The firm states that *"The Reference Batch FC207A showed much more rapid dissolution at pH 6.5 and pH 6.8 than the Test Batch EMM196. This may explain the early absorption of mesalamine (in the proximal small intestine) and greater subjects with much earlier T_{max} associated with the Reference product in Study MSNP2- 481."* The reviewer summarized some Fed studies T_{max} results from the in-house ANDAs. It seems the slower release of RLD product also had later T_{max} median in BE study under Fed condition. However, it should be noted that the T_{max} results might also be impacted by food interaction from the given breakfast, study subject GI condition, firm's analytical method, BE study sampling time points, etc. In addition, different analytical lab's practice on dissolution might also impact the dissolution result.

³⁷ As per Lialda® label, plasma concentrations of mesalamine reached a maximum by 9-12 hours on average for the doses studied.

Observed $T_{\max}$ from in-house ANDAs Fed Studies

In vitro BE dissolution at pH 6.8	ANDA # (Dose)	Observed Tmax (Median, hr)
(b) (4)	203574 (2.4 g)	16.50
	91640 (1.2 g, FC207A)	14/17.279
	91640 (1.2 g, LC089A)	22
	(b) (4) (1.2 g)	24
	(1.2 g)	21/22

In Summary, based on above discussion, the two pilot BE studies failed 90% CI for $C_{\max}$ due to insufficient sampling time points to estimate the $C_{\max}$.

Management Decision

- 1) The firm should be requested to validate its in vitro BE dissolution method and re-conduct its study for the evaluation stage of pH 6.8.
- 2) The firm should be requested to conduct in vitro BE dissolution Study for additional evaluation stage of pH (b) (4)
- 3) The observed $T_{\max}$ difference in the Fed Study MSN-P3-482 is acceptable.
- 4) The firm's failed pilot BE studies under Fed condition is deemed acceptable.

³⁸ The application is pending DB review.

³⁹ The application is currently refused to file as the firm did not include all the completed subjects in its statistical analysis.

4.7 SAS Output

4.7.1 Fasting Study Data

Fasting CONCENTRATION DATASET

Obs	sub	sequ	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
1	(b) (6)	ABB	1	A	0.00	0.00	88.37	3610.45	5098.51	1482.85	724.17	501.94	341.87	202.65	191.52	205.64	178.31	167.56	160.14
2		ABB	2	B1	0.00	3.23	425.37	5495.36	3173.76	1294.75	607.91	513.98	497.61	459.03	373.73	323.60	274.57	204.72	190.83
3		ABB	3	B2	0.00	0.00	28.70	2817.92	5404.78	1638.05	779.11	456.17	282.02	202.49	149.86	188.63	209.87	204.27	191.21
4		BBA	1	B1	0.00	0.00	26.59	702.37	193.04	259.57	286.82	398.42	432.69	541.05	524.06	508.81	455.85	451.35	433.52
5		BBA	2	B2	0.00	0.00	5.17	5.28	4.61	73.88	273.91	627.68	905.48	833.20	608.12	620.96	557.42	526.48	326.76
6		BBA	3	A	0.00	0.00	0.00	0.00	0.00	0.00	9.11	99.39	173.36	249.90	413.54	463.23	429.77	421.91	344.24
7		BAB	1	B1	0.00	0.00	1901.67	2877.55	2373.00	594.59	186.36	104.33	74.27	90.40	97.09	293.24	303.43	308.04	249.20
8		BAB	2	A	0.00	0.00	487.33	207.55	127.67	109.24	153.85	134.80	119.08	129.56	129.88	194.48	242.19	207.56	145.44
9		BAB	3	B2	0.00	0.00	112.74	632.99	1934.49	1421.59	671.54	397.04	386.44	397.35	376.83	318.93	322.32	294.07	238.95
10		BAB	1	B1	0.00	0.00	0.00	4.91	143.43	109.11	49.48	49.59	198.43	270.97	220.69	179.73	112.04	93.40	77.85
11		BAB	2	A	0.00	0.00	0.00	0.00	16.63	52.23	111.05	130.22	128.17	165.76	206.50	192.43	180.40	187.52	180.35
12		BAB	3	B2	0.00	0.00	139.93	552.67	221.17	222.50	348.50	372.97	334.70	342.08	244.23	196.24	170.07	108.82	59.16
13		ABB	1	A	0.00	0.00	0.00	0.00	5.38	84.34	149.73	152.85	150.41	156.99	114.82	137.02	141.89	127.21	141.57
14		ABB	2	B1	0.00	0.00	0.00	6.93	5.94	17.08	17.71	22.71	26.47	39.72	58.52	65.39	79.38	92.91	100.76
15		ABB	3	B2	0.00	0.00	0.00	2.70	5.10	72.89	197.21	243.58	274.08	438.25	329.39	460.27	448.49	286.55	185.31
16		BBA	1	B1	0.00	0.00	0.00	484.90	1486.11	4370.96	4582.53	4538.97	4310.88	2437.57	1222.22	552.79	337.19	222.69	122.01
17		BBA	2	B2	0.00	0.00	0.00	0.00	233.26	1742.34	4341.62	4164.21	4277.03	2687.56	1592.68	1368.31	770.18	503.71	365.22
18		BBA	3	A	0.00	0.00	344.17	1934.49	3574.24	1424.59	795.75	1496.89	1942.94	1673.76	1458.22	840.56	557.33	314.18	225.97
19		ABB	1	A	0.00	0.00	0.00	122.18	247.34	411.88	598.80	898.41	968.97	709.73	549.03	601.14	422.44	350.73	219.36
20		ABB	2	B1	0.00	0.00	88.25	174.48	328.07	511.92	694.06	868.10	921.18	931.11	922.34	828.94	639.42	592.20	517.09
21		ABB	3	B2	0.00	0.00	6.81	117.54	1497.93	1049.12	927.10	1065.49	1245.62	946.16	614.60	597.60	420.39	285.48	199.11
22		BAB	1	B1	0.00	0.00	0.00	546.33	1407.09	432.03	486.67	524.42	574.34	599.56	567.05	464.37	423.96	365.66	296.38
23		BAB	2	A	0.00	0.00	4.81	49.70	161.14	502.02	937.17	1034.60	1301.49	1099.29	1016.50	929.13	665.68	504.85	465.65

Obs	sub	sequ	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
24	(b) (6)	BAB	3	B2	0.00	0.00	526.83	285.77	636.64	717.94	1464.73	1533.25	1566.70	1431.38	1221.76	1158.38	928.30	763.43	677.60
25		BBA	1	B1	0.00	0.00	0.00	52.14	15.05	49.56	66.49	140.16	144.66	175.35	126.91	125.38	98.07	99.74	81.71
26		BBA	2	B2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	3.24	3.81	7.69	10.88	11.42	11.71	15.62
27		BBA	3	A	0.00	0.00	12.81	405.87	120.30	435.69	503.94	517.60	449.90	324.77	301.44	228.66	215.02	189.43	160.42
28		ABB	1	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	3.84	14.56	65.50	146.91	176.42	186.16	213.41
29		ABB	2	B1	0.00	3.76	598.33	449.13	126.71	615.64	829.08	881.42	764.81	719.89	568.31	545.21	497.03	328.79	241.72
30		ABB	3	B2	0.00	5.14	382.13	197.51	121.12	486.66	883.08	908.05	884.47	706.42	605.50	528.31	394.57	247.86	195.29
31		BAB	1	B1	0.00	0.00	177.08	148.84	5372.55	923.36	623.73	359.27	348.49	379.37	353.49	319.71	311.27	220.64	180.90
32		BAB	2	A	0.00	0.00	0.00	66.22	137.34	447.06	540.70	558.71	535.36	500.17	628.65	413.74	293.67	187.36	128.21
33		BAB	3	B2	0.00	0.00	67.52	646.14	298.96	583.20	746.97	779.66	796.48	605.27	466.83	388.76	314.37	196.10	146.87
34		BBA	1	B1	0.00	0.00	257.85	119.36	283.67	656.59	873.48	1151.87	908.54	774.62	546.83	459.62	376.58	244.79	152.62
35		BBA	2	B2	0.00	0.00	109.51	178.79	359.14	571.42	913.29	977.39	916.94	1007.09	949.01	636.81	519.18	324.68	209.82
36		BBA	3	A	0.00	0.00	267.74	167.49	268.28	469.86	585.78	801.08	811.93	631.80	542.89	508.76	398.86	278.97	221.14
37		ABB	1	A	0.00	0.00	0.00	0.00	5.21	6.27	32.98	64.86	90.17	140.65	160.06	218.24	287.75	301.78	299.47
38		ABB	2	B1	0.00	0.00	3131.63	1170.60	910.73	832.80	952.06	840.30	682.88	686.06	645.84	462.76	382.31	245.30	167.14
39		ABB	3	B2	0.00	0.00	19.67	1862.91	564.90	387.32	360.10	407.61	651.96	1028.79	1094.99	837.63	760.72	673.98	420.23
40		BAB	1	B1	0.00	0.00	527.87	788.52	152.32	93.34	174.68	422.97	627.83	725.29	501.66	444.52	391.20	351.21	208.68
41		BAB	2	A	0.00	0.00	0.00	85.57	38.11	92.78	256.80	448.77	441.79	444.16	402.94	426.88	491.95	362.74	254.74
42		BAB	3	B2	0.00	0.00	0.00	49.57	35.05	157.15	603.66	1138.92	1348.81	1010.86	831.35	742.72	646.35	474.96	336.93
43		ABB	1	A	0.00	0.00	0.00	0.00	8.63	52.40	80.53	204.26	355.56	346.81	339.69	213.95	269.70	230.79	137.74
44		ABB	2	B1	0.00	0.00	14.56	36.23	91.39	514.02	595.31	814.98	1210.58	858.18	718.59	591.05	379.82	215.39	177.75
45		ABB	3	B2	0.00	4.48	6.74	13.08	36.11	203.85	616.83	585.67	706.16	735.21	744.29	568.73	438.64	302.42	210.01
46		BBA	1	B1	0.00	0.00	53.88	51.02	27.82	22.67	392.00	456.99	488.68	479.46	548.77	604.04	577.36	578.20	554.05
47		BBA	2	B2	0.00	0.00	0.00	28.91	187.50	28.63	210.88	410.32	487.41	378.48	325.15	374.29	379.71	400.80	416.45
48		BBA	3	A	0.00	0.00	383.11	798.64	490.63	393.07	514.32	688.65	759.97	811.29	765.18	677.35	567.54	418.78	328.45
49		BBA	1	B1	0.00	0.00	0.00	4.26	145.00	250.88	135.79	74.92	211.58	354.12	333.38	326.16	330.57	276.33	244.75
50		BBA	2	B2	0.00	0.00	0.00	39.82	121.19	94.85	28.95	14.51	21.69	210.11	188.87	185.60	173.10	163.58	146.22
51		BBA	3	A	0.00	0.00	0.00	0.00	5.47	3.34	18.68	43.36	53.41	88.89	123.44	128.16	115.89	128.74	124.34
52		ABB	1	A	0.00	0.00	0.00	17.89	190.58	316.53	423.17	486.43	474.01	420.88	385.44	359.91	372.14	362.45	306.50

Obs	sub	sequ	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
53	(b) (6)	ABB	2	B1	0.00	0.00	196.36	191.77	594.64	1097.64	995.90	962.83	734.58	678.79	608.03	472.17	319.32	332.69	257.26
54		ABB	3	B2	0.00	0.00	514.52	1478.72	375.36	672.24	1008.33	1302.00	1377.60	1445.82	1115.48	915.42	642.34	485.02	395.64
55		BAB	1	B1	0.00	0.00	493.93	327.72	210.54	30.55	10.87	4.74	3.05	0.00	0.00	0.00	0.00	0.00	0.00
56		BAB	2	A	0.00	0.00	0.00	0.00	13.80	1152.70	1201.85	386.13	534.21	519.08	606.85	530.42	392.72	287.00	236.83
57		BAB	3	B2	0.00	0.00	0.00	0.00	0.00	70.52	72.47	79.63	82.83	236.99	178.19	134.27	122.07	115.28	125.23
58		BBA	1	B1	0.00	0.00	1842.76	921.37	337.86	279.38	547.04	911.29	761.63	732.52	579.39	495.90	440.44	369.54	270.36
59		BBA	2	B2	0.00	0.00	298.30	409.17	265.10	266.62	365.46	498.23	544.73	621.78	484.61	450.27	461.28	334.13	311.47
60		BBA	3	A	0.00	0.00	431.84	186.93	229.24	248.26	428.14	362.01	336.66	295.13	278.98	310.99	286.63	270.65	230.71
61		ABB	1	A	0.00	0.00	26.68	242.07	448.66	590.49	571.62	774.86	818.49	733.65	759.99	529.90	393.73	289.95	200.12
62		ABB	2	B1	0.00	0.00	0.00	610.51	1928.30	492.98	319.28	579.37	1074.45	1084.58	946.74	539.35	499.48	348.41	264.78
63		ABB	3	B2	0.00	0.00	0.00	5.29	48.48	171.16	359.04	463.45	662.90	783.13	936.53	893.85	747.40	685.94	328.71
64		ABB	1	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	3.17	13.92	98.85	181.03	269.80	341.97	506.00
65		ABB	2	B1	0.00	0.00	0.00	740.10	343.70	551.28	746.37	980.09	959.29	1211.30	932.07	627.95	468.30	346.59	266.52
66		ABB	3	B2	0.00	0.00	0.00	179.48	93.20	71.43	43.65	32.43	43.56	81.62	165.74	265.07	316.66	369.23	411.67
67		BBA	1	B1	0.00	0.00	1654.68	626.92	226.77	136.76	107.87	106.25	285.31	739.41	733.11	608.77	704.95	504.28	354.67
68		BBA	2	B2	0.00	0.00	15.17	50.76	81.26	71.38	193.54	512.37	661.34	841.72	813.13	524.68	432.72	347.40	278.82
69		BBA	3	A	0.00	0.00	62.35	197.59	246.72	324.81	520.42	723.27	767.66	752.95	674.76	579.16	564.50	521.44	455.92
70		BAB	1	B1	0.00	0.00	0.00	282.74	1157.73	1970.21	1785.52	1494.97	697.10	408.11	420.67	362.84	338.62	309.04	291.88
71		BAB	2	A	0.00	0.00	0.00	16.44	543.46	896.18	604.36	329.69	246.88	191.10	338.18	498.36	429.20	447.24	292.75
72		BAB	3	B2	0.00	0.00	29.91	733.04	1772.24	1058.68	3193.33	2160.65	1479.79	546.65	650.28	502.76	519.49	365.18	288.08
73		BBA	1	B1	0.00	0.00	161.59	166.76	174.76	409.00	752.25	1023.07	1000.02	695.29	710.68	516.88	367.09	288.88	179.64
74		BBA	2	B2	0.00	0.00	121.86	114.31	252.85	390.73	633.91	947.46	941.45	946.79	951.18	697.91	623.78	469.88	317.47
75		BBA	3	A	0.00	0.00	0.00	30.34	126.89	242.33	227.00	194.98	295.99	539.45	768.63	798.98	850.49	823.30	889.94
76		ABB	1	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.91	9.57	43.97	53.85	88.07	143.97
77		ABB	2	B1	0.00	0.00	416.72	143.57	123.36	192.15	203.27	211.16	223.32	222.78	258.13	226.11	228.86	197.28	220.45
78		ABB	3	B2	0.00	0.00	5.25	53.27	24.91	112.91	150.32	199.65	245.21	246.98	392.36	425.67	338.89	313.21	279.40
79		BAB	1	B1	0.00	0.00	24.95	13.27	35.88	81.10	158.47	455.11	770.88	843.58	683.04	482.63	472.41	425.67	237.15
80		BAB	2	A	0.00	0.00	12.39	6.31	14.86	13.37	10.21	7.48	36.83	189.55	239.19	344.57	392.43	426.13	444.69
81		BAB	3	B2	0.00	0.00	57.32	20.41	59.93	138.08	333.01	851.94	1101.62	1151.38	914.79	620.87	541.09	385.37	264.85

Obs	sub	sequ	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
82	(b) (6)	BBA	1	B1	0.00	0.00	0.00	4.05	10.12	28.04	117.60	227.14	173.95	176.09	158.00	155.59	166.04	157.92	161.37
83		BBA	2	B2	0.00	0.00	153.32	271.32	420.52	441.42	536.44	372.35	363.65	387.23	209.62	174.07	99.41	74.10	56.41
84		BBA	3	A	0.00	0.00	0.00	6.82	41.35	55.49	80.61	101.40	145.73	328.88	440.13	537.89	581.89	591.63	555.74
85		BAB	1	B1	0.00	0.00	45.73	691.12	176.72	97.05	246.65	428.74	529.74	480.21	399.22	329.88	296.67	303.18	234.70
86		BAB	2	A	0.00	0.00	206.03	1383.00	358.78	248.47	319.04	527.76	548.41	483.93	363.62	341.59	355.91	259.47	234.78
87		BAB	3	B2	0.00	0.00	757.48	888.44	215.14	318.55	504.31	612.14	624.24	550.09	464.71	516.80	458.33	466.26	405.15
88		ABB	1	A	0.00	0.00	830.93	4486.72	1387.05	896.42	773.61	765.84	641.05	627.84	487.93	280.09	206.46	150.79	59.86
89		ABB	2	B1	0.00	0.00	9.03	819.82	446.99	358.06	299.55	348.56	401.40	360.98	413.74	460.72	449.41	425.86	344.40
90		ABB	3	B2	0.00	0.00	0.00	65.94	67.96	250.78	986.50	1407.15	1295.92	1445.81	1228.17	1043.60	884.01	619.74	285.00
91		BBA	1	B1	0.00	0.00	0.00	0.00	0.00	0.00	4.11	11.40	41.95	86.92	121.08	177.71	202.52	252.02	309.22
92		BBA	2	B2	0.00	0.00	0.00	81.14	787.42	2031.32	561.08	539.50	662.83	855.11	769.65	704.29	540.45	526.11	396.06
93		BBA	3	A	0.00	0.00	0.00	67.06	328.57	142.50	45.98	66.49	114.63	249.86	570.21	712.06	804.78	796.24	683.08
94		BAB	1	B1	0.00	0.00	34.14	114.21	50.06	12.33	150.44	455.85	602.59	703.91	660.87	516.85	422.63	359.67	289.58
95		BAB	2	A	0.00	0.00	0.00	0.00	28.74	25.51	10.08	39.96	102.77	139.02	135.23	164.31	146.48	213.32	236.57
96		BAB	3	B2	0.00	0.00	0.00	0.00	275.35	195.11	421.11	278.10	231.80	248.33	182.64	142.07	109.37	106.29	76.45
97		ABB	1	A	0.00	0.00	0.00	0.00	11.70	22.91	44.82	75.61	66.15	121.58	90.27	62.67	113.13	102.50	96.65
98		ABB	2	B1	0.00	0.00	0.00	334.50	1280.98	458.74	144.88	109.80	150.19	145.05	119.50	123.36	98.74	101.44	105.21
99		ABB	3	B2	0.00	0.00	308.62	950.74	293.70	118.28	134.68	400.57	406.05	336.60	263.15	223.50	216.74	181.83	160.40
100		BBA	1	B1	0.00	0.00	65.36	90.19	23.88	33.51	72.34	151.69	308.48	272.96	310.66	295.74	306.61	257.75	204.40
101		BBA	2	B2	0.00	0.00	1032.12	432.14	144.37	113.38	143.32	354.21	541.06	467.47	506.53	421.69	345.32	306.72	232.08
102		BBA	3	A	0.00	0.00	84.30	48.31	58.26	59.77	69.87	177.10	213.50	280.07	306.66	306.68	312.97	291.67	301.98
103		ABB	1	A	0.00	0.00	1885.05	769.24	377.84	222.75	507.86	799.13	739.33	723.95	537.38	504.87	399.81	283.37	178.30
104		ABB	2	B1	0.00	0.00	119.28	748.60	202.67	258.25	508.13	972.47	1132.88	1091.31	896.49	620.58	500.43	291.98	198.66
105		ABB	3	B2	0.00	0.00	3.23	3.53	14.28	47.22	107.27	128.65	186.38	233.37	289.73	359.13	356.98	352.45	383.75
106		BAB	1	B1	0.00	0.00	0.00	0.00	14.00	368.76	1667.77	683.50	783.79	1068.31	957.75	942.99	912.84	810.56	705.11
107		BAB	2	A	0.00	0.00	0.00	314.90	502.03	451.64	331.31	345.07	487.51	494.36	406.45	280.91	173.61	114.90	93.80
108		BAB	3	B2	0.00	0.00	0.00	3.19	151.80	1466.03	1163.66	572.68	703.80	902.72	866.05	823.57	759.55	624.70	514.34
109		BAB	1	B1	0.00	0.00	246.79	150.88	328.81	344.90	754.33	751.03	946.71	803.51	709.86	506.29	403.81	287.96	222.62
110		BAB	2	A	0.00	0.00	21.95	68.58	91.78	259.98	454.76	486.98	548.95	515.17	528.47	538.02	501.76	394.41	315.94

Obs	sub	sequ	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
111	(b) (6)	BAB	3	B2	0.00	0.00	0.00	479.81	111.31	122.12	245.45	414.18	473.12	504.27	507.34	492.14	444.15	353.75	238.99
112		BBA	1	B1	0.00	0.00	7.94	660.75	230.20	391.81	812.98	720.93	813.35	625.41	617.75	550.60	546.40	386.52	325.27
113		BBA	2	B2	0.00	2.76	183.69	1659.32	534.30	384.01	376.54	330.58	350.61	386.85	355.94	422.13	481.33	499.42	409.11
114		BBA	3	A	3.04	3.45	3.65	3.08	338.56	68.83	128.03	177.09	244.28	286.71	466.95	665.46	599.93	558.19	550.16
115		ABB	1	A	0.00	0.00	1826.01	295.05	215.31	302.85	337.14	403.05	364.23	405.33	389.21	257.41	167.06	138.96	115.68
116		ABB	2	B1	0.00	0.00	208.58	216.27	122.27	290.47	447.62	714.20	749.29	655.49	547.04	384.45	218.44	207.66	138.48
117		ABB	3	B2	0.00	0.00	38.54	124.38	272.87	566.37	749.88	729.65	659.91	541.44	645.92	445.41	313.10	197.28	163.88
118		ABB	1	A	0.00	0.00	0.00	0.00	0.00	3.41	4.08	6.37	136.59	303.64	370.43	355.95	440.36	265.53	251.68
119		ABB	2	B1	0.00	0.00	0.00	0.00	8.16	16.78	53.27	210.42	287.65	364.25	341.45	305.85	331.16	264.64	252.28
120		ABB	3	B2	0.00	0.00	174.17	2413.34	779.96	524.28	317.74	338.15	388.02	395.22	471.53	500.29	493.68	545.87	572.63
121		BBA	1	B1	0.00	0.00	4.29	231.27	39.35	19.18	31.46	74.95	104.94	160.72	161.99	209.79	208.07	181.59	193.25
122		BBA	2	B2	0.00	0.00	0.00	2.77	5.63	928.49	4501.98	2329.49	1126.94	778.57	657.83	525.95	426.37	354.81	220.49
123		BBA	3	A	0.00	0.00	4.23	537.76	195.40	238.02	291.30	329.67	357.97	515.88	583.12	400.47	348.40	249.83	158.83
124		ABB	1	A	0.00	0.00	0.00	0.00	0.00	4.38	5.62	5.73	6.60	8.54	10.51	19.80	20.44	50.16	63.34
125		ABB	2	B1	0.00	0.00	0.00	17.79	39.84	92.05	177.72	203.01	296.71	233.43	396.83	341.03	339.23	218.08	158.49
126		ABB	3	B2	0.00	0.00	0.00	105.30	22.86	86.00	145.45	188.57	346.27	440.41	342.08	337.55	263.12	194.53	133.49
127		BBA	1	B1	0.00	0.00	901.08	752.88	193.42	491.25	865.30	1023.68	1161.55	954.46	993.81	765.54	759.45	584.18	515.81
128		BBA	2	B2	0.00	0.00	2706.33	3805.98	988.05	548.86	791.70	799.51	862.06	771.39	665.16	683.43	639.94	533.50	455.44
129		BBA	3	A	0.00	0.00	129.31	3021.02	638.18	607.97	710.34	738.10	861.34	811.28	689.26	574.32	548.08	379.67	276.99
130		BAB	1	B1	0.00	0.00	0.00	5.49	13.65	55.34	132.36	304.55	769.00	920.56	1022.49	823.05	646.71	485.21	284.65
131		BAB	2	A	0.00	0.00	0.00	0.00	0.00	992.35	514.63	615.60	682.83	813.46	721.94	612.07	750.46	616.09	384.45
132		BAB	3	B2	0.00	0.00	11.98	262.14	1080.93	260.37	514.65	1041.07	1180.63	1267.32	1013.32	835.55	761.16	588.15	367.06
133		BBA	1	B1	0.00	0.00	0.00	77.44	100.71	64.10	26.56	56.74	459.58	567.84	575.71	400.55	323.11	245.00	215.22
134		BBA	2	B2	0.00	0.00	0.00	96.11	79.18	18.61	99.52	111.03	77.33	71.09	50.02	40.54	33.91	24.46	19.17
135		BBA	3	A	0.00	0.00	0.00	3.29	0.00	0.00	0.00	35.56	189.59	325.76	422.57	449.36	413.72	405.44	442.20
136		BAB	1	B1	0.00	0.00	339.00	86.74	45.57	187.33	323.82	412.97	715.38	772.67	787.45	684.69	555.09	457.28	296.38
137		BAB	2	A	0.00	0.00	1925.75	578.29	611.73	921.76	1198.62	1265.48	1304.46	927.80	879.25	672.72	520.38	435.59	349.93
138		BAB	3	B2	0.00	0.00	1151.60	478.24	397.17	978.59	1200.19	1418.23	1406.30	1235.85	1040.27	921.83	721.15	636.52	508.24
139		ABB	1	A	0.00	0.00	281.84	1637.30	543.33	145.05	86.04	275.95	333.47	301.58	325.64	299.20	267.05	196.99	162.21

Obs	sub	sequ	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
140	(b) (6)	ABB	2	B1	0.00	0.00	0.00	0.00	14.63	115.08	54.55	71.82	281.16	345.96	417.88	501.52	433.23	323.58	210.09
141		ABB	3	B2	0.00	0.00	0.00	385.44	338.88	95.26	144.26	349.53	402.61	436.17	446.31	432.03	291.92	240.09	183.88
142		BAB	1	B1	0.00	0.00	0.00	0.00	0.00	10.54	42.91	113.41	236.30	204.02	300.62	305.41	229.94	202.98	153.60
143		BAB	2	A	0.00	0.00	0.00	13.48	53.64	143.27	250.94	530.78	795.78	825.57	885.71	1008.76	942.92	807.08	903.84
144		BAB	3	B2	0.00	0.00	62.34	17.59	56.68	593.05	922.40	1012.06	1276.36	1332.81	1135.73	1107.22	939.47	630.77	488.35
145		ABB	1	A	0.00	0.00	1077.52	928.73	541.11	652.94	666.69	591.15	663.59	650.89	556.01	485.53	325.68	314.26	278.93
146		ABB	2	B1	0.00	0.00	2903.83	1333.60	602.58	558.06	623.94	639.24	847.08	1013.09	914.48	1024.43	1082.40	919.98	836.71
147		ABB	3	B2	0.00	0.00	434.74	173.38	207.23	310.28	582.48	659.40	881.90	976.24	945.90	1029.04	849.31	665.11	472.79
148		BBA	1	B1	0.00	0.00	6.27	25.34	60.55	110.52	164.53	317.66	394.51	355.20	435.44	445.36	413.75	373.20	373.11
149		BBA	2	B2	0.00	0.00	13.17	68.88	238.71	776.91	1201.41	1174.68	769.51	593.43	466.30	317.83	225.60	110.89	83.77
150		BBA	3	A	0.00	0.00	0.00	37.87	81.33	179.33	321.40	302.07	298.95	280.67	379.81	309.32	191.88	111.54	74.77
151		ABB	1	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.62	7.16	24.64	79.86	142.63	219.38	224.65	247.09
152		ABB	2	B1	0.00	0.00	0.00	15.68	8.37	89.76	281.80	316.95	267.85	209.63	385.18	408.27	368.49	329.01	340.05
153		ABB	3	B2	0.00	0.00	0.00	0.00	7.50	6.28	14.01	25.21	50.92	82.66	118.54	192.20	256.16	254.90	276.23
154		BAB	1	B1	0.00	0.00	0.00	13.25	129.59	54.25	38.98	76.17	96.95	213.19	306.36	406.20	482.21	526.37	556.00
155		BAB	2	A	0.00	0.00	426.56	2151.77	667.85	468.44	387.21	389.01	406.13	483.24	674.89	595.47	475.71	399.36	321.11
156		BAB	3	B2	0.00	0.00	138.12	417.45	157.77	291.56	427.04	528.79	492.80	461.81	457.43	467.68	413.77	347.70	302.31
157		BAB	1	B1	0.00	0.00	13.13	75.94	50.54	55.01	87.82	146.27	347.25	360.45	380.96	345.81	301.01	249.38	193.43
158		BAB	2	A	0.00	0.00	17.07	514.15	2438.40	2057.70	529.79	262.77	335.55	349.11	331.31	283.68	233.37	185.47	132.82
159		BAB	3	B2	0.00	0.00	0.00	182.47	140.16	110.05	103.76	105.40	119.31	196.20	258.62	293.26	266.64	236.54	220.02
160		BBA	1	B1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	44.34	795.77	462.83	404.90	354.08	295.63	231.24
161		BBA	2	B2	0.00	0.00	13.47	1994.15	436.31	304.99	272.83	357.32	448.99	375.37	338.92	255.80	191.63	151.64	123.90
162		BBA	3	A	0.00	0.00	0.00	90.66	170.09	238.49	331.24	382.74	441.20	503.52	523.50	611.39	593.80	623.94	588.29
163		ABB	1	A	0.00	0.00	30.99	51.81	330.58	433.24	812.10	963.40	782.31	685.71	572.72	386.41	242.30	163.67	113.69
164		ABB	2	B1	0.00	0.00	67.48	156.90	144.09	423.57	563.75	661.03	638.74	590.14	490.42	360.45	256.52	168.77	123.13
165		ABB	3	B2	0.00	0.00	13.59	11.35	60.50	223.73	463.57	588.43	609.79	480.90	472.76	336.53	224.32	152.42	101.43
166		ABB	1	A	0.00	0.00	80.91	63.99	149.55	263.86	268.50	224.42	226.25	247.06	307.49	298.99	321.34	309.26	259.42
167		ABB	2	B1	0.00	0.00	192.73	131.30	55.02	131.22	248.63	447.42	635.06	472.23	414.25	410.79	292.52	182.85	102.73
168		ABB	3	B2	0.00	0.00	17.27	497.47	150.17	396.89	637.53	742.61	740.68	586.30	390.48	398.38	262.95	141.95	86.25

Obs	sub	sequ	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
169	(b) (6)	BBA	1	B1	0.00	0.00	0.00	0.00	4.78	86.76	739.64	1017.04	1387.73	1493.03	1367.96	1236.71	929.12	655.63	355.87
170		BBA	2	B2	0.00	0.00	0.00	2.91	37.30	889.38	1707.78	1951.58	2926.11	2703.44	2367.91	1894.50	1234.58	809.04	554.26
171		BBA	3	A	0.00	0.00	0.00	0.00	18.26	352.12	854.44	1147.74	1354.97	2163.25	1934.99	1695.61	1219.62	854.61	560.67
172		BAB	1	B1	0.00	0.00	0.00	0.00	3.15	23.67	21.54	20.63	70.62	60.53	120.83	116.01	98.22	109.16	73.97
173		BAB	2	A	0.00	0.00	0.00	3.39	4.26	54.59	90.24	87.10	92.67	100.24	133.72	179.53	282.74	266.29	303.40
174		BAB	3	B2	0.00	0.00	0.00	0.00	25.06	116.41	349.77	627.16	644.88	606.50	712.61	746.32	533.00	348.60	254.93

Obs	c16	c17	c18	c19	c20	c21	c22	c23	c24	c25	trt	seq
1	105.91	108.33	121.89	67.60	58.25	105.59	92.73	106.93	58.24	0.00	1	1
2	110.20	110.88	115.24	110.27	99.22	106.63	125.56	183.37	18.71	0.00	2	1
3	154.06	137.00	162.33	138.86	160.80	173.37	188.70	278.03	5.88	0.00	3	1
4	210.33	162.04	143.19	167.99	174.93	148.06	121.19	60.14	25.84	0.00	2	3
5	170.35	116.58	98.69	100.85	116.70	128.83	93.84	96.73	43.27	0.00	3	3
6	281.24	176.64	157.32	257.64	220.81	240.60	199.27	134.55	98.49	8.77	1	3
7	168.37	127.91	133.59	128.02	132.14	119.55	104.65	68.44	70.25	0.00	2	2
8	151.59	120.39	127.35	120.67	138.75	145.63	145.11	90.07	40.75	8.28	1	2
9	163.95	111.29	101.53	106.48	124.05	133.66	121.53	77.98	30.29	5.38	3	2
10	79.56	65.39	48.45	48.97	48.91	48.83	72.75	82.69	3.80	0.00	2	2
11	129.35	86.00	69.11	72.40	101.05	86.16	51.31	27.90	7.24	0.00	1	2
12	28.46	20.18	19.72	30.03	41.08	49.46	50.76	59.16	5.22	0.00	3	2
13	112.26	122.57	120.14	151.41	320.24	455.48	507.03	659.53	171.89	0.00	1	1
14	133.21	145.35	249.98	338.73	443.52	136.41	148.74	122.29	36.28	0.00	2	1
15	109.12	64.43	110.58	94.45	109.26	95.29	108.21	52.40	123.22	19.81	3	1
16	80.81	57.27	39.06	39.56	34.98	33.66	24.57	17.03	12.96	7.26	2	3
17	163.76	93.19	72.58	62.33	56.97	87.11	82.16	40.82	23.16	6.67	3	3
18	128.58	90.60	80.51	82.74	106.92	91.78	75.29	35.28	25.30	0.00	1	3
19	194.74	154.38	150.04	171.83	182.27	148.79	152.55	90.19	43.73	0.00	1	1
20	443.94	339.53	324.30	316.28	321.89	190.81	158.78	53.55	28.40	0.00	2	1
21	151.89	136.41	127.36	137.99	129.22	98.56	99.45	64.89	44.38	0.00	3	1
22	152.02	106.01	62.00	142.47	115.98	160.68	119.08	61.97	20.22	7.23	2	2
23	267.57	163.79	139.25	103.28	110.14	132.95	101.01	84.79	27.99	5.51	1	2
24	508.60	314.45	206.44	339.42	317.64	340.80	269.35	174.05	30.05	5.86	3	2
25	57.46	37.76	42.52	47.90	84.06	92.19	94.13	98.01	224.49	139.46	2	3
26	17.33	26.63	22.70	16.83	72.49	105.50	150.41	176.40	60.08	0.00	3	3
27	162.20	112.99	97.45	126.96	137.51	129.54	156.93	109.52	215.73	114.50	1	3
28	175.77	249.17	350.65	493.18	869.58	112.86	35.20	15.98	2.65	0.00	1	1
29	172.61	98.38	101.72	112.36	148.07	136.11	123.79	83.65	46.03	0.00	2	1
30	128.89	82.73	99.35	81.97	123.11	93.47	89.89	94.16	52.91	0.00	3	1
31	86.15	65.38	72.52	99.12	98.61	90.84	100.90	46.84	35.05	29.49	2	2
32	84.37	62.54	65.99	80.73	87.85	82.23	90.73	89.85	40.71	17.12	1	2
33	89.02	81.79	50.00	46.51	81.72	87.03	97.55	78.33	68.34	9.33	3	2
34	65.99	94.08	83.63	77.40	21.13	27.59	10.59	7.09	3.68	0.00	2	3
35	120.96	93.27	91.29	34.11	13.00	14.08	12.38	7.48	0.00	0.00	3	3
36	171.73	160.82	149.25	98.70	41.76	36.03	44.36	31.58	4.00	0.00	1	3
37	281.12	278.50	287.93	511.40	980.45	742.29	837.56	563.09	11.31	0.00	1	1
38	156.25	143.85	178.23	185.51	242.26	269.98	222.88	240.36	80.67	0.00	2	1
39	278.12	230.44	193.20	207.59	312.50	264.18	452.79	392.56	13.93	0.00	3	1
40	112.42	70.03	73.27	83.71	123.75	110.82	99.32	93.24	46.29	4.27	2	2

Obs	c16	c17	c18	c19	c20	c21	c22	c23	c24	c25	trt	seq
41	152.75	125.64	159.60	117.57	183.37	176.48	170.15	102.75	87.03	7.11	1	2
42	178.22	104.19	95.38	125.89	143.27	168.56	211.74	149.19	83.23	2.78	3	2
43	132.16	89.07	134.08	109.57	98.21	112.07	101.14	51.93	5.16	0.00	1	1
44	121.28	40.38	45.86	51.86	46.51	54.90	34.56	6.75	0.00	0.00	2	1
45	88.61	55.56	69.73	50.67	62.49	82.02	93.09	70.58	8.82	0.00	3	1
46	376.69	289.74	256.10	365.29	316.61	170.56	169.94	39.92	0.00	0.00	2	3
47	356.16	257.90	240.12	362.44	341.00	359.23	323.23	112.69	44.28	0.00	3	3
48	247.03	104.60	113.88	166.76	205.82	182.69	188.93	113.73	32.11	0.00	1	3
49	153.90	121.63	87.06	68.13	92.17	106.23	96.19	100.55	55.01	6.95	2	3
50	115.35	95.68	67.66	84.38	108.15	81.83	72.66	90.79	58.84	0.00	3	3
51	104.74	95.27	89.51	87.71	119.56	108.79	112.98	81.35	49.58	16.89	1	3
52	249.75	186.55	192.39	281.23	272.27	296.97	192.36	139.97	72.71	0.00	1	1
53	171.09	149.19	150.18	86.48	90.49	100.09	24.30	8.61	4.06	0.00	2	1
54	239.25	197.09	178.62	180.44	240.88	229.23	204.98	70.54	35.46	0.00	3	1
55	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2	2
56	157.77	184.94	152.06	62.79	6.03	0.00	0.00	0.00	0.00	0.00	1	2
57	70.64	57.01	48.19	107.61	67.99	62.15	49.28	11.14	0.00	0.00	3	2
58	202.01	158.56	134.97	165.96	231.91	283.66	289.92	56.57	0.00	0.00	2	3
59	250.84	182.35	182.86	261.55	286.56	341.79	154.99	6.71	0.00	0.00	3	3
60	196.06	168.36	202.28	125.30	35.87	39.85	44.15	2.69	0.00	0.00	1	3
61	143.62	126.41	103.67	93.95	128.54	109.30	90.53	51.44	36.82	0.00	1	1
62	273.89	160.26	89.38	60.90	96.10	87.86	61.24	39.66	19.26	5.81	2	1
63	212.36	173.37	88.89	97.76	96.48	98.48	80.88	21.64	7.59	0.00	3	1
64	515.07	536.87	506.44	619.90	648.15	562.05	474.15	403.03	168.71	0.00	1	1
65	224.28	200.23	146.76	139.57	173.20	184.87	137.22	89.87	41.56	0.00	2	1
66	417.43	372.95	481.09	539.34	629.07	697.11	498.48	289.58	151.19	0.00	3	1
67	210.78	127.67	86.15	78.12	82.63	84.00	86.13	55.19	36.56	9.28	2	3
68	192.81	86.08	75.71	60.33	65.39	56.13	62.93	30.49	23.87	11.00	3	3
69	293.06	193.12	157.82	138.89	181.47	168.25	163.86	92.31	54.90	2.74	1	3
70	206.39	115.82	95.38	58.87	75.11	79.05	77.03	39.99	11.19	3.20	2	2
71	202.12	99.56	93.86	101.92	93.12	81.25	88.07	64.40	36.15	10.75	1	2
72	169.12	58.74	42.80	42.72	51.38	49.78	54.93	39.70	7.58	2.69	3	2
73	118.44	85.74	106.56	113.82	95.65	82.45	85.09	62.69	13.68	4.55	2	3
74	159.16	106.89	84.23	120.11	86.39	81.73	86.29	60.63	33.29	3.11	3	3
75	607.74	273.56	215.46	185.58	166.17	158.03	169.48	79.35	67.30	3.88	1	3
76	205.68	219.73	247.46	173.02	404.45	386.05	335.22	231.25	183.27	0.00	1	1
77	200.65	165.40	201.73	277.87	272.10	226.49	212.89	172.03	105.48	0.00	2	1
78	191.94	132.61	161.06	272.06	240.09	153.08	145.07	4.30	0.00	0.00	3	1
79	116.73	167.33	109.20	102.68	97.21	78.08	76.27	40.27	26.04	5.03	2	2
80	365.75	277.85	184.27	330.56	487.00	404.22	209.19	170.08	80.56	7.23	1	2

Obs	c16	c17	c18	c19	c20	c21	c22	c23	c24	c25	trt	seq
81	161.74	122.81	97.42	124.34	122.54	67.96	71.79	53.30	15.60	3.60	3	2
82	162.08	100.07	119.57	136.64	176.30	219.10	191.77	178.58	88.12	0.00	2	3
83	40.77	31.55	25.26	20.20	23.80	20.95	14.91	4.08	3.99	0.00	3	3
84	467.55	346.72	301.79	372.66	353.92	295.40	223.83	64.99	64.14	0.00	1	3
85	156.01	97.28	89.85	99.16	87.93	103.71	69.69	57.65	31.87	0.00	2	2
86	129.94	90.27	86.45	88.46	102.00	94.37	84.48	49.20	21.60	0.00	1	2
87	234.64	160.21	114.14	114.64	125.70	128.25	124.13	72.92	37.63	0.00	3	2
88	40.75	36.58	24.79	35.21	49.24	38.15	43.99	37.96	33.16	0.00	1	1
89	259.99	143.63	124.15	89.97	95.72	99.46	98.43	73.42	60.99	3.43	2	1
90	135.86	88.24	53.67	62.24	91.72	87.72	79.02	82.88	16.75	0.00	3	1
91	376.55	359.56	298.78	278.31	327.28	316.66	263.80	152.70	268.00	48.31	2	3
92	292.08	199.01	97.10	92.23	110.06	103.49	84.02	51.33	14.56	13.86	3	3
93	435.06	222.21	179.22	158.76	162.99	148.63	161.37	123.89	51.10	31.34	1	3
94	221.27	177.15	145.12	120.76	125.02	160.51	137.28	99.06	57.05	24.11	2	2
95	330.55	357.88	379.61	469.20	369.01	307.22	310.56	208.51	169.73	112.00	1	2
96	65.66	72.31	75.80	180.91	238.84	275.79	325.55	283.67	223.61	60.80	3	2
97	96.12	84.18	97.23	92.23	117.35	144.16	148.60	163.41	133.73	48.71	1	1
98	77.70	83.77	81.26	94.12	115.33	168.55	147.65	121.87	100.21	116.82	2	1
99	136.30	113.85	102.37	88.06	103.57	120.54	120.66	167.24	96.98	108.98	3	1
100	113.63	71.59	58.53	58.39	56.09	76.96	47.54	46.31	35.91	10.59	2	3
101	152.66	78.29	68.12	76.27	78.50	89.56	74.25	45.92	50.55	24.44	3	3
102	175.09	131.27	117.36	143.24	172.97	179.21	138.53	128.47	108.44	58.80	1	3
103	85.57	56.74	53.84	75.95	94.99	100.01	100.54	75.09	83.61	0.00	1	1
104	111.03	65.96	49.73	56.35	66.89	62.09	58.07	43.34	32.05	3.29	2	1
105	335.54	395.52	379.41	456.58	377.87	527.28	560.84	35.06	0.00	0.00	3	1
106	492.70	206.96	128.95	117.46	70.29	74.52	32.42	10.70	0.00	0.00	2	2
107	68.10	49.36	40.14	25.49	9.11	9.11	7.45	4.70	0.00	0.00	1	2
108	287.88	216.14	143.60	108.38	114.63	92.39	44.36	17.99	0.00	0.00	3	2
109	128.93	100.01	72.91	76.76	98.83	100.05	87.17	71.14	39.99	0.00	2	2
110	135.55	66.04	70.74	57.00	78.53	78.76	76.61	77.88	7.14	0.00	1	2
111	175.10	75.77	69.45	79.13	71.93	40.48	33.20	29.37	0.00	0.00	3	2
112	158.39	124.05	92.72	110.33	97.23	109.99	75.62	49.94	39.25	24.18	2	3
113	379.61	299.31	274.69	285.15	251.70	239.53	229.48	121.04	85.44	59.42	3	3
114	367.60	339.92	369.93	308.48	315.75	307.54	222.12	148.72	72.45	22.79	1	3
115	72.81	45.64	51.32	38.59	45.20	39.63	38.99	37.52	5.11	0.00	1	1
116	87.44	92.45	68.79	71.25	65.72	65.23	108.93	17.26	4.85	0.00	2	1
117	92.70	85.94	81.69	78.63	58.22	55.06	57.06	56.66	34.75	0.00	3	1
118	214.56	209.89	170.59	161.67	176.11	152.45	109.99	63.52	31.07	11.06	1	1
119	200.55	170.96	182.36	226.94	230.86	245.83	130.98	80.84	29.14	2.72	2	1
120	499.67	459.10	485.05	305.61	194.76	164.38	190.16	50.54	27.70	0.00	3	1

Obs	c16	c17	c18	c19	c20	c21	c22	c23	c24	c25	trt	seq
121	199.84	190.03	172.62	178.21	201.18	179.23	173.83	129.23	99.52	61.07	2	3
122	134.11	55.89	46.93	28.23	23.63	22.98	21.34	15.31	10.01	10.40	3	3
123	120.22	82.39	74.11	46.86	76.29	60.12	54.09	35.14	19.91	11.35	1	3
124	91.99	116.44	104.77	126.25	252.26	30.91	11.57	12.08	7.54	0.00	1	1
125	96.14	79.32	85.01	75.73	127.93	152.45	66.67	34.24	5.94	0.00	2	1
126	82.43	65.16	66.50	130.88	156.10	153.73	163.69	90.79	29.41	0.00	3	1
127	348.55	280.16	168.81	137.11	172.44	135.89	128.05	96.05	53.52	3.30	2	3
128	383.01	336.51	187.24	116.95	119.97	110.67	103.73	100.68	34.91	13.28	3	3
129	152.70	76.81	66.40	63.29	69.77	70.61	93.32	93.31	77.86	0.00	1	3
130	120.14	88.38	77.69	101.90	142.37	110.72	79.61	60.07	21.65	0.00	2	2
131	139.69	110.38	101.01	99.30	120.65	172.96	168.94	115.08	72.47	5.97	1	2
132	191.84	113.42	118.30	112.48	120.31	106.93	79.07	67.25	40.25	0.00	3	2
133	140.15	140.77	124.83	119.50	95.98	77.14	18.41	3.78	0.00	0.00	2	3
134	14.49	13.63	10.93	9.48	10.59	10.07	8.00	4.77	0.00	0.00	3	3
135	365.98	358.14	366.27	249.82	65.10	48.89	43.60	18.85	4.87	0.00	1	3
136	209.06	147.83	99.02	69.50	55.39	53.67	47.05	37.66	35.86	2.90	2	2
137	198.34	156.14	157.02	151.87	170.39	126.83	114.18	116.04	3.75	0.00	1	2
138	212.87	140.34	136.85	196.47	210.83	146.54	61.19	46.30	17.04	0.00	3	2
139	119.94	100.16	79.65	72.93	135.40	103.03	95.57	60.02	53.57	28.30	1	1
140	119.20	106.52	90.90	94.09	102.99	86.25	62.48	55.38	33.62	4.41	2	1
141	90.13	73.37	54.80	60.16	73.90	85.96	64.57	52.87	34.36	0.00	3	1
142	107.45	82.60	95.09	102.38	135.12	157.13	145.68	65.22	37.72	3.64	2	2
143	716.14	354.79	236.15	192.06	346.14	273.58	308.72	258.60	126.51	0.00	1	2
144	253.30	121.16	95.41	89.19	128.64	151.80	97.33	71.15	13.58	0.00	3	2
145	124.78	133.55	84.87	123.98	99.32	82.99	83.96	59.65	5.95	0.00	1	1
146	392.59	209.19	163.67	113.92	96.93	85.54	82.27	44.77	11.53	0.00	2	1
147	385.31	184.22	135.92	99.87	134.94	92.75	97.38	43.87	9.29	0.00	3	1
148	345.11	294.42	220.84	194.78	269.11	223.15	189.15	199.56	133.72	4.47	2	3
149	71.09	109.53	66.72	99.41	95.24	94.11	109.20	98.57	47.51	31.24	3	3
150	80.91	72.39	90.33	96.76	107.55	63.75	57.09	87.15	47.96	0.00	1	3
151	286.52	379.29	478.15	636.50	682.41	566.61	467.92	370.42	208.33	17.66	1	1
152	245.28	216.25	204.67	287.04	290.63	220.53	259.23	170.28	97.18	21.87	2	1
153	282.55	386.95	464.48	657.71	683.53	632.39	575.31	513.13	339.17	0.00	3	1
154	538.32	516.35	549.52	535.09	528.82	460.50	558.71	421.40	3.03	0.00	2	2
155	213.90	149.98	135.12	202.18	118.66	107.76	162.83	21.79	6.16	0.00	1	2
156	266.92	255.81	242.30	299.09	561.41	572.71	487.05	286.37	143.62	0.00	3	2
157	91.80	46.62	44.47	43.81	66.67	56.62	57.61	43.56	19.87	0.00	2	2
158	87.34	53.58	45.30	50.37	76.85	54.58	47.47	27.83	6.48	0.00	1	2
159	132.44	68.19	50.66	60.57	108.36	120.69	97.54	51.43	18.35	0.00	3	2
160	309.88	329.86	285.84	330.33	349.89	324.04	303.09	165.61	115.58	12.90	2	3

Obs	c16	c17	c18	c19	c20	c21	c22	c23	c24	c25	trt	seq
161	105.50	98.90	124.16	114.56	141.03	150.42	158.63	75.57	46.94	28.69	3	3
162	456.49	325.56	248.22	224.55	284.81	273.68	262.32	206.04	119.93	0.00	1	3
163	69.27	43.56	52.01	42.10	77.19	54.00	65.57	55.07	32.57	4.53	1	1
164	76.65	66.65	82.78	67.31	138.92	97.08	107.68	60.60	38.67	0.00	2	1
165	55.42	44.45	38.33	63.25	84.48	59.92	82.13	56.30	26.56	0.00	3	1
166	226.87	239.17	241.99	293.36	488.52	108.22	58.18	29.25	13.36	0.00	1	1
167	53.19	40.63	40.72	51.96	47.71	37.64	26.55	12.29	6.28	3.50	2	1
168	37.22	30.80	29.49	62.35	47.45	42.47	34.37	29.14	7.35	0.00	3	1
169	215.10	133.20	167.57	162.36	150.78	146.18	161.54	75.55	51.35	21.84	2	3
170	213.00	130.57	125.13	199.48	244.78	260.23	144.07	62.68	38.90	16.09	3	3
171	280.19	184.99	175.66	262.73	190.76	215.72	166.50	115.81	50.98	26.54	1	3
172	233.94	132.21	151.17	135.75	180.04	167.79	182.61	112.39	17.04	5.24	2	2
173	252.33	319.07	381.86	377.94	400.55	415.65	273.93	231.64	44.98	0.00	1	2
174	191.82	105.50	126.55	149.85	169.30	156.87	119.73	66.56	29.25	9.97	3	2

Obs	sub	sequ	per	treat	CMAX	TMAX	AUCT	AUC _{0-48hr}	THALF	KE	trt	seq
1	(b) (6)	ABB	1	A	5098.51	6.0000	15894.84	5208.39			1	1
2		ABB	2	B1	5495.36	5.0000	17725.92	6813.58			2	1
3		ABB	3	B2	5404.78	6.0000	17809.48	7516.13			3	1
4		BBA	1	B1	702.37	5.0000	8641.03	7303.19	0.08839	7.8416	2	3
5		BBA	2	B2	905.48	10.0000	8510.11	8281.63	0.04951	13.9989	3	3
6		BBA	3	A	463.23	13.0000	9331.16	8039.49	0.07257	9.5509	1	3
7		BAB	1	B1	2877.55	5.0000	13556.76	4813.90	0.02974	23.3057	2	2
8		BAB	2	A	487.33	4.0000	6548.68	4701.40	0.06579	10.5357	1	2
9		BAB	3	B2	1934.49	6.0000	10867.80	6038.78	0.07432	9.3266	3	2
10		BAB	1	B1	270.97	11.0000	3286.79	3004.60	0.17724	3.9108	2	2
11		BAB	2	A	206.50	12.0000	3229.36	3104.97	0.10931	6.3411	1	2
12		BAB	3	B2	552.67	5.0000	4557.08	3176.60	0.13751	5.0406	3	2
13		ABB	1	A	659.53	36.0000	12989.59	12815.25			1	1
14		ABB	2	B1	443.52	26.0000	5391.26	5352.45			2	1
15		ABB	3	B2	460.27	13.0000	7563.11	5668.63			3	1
16		BBA	1	B1	4582.53	8.0000	25872.46	16996.58	0.02375	29.1861	2	3
17		BBA	2	B2	4341.62	8.0000	24497.28	19989.18	0.05017	13.8157	3	3
18		BBA	3	A	3574.24	6.0000	18800.90	10953.45	0.06757	10.2584	1	3
19		ABB	1	A	968.97	10.0000	9898.08	8817.28	0.06812	10.1760	1	1
20		ABB	2	B1	931.11	11.0000	13480.80	11986.93	0.09697	7.1480	2	1
21		ABB	3	B2	1497.93	6.0000	11881.55	8743.20	0.04211	16.4618	3	1
22		BAB	1	B1	1407.09	6.0000	9799.14	6840.96	0.06705	10.3382	2	2
23		BAB	2	A	1301.49	10.0000	12478.31	10887.65	0.07219	9.6017	1	2

Obs	sub (b) (6)	sequ	per	treat	CMAX	TMAX	AUCT	AUC _{8-48hr}	THALF	KE	trt	seq
24		BAB	3	B2	1566.70	10.0000	20836.92	17243.04	0.09289	7.4620	3	2
25		BBA	1	B1	224.49	48.0000	8909.20	4393.94			2	3
26		BBA	2	B2	176.40	36.0000	3144.06	3144.06			3	3
27		BBA	3	A	517.60	9.0000	12356.31	7160.50			1	3
28		ABB	1	A	869.58	26.0000	5715.72	5715.72	0.14456	4.7950	1	1
29		ABB	2	B1	881.42	9.0000	10656.31	8145.27	0.05418	12.7924	2	1
30		ABB	3	B2	908.05	9.0000	9587.91	7757.61	0.03214	21.5690	3	1
31		BAB	1	B1	5372.55	6.0333	12712.28	4935.15	0.01204	57.5490	2	2
32		BAB	2	A	628.65	12.0000	7544.09	5929.16	0.04215	16.4450	1	2
33		BAB	3	B2	796.48	10.0000	9455.29	6518.61	0.06251	11.0882	3	2
34		BBA	1	B1	1151.87	9.0000	7880.38	5997.24	0.05814	11.9220	2	3
35		BBA	2	B2	1007.09	11.0000	8638.12	6907.86	0.08020	8.6429	3	3
36		BBA	3	A	811.93	10.0000	8001.26	6401.13	0.13298	5.2124	1	3
37		ABB	1	A	980.45	26.0000	16377.52	16348.24	0.25151	2.7559	1	1
38		ABB	2	B1	3131.63	4.0000	18655.81	10568.20	0.05804	11.9428	2	1
39		ABB	3	B2	1862.91	5.0000	17706.74	14657.47	0.20553	3.3726	3	1
40		BAB	1	B1	788.52	5.0000	9062.26	6542.21	0.08760	7.9122	2	2
41		BAB	2	A	491.95	14.1833	8990.68	7518.49	0.07133	9.7170	1	2
42		BAB	3	B2	1348.81	10.0000	12919.02	11343.30	0.11506	6.0242	3	2
43		ABB	1	A	355.56	10.0000	4562.14	4460.85	0.16918	4.0971	1	1
44		ABB	2	B1	1210.58	10.0000	7200.34	6239.20	0.26435	2.6221	2	1
45		ABB	3	B2	744.29	12.0000	7163.74	6583.21	0.13698	5.0604	3	1
46		BBA	1	B1	604.04	13.0000	9488.41	9110.08	0.19978	3.4696	2	3
47		BBA	2	B2	487.41	10.0000	10243.27	9892.79	0.10768	6.4370	3	3
48		BBA	3	A	811.29	11.0333	11966.18	9452.02	0.09945	6.9701	1	3
49		BBA	1	B1	354.12	11.0000	6425.48	5220.09	0.07593	9.1286	2	3
50		BBA	2	B2	210.11	11.0000	4028.49	3758.16			3	3
51		BBA	3	A	128.74	15.0000	4388.67	3569.00	0.04369	15.8656	1	3
52		ABB	1	A	486.43	9.0000	9699.81	8963.23	0.05413	12.8064	1	1
53		ABB	2	B1	1097.64	7.0000	9362.88	6686.34	0.14540	4.7672	2	1
54		ABB	3	B2	1478.72	5.0000	16382.13	12579.87	0.09416	7.3617	3	1
55		BAB	1	B1	493.93	4.0000	1326.84	11.70	0.77426	0.8952	2	2
56		BAB	2	A	1201.85	8.0000	7101.16	5333.73	0.80688	0.8590	1	2
57		BAB	3	B2	236.99	11.0000	2337.82	2231.06	0.22248	3.1155	3	2
58		BBA	1	B1	1842.76	4.0000	13229.57	8653.30	0.21788	3.1813	2	3
59		BBA	2	B2	621.78	11.0000	9268.03	7696.96	0.49870	1.3899	3	3
60		BBA	3	A	431.84	4.0000	5947.56	4421.30	0.36681	1.8897	1	3
61		ABB	1	A	818.49	10.0000	8950.59	7343.54	0.05720	12.1170	1	1
62		ABB	2	B1	1928.30	6.0000	11375.70	7883.43	0.05287	13.1114	2	1
63		ABB	3	B2	936.53	12.0000	8348.74	7944.29	0.12589	5.5061	3	1

Obs	sub	sequ	per	treat	CMAX	TMAX	AUCT	AUC _{8-48hr}	THALF	KE	trt	seq
64	(b) (6)	ABB	1	A	648.15	26.0000	14972.72	14972.72	0.05874	11.8005	1	1
65		ABB	2	B1	1211.30	11.0000	12055.87	10047.61	0.06606	10.4927	2	1
66		ABB	3	B2	697.11	28.0000	14060.84	13694.90	0.06455	10.7385	3	1
67		BBA	1	B1	1654.68	4.0000	10716.33	6667.43	0.05162	13.4281	2	3
68		BBA	2	B2	841.72	11.0000	7137.93	6398.43	0.02889	23.9965	3	3
69		BBA	3	A	767.66	10.0000	11393.79	9569.41	0.09656	7.1786	1	3
70		BAB	1	B1	1970.21	7.0000	11839.24	7363.12	0.07420	9.3419	2	2
71		BAB	2	A	896.18	7.0000	8040.00	5718.94	0.04993	13.8814	1	2
72		BAB	3	B2	3193.33	8.0000	15034.16	9705.43	0.07057	9.8224	3	2
73		BBA	1	B1	1023.07	9.0000	9027.26	7439.47	0.07017	9.8782	2	3
74		BBA	2	B2	951.18	12.0000	10433.64	8739.20	0.08483	8.1711	3	3
75		BBA	3	A	889.94	16.0000	12096.40	10729.18	0.07631	9.0832	1	3
76		ABB	1	A	404.45	26.0000	8208.86	8208.86	0.03618	19.1570	1	1
77		ABB	2	B1	416.72	4.0000	8907.85	7722.06	0.03926	17.6536	2	1
78		ABB	3	B2	425.67	13.0000	5825.22	5551.09	0.47883	1.4476	3	1
79		BAB	1	B1	843.58	11.0000	7340.30	6720.97	0.06207	11.1675	2	2
80		BAB	2	A	487.00	26.0000	10365.11	9253.40	0.08954	7.7411	1	2
81		BAB	3	B2	1151.38	11.0000	9084.40	8373.48	0.07259	9.5493	3	2
82		BBA	1	B1	227.14	9.0000	6344.29	6243.38	0.04426	15.6613	2	3
83		BBA	2	B2	536.44	8.0000	4112.36	2480.90	0.09659	7.1762	3	3
84		BBA	3	A	591.63	15.0000	9884.22	9740.25	0.07344	9.4376	1	3
85		BAB	1	B1	691.12	5.0000	6656.54	5499.73	0.04431	15.6421	2	2
86		BAB	2	A	1383.00	5.0000	7944.11	5485.29	0.07468	9.2810	1	2
87		BAB	3	B2	888.44	5.0000	10499.71	7689.20	0.06350	10.9161	3	2
88		ABB	1	A	4486.72	5.0000	13206.16	4802.77	.	.	1	1
89		ABB	2	B1	819.82	5.0000	9139.48	6575.57	.	.	2	1
90		ABB	3	B2	1445.81	11.0500	11926.17	11048.24	.	.	3	1
91		BBA	1	B1	376.55	18.0000	13109.04	9311.27	.	.	2	3
92		BBA	2	B2	2031.32	7.0000	11674.92	8153.46	0.07583	9.1405	3	3
93		BBA	3	A	804.78	14.0000	10585.82	9035.42	0.03821	18.1402	1	3
94		BAB	1	B1	703.91	11.0000	9194.52	7914.86	0.03877	17.8775	2	2
95		BAB	2	A	469.20	24.0000	13303.18	9862.82	0.01727	40.1317	1	2
96		BAB	3	B2	421.11	8.0000	12849.16	8639.09	0.04344	15.9582	3	2
97		ABB	1	A	163.41	36.0000	7175.48	4929.57	.	.	1	1
98		ABB	2	B1	1280.98	6.0000	9359.51	4608.49	.	.	2	1
99		ABB	3	B2	950.74	5.0000	10684.05	6235.44	.	.	3	1
100		BBA	1	B1	310.66	12.0000	4782.56	3941.99	0.04236	16.3638	2	3
101		BBA	2	B2	1032.12	4.0000	8655.96	5463.56	0.02500	27.7284	3	3
102		BBA	3	A	312.97	14.0000	8906.52	6567.59	0.02225	31.1504	1	3
103		ABB	1	A	1885.05	4.0000	11474.39	7023.05	.	.	1	1

Obs	sub	sequ	per	treat	CMAX	TMAX	AUCT	AUC _{8-48hr}	THALF	KE	trt	seq
104	(b) (6)	ABB	2	B1	1132.88	10.0000	9763.52	7696.94	.	.	2	1
105		ABB	3	B2	560.84	30.0000	9952.40	9828.89	.	.	3	1
106		BAB	1	B1	1667.77	8.0000	11611.48	10394.83	0.20159	3.4383	2	2
107		BAB	2	A	502.03	6.0000	4490.71	3056.48	0.08135	8.5203	1	2
108		BAB	3	B2	1466.03	7.0000	10966.71	8763.86	0.16066	4.3144	3	2
109		BAB	1	B1	946.71	10.0000	9076.07	7504.13	0.04476	15.4875	2	2
110		BAB	2	A	548.95	10.0000	6930.18	6249.54	0.14062	4.9293	1	2
111		BAB	3	B2	507.34	12.0000	5751.23	4915.27	0.13260	5.2272	3	2
112		BBA	1	B1	813.35	10.0000	9990.88	7528.56	0.02015	34.3952	2	3
113		BBA	2	B2	1659.32	5.0000	14393.97	9608.70	0.01910	36.2865	3	3
114		BBA	3	A	665.46	13.0000	12200.75	10567.97	0.05154	13.4474	1	3
115		ABB	1	A	1826.01	4.0000	7298.82	3578.02	0.12050	5.7522	1	1
116		ABB	2	B1	749.29	10.0000	6595.71	5430.02	0.16329	4.2449	2	1
117		ABB	3	B2	749.88	8.0000	7401.00	6004.63	0.02944	23.5480	3	1
118		ABB	1	A	440.36	14.0000	6138.04	5627.03	0.04777	14.5108	1	1
119		ABB	2	B1	364.25	11.0000	6889.17	6456.03	0.09487	7.3060	2	1
120		ABB	3	B2	2413.34	5.0000	13887.12	9749.42	0.10451	6.6322	3	1
121		BBA	1	B1	231.27	5.0000	8344.29	6105.39	0.02075	33.3987	2	3
122		BBA	2	B2	4501.98	8.0000	13121.35	9689.02	.	.	3	3
123		BBA	3	A	583.12	12.0000	6239.99	4742.21	0.03027	22.9026	1	3
124		ABB	1	A	252.26	26.0000	1872.27	1865.08	0.02600	26.6583	1	1
125		ABB	2	B1	396.83	12.0000	4434.11	4198.56	0.13600	5.0967	2	1
126		ABB	3	B2	440.41	11.0000	5633.55	5346.66	0.09516	7.2837	3	1
127		BBA	1	B1	1161.55	10.0000	15470.72	11651.00	.	.	2	3
128		BBA	2	B2	3805.98	5.1500	20494.07	10075.62	.	.	3	3
129		BBA	3	A	3021.02	5.0000	12979.27	8062.42	.	.	1	3
130		BAB	1	B1	1022.49	12.0000	7886.15	7745.49	0.07774	8.9159	2	2
131		BAB	2	A	992.35	7.0000	11471.67	9280.72	0.07969	8.6980	1	2
132		BAB	3	B2	1267.32	11.0000	12072.87	10194.13	0.03827	18.1098	3	2
133		BBA	1	B1	575.71	12.0000	4701.89	4446.36	0.33874	2.0463	2	3
134		BBA	2	B2	111.03	9.0000	915.35	671.69	0.09174	7.5559	3	3
135		BBA	3	A	449.36	13.0000	6192.47	6189.07	0.11823	5.8629	1	3
136		BAB	1	B1	787.45	12.0000	8458.61	7003.44	0.06413	10.8086	2	2
137		BAB	2	A	1925.75	4.0000	16238.88	10616.09	0.12560	5.5187	1	2
138		BAB	3	B2	1418.23	9.0000	15792.33	11610.83	0.07278	9.5243	3	2
139		ABB	1	A	1637.30	5.0000	8526.22	4752.32	0.02170	31.9441	1	1
140		ABB	2	B1	501.52	13.0000	5480.87	4867.52	0.07234	9.5822	2	1
141		ABB	3	B2	446.31	12.0000	5655.23	4763.52	0.03517	19.7079	3	1
142		BAB	1	B1	305.41	13.0000	5128.41	4600.10	0.08436	8.2164	2	2
143		BAB	2	A	1008.76	13.0000	16172.75	15836.89	0.05099	13.5930	1	2

Obs	sub	sequ	per	treat	CMAX	TMAX	AUCT	AUC _{8-48hr}	THALF	KE	trt	seq
144	(b) (6)	BAB	3	B2	1332.81	11.0000	12640.33	11418.30	0.11567	5.9922	3	2
145		ABB	1	A	1077.52	4.0000	10618.78	6546.38	0.15349	4.5160	1	1
146		ABB	2	B1	2903.83	4.0000	18175.03	10936.37	0.10919	6.3483	2	1
147		ABB	3	B2	1029.04	13.0000	11540.43	9913.44	0.13037	5.3168	3	1
148		BBA	1	B1	445.36	13.0000	11778.07	9835.16			2	3
149		BBA	2	B2	1201.41	8.0000	9715.75	7065.79			3	3
150		BBA	3	A	379.81	12.0000	4930.18	4470.95			1	3
151		ABB	1	A	682.41	26.0000	16297.81	13585.93	0.08715	7.9535	1	1
152		ABB	2	B1	408.27	13.0000	10706.36	9023.26	0.05811	11.9282	2	1
153		ABB	3	B2	683.53	26.0000	16598.28	16577.49	0.03033	22.8570	3	1
154		BAB	1	B1	558.71	30.0000	15480.34	15263.76			2	2
155		BAB	2	A	2151.77	5.0500	10947.97	6839.60	0.12179	5.6914	1	2
156		BAB	3	B2	572.71	28.0000	14922.61	13633.03	0.06645	10.4309	3	2
157		BAB	1	B1	380.96	12.0000	4151.96	3906.87	0.06003	11.5459	2	2
158		BAB	2	A	2438.40	6.0000	8961.41	3660.66	0.11218	6.1790	1	2
159		BAB	3	B2	293.26	13.0000	4387.39	3902.83	0.09383	7.3874	3	2
160		BBA	1	B1	795.77	11.0000	11502.18	9960.42	0.07068	9.8073	2	3
161		BBA	2	B2	1994.15	5.0000	9307.00	5507.37	0.02599	26.6695	3	3
162		BBA	3	A	623.94	15.0000	12642.85	11977.99	0.04371	15.8572	1	3
163		ABB	1	A	963.40	9.0000	7716.08	6002.72	0.07122	9.7331	1	1
164		ABB	2	B1	661.03	9.0000	7006.72	5899.06	0.05066	13.6811	2	1
165		ABB	3	B2	609.79	10.0000	5483.11	4935.36	0.06270	11.0548	3	1
166		ABB	1	A	488.52	26.0000	6963.60	6230.58	0.07939	8.7310	1	1
167		ABB	2	B1	635.06	10.0000	4770.98	3931.72	0.03548	19.5347	2	1
168		ABB	3	B2	742.61	9.0000	6044.09	4654.89	0.08389	8.2623	3	1
169		BBA	1	B1	1493.03	11.0000	13922.42	12582.78	0.03464	20.0114	2	3
170		BBA	2	B2	2926.11	10.0000	21735.98	19292.62	0.03763	18.4191	3	3
171		BBA	3	A	2163.25	11.0000	17942.10	16260.77	0.04940	14.0318	1	3
172		BAB	1	B1	233.94	18.0000	4870.73	4565.78	0.08384	8.2673	2	2
173		BAB	2	A	415.65	28.0000	9494.37	9387.01	0.10554	6.5675	1	2
174		BAB	3	B2	746.32	13.0000	8616.59	7829.59	0.05161	13.4306	3	2

4.7.2 Fasting Study Codes

```

/*=====
=====
/ Program   : HVSscale3Period.SAS
/ SubMacros :
/ Updated   : 15 Aug 2009
/ Purpose   : To analyze three period reference-scaled bioequivalence
studies.
/
/ Notes     : EXCEL DATA FILE MUST BE OPEN WHEN RUNNING THIS PROGRAM.

```



```

/                               : OUTPUT FILE (WORD DOCUMENT) CONTAINING SUMMARY TABLES IS
CREATED.
/
/=====
====
/ PARAMETERS:  THE FOLLOWING COLUMNS SHOULD BE IN THE INPUT DATASET (EXCEL
FILE).
/-----name-----description-----
----
NAME OF VARIABLE
      SUBJ          SUBJECT NUMBER
      TRT           TREATMENT - CHARACTER (EITHER A OR B) A=TEST; B=REF
      SEQ           SEQUENCE NUMBER - NUMERIC (EITHER 1, 2, OR 3)
      PER           PERIOD NUMBER - NUMERIC (EITHER 1, 2, 3, OR 4)
      AUCT          AREA UNDER CURVE 0-T
      AUCI          AREA UNDER CURVE 0-INF
      CMAX          CMAX
      TMAX          TMAX
      KEL           ELIMINATION RATE CONSTANT
      THALF         HALF LIFE

      sequence 1      T      R      R
      sequence 2      R      T      R
      sequence 3      R      R      T

/=====
====
/ AMENDMENT HISTORY:
/ Init --Date-- -----Description-----
/
/=====
====*/
options nofmterr nocenter nodate symbolgen mlogic macrogen mprint ps=65
ls=80;

*****STEP 1: ENTER ANDA INFORMATION *****;
%let drug= ;
%let anda=091640-fasting;
%let studytype=Fasting;

*****STEP 2: ENTER UNITS FOR PK PARAMETERS *****;
%let aucunit = ng hr/mL;
%let cmaxunit = ng/mL;
%let timeunit = hr;

***** STEP 3: ENTER LOCATION OF DATASETS AND LOCATION FOR SAVING OUTPUT
REPORTS *****;
%let studydir=M:\BE\Mesalamine 091640\Fasting\Scaled;

***** STEP 4:  ENTER THE NAME OF THE DATASET FILE (EXCEL FILE) *****;
%let excelfile = Drpscale.xls;

***** STEP 5:  ENTER THE NAME OF THE EXCEL WORKSHEET NAME CONTAINING STUDY
DATA *****;
FILENAME ORGPK DDE 'EXCEL|pk!R2C2:R175C11';

```

```

*%let sheetname = pk;

/*
proc import datafile="&excelfile"
    out=base
    dbms=excel replace;
        sheet="&sheetname";
        getnames=yes;
        mixed=yes;
run;
*/

libname studylib "&studydir";

***** STEP 5:  PROVIDE NAMES OF THE VARIABLES TO READ IN FROM EXCEL FILE
*****;
***** PROVIDE STANDARD VARIABLE NAMES FROM THE PARAMETER LIST ABOVE *****;
***** VARIABLE NAMES: SUBJ TRT(A,B) SEQ(1,2) PER(1,2,3) AUCT AUCINF CMAX TMAX
KEL THALF *****;

data base;
*   set base;
    infile orgpk;
    input subj sequ $   per treat $   CMAX TMAX AUCI AUCT KEL THALF;

/*sequence 1           T       R       R
   sequence 2           R       T       R
   sequence 3           R       R       T
*/

IF SEQU="ABB" THEN SEQ=1;
ELSE IF SEQU="BAB" THEN SEQ=2;
ELSE IF SEQU="BBA" THEN SEQ=3;

IF TREAT="B" THEN TRT="B";
ELSE IF TREAT="A" THEN TRT="A";

run;

proc print data=base;
run;

*****
;
        ***** DO NOT CHANGE ANYTHING BELOW THIS LINE *****;
*****
;

data pk;

```

```

    set base;

    LAUCT=log(auct);
    LAUCINF=log(auci);
    LCMAX=log(cmax);

run;

data pkn;
    set pk;
run;

data full;
    set pkn;

run;

proc sort
    data=pkn;
    by seq subj per;
run;

data test; set pkn; if trt='A'; latt=LAUCT; lait=LAUCINF; lct=LCMAX;
run;

data ref; set pkn; if trt='B';
run;

    /*sequence 1          T      R      R
       sequence 2          R      T      R
       sequence 3          R      R      T
    */
    /** ORIGINAL DON'S CODE **
data ref1; set ref; if (seq=1 and per=1) or (seq=2 and per=2) or (seq=3 and
per=1); lat1r=LAUCT; lai1r=LAUCINF; lc1r=LCMAX;
run;
**/
data ref1; set ref; if (seq=1 and per=2) or (seq=2 and per=1) or (seq=3 and
per=1); lat1r=LAUCT; lai1r=LAUCINF; lc1r=LCMAX;
run;

data ref2; set ref; if (seq=1 and per=3) or (seq=2 and per=3) or (seq=3 and
per=2); lat2r=LAUCT; lai2r=LAUCINF; lc2r=LCMAX;
run;

title "ref1";
proc print data=ref1;
run;

title "ref2";
proc print data=ref2;
run;

```

```

title;

data scavbe; merge test ref1 ref2; by seq subj;
ilat=latt-(0.5*(lat1r+lat2r)); *auct;
ilai=lait-(0.5*(lai1r+lai2r)); *auci;
ilc=lct-(0.5*(lc1r+lc2r)); *cmax;

dlat=lat1r-lat2r; *auct;
dlai=lai1r-lai2r; *auci;
dlc=lc1r-lc2r; *cmax;
keep seq subj per trt ilat dlat ilai dlai ilc dlc;
run;

proc print data=scavbe;
title1 'dataset for scaled average BE';
run;

%macro calc(param,no);

PROC MIXED data=pkn;
CLASSES SEQ SUBJ PER TRT;
MODEL &param = SEQ PER TRT/ DDFM=SATTERTH;
RANDOM TRT/TYPE=FA0(2) SUB=SUBJ G;
REPEATED/GRP=TRT SUB=SUBJ;
ESTIMATE 'T vs. R' TRT 1 -1/CL ALPHA=0.1;
lsmeans trt; /* DEV */
ods output lsmeans=lsm&param(keep=trt estimate); /* DEV */
ods output Estimates=unsc&no;
title1 'unscaled BE 90% CI - guidance version';
run;

DATA UPARAM&NO(KEEP=PARAMETER LCI UCI);
SET UNSC&NO;

ESTIMATE = 100 * EXP(ESTIMATE);
PARAMETER = "&PARAM";
LCI = 100 * EXP(LOWER);
UCI = 100 * EXP(UPPER);
RUN;

*** for scaled dataset***;
DATA UNSC&PARAM;
SET UNSC&NO;
RUN;

%mend calc;

%calc(LCMAX,1);
%calc(LAUCT,2);
%calc(LAUCINF,3);

*****;
* LAUCT DOES NOT CONVERGE. SET INITIAL PARAMTERS;

**** without the repeated statement to get a starting point for the PARMS
statement as follows;

```



```

%macro calc1(param,no);

PROC MIXED data=pkn;
  CLASS SEQ SUBJ PER TRT;
  MODEL &param = SEQ PER TRT/ DDFM=SATTERTH;
  RANDOM TRT/TYPE=FA0(2) SUB=SUBJ G;
  ESTIMATE 'T vs. R' TRT 1 -1/CL ALPHA=0.1;
/* ods output Estimates=unsc&param; */
  title1 'unscaled BE 90% CI - guidance version';
  title2 '&param';
  title4 'without repeated';
run;
quit;

/*
Covariance Parameter Estimates

Cov Parm      Subject      Estimate

FA(1,1)        subj          0.5596
FA(2,1)        subj          0.2676
FA(2,2)        subj          0.2540
Residual                          0.1214

*/

**** NORMAL MODEL WITH INITIAL PARAMETERS ****;
PROC MIXED data=pkn;
  CLASS SEQ SUBJ PER TRT;
  MODEL &param = SEQ PER TRT/ DDFM=SATTERTH;
  RANDOM TRT/TYPE=FA0(2) SUB=SUBJ G;
  REPEATED/GRP=TRT SUB=SUBJ;
  PARMS (0.5596) (0.2676) (0.01) (0.01) (0.1214);
  ESTIMATE 'T vs. R' TRT 1 -1/CL ALPHA=0.1;
  lsmeans trt;

  ods output lsmeans=lsm&param(keep=trt estimate); /* DEV */
  ods output Estimates=unsc&no;

  title1 'unscaled BE 90% CI - guidance version';
  title2 '&param';
  title4 'with repeated WITH INITIAL PARAMETERS';
run;
QUIT;

DATA UPARAM&NO(KEEP=PARAMETER LCI UCI);
  SET UNSC&NO;

  ESTIMATE = 100 * EXP(ESTIMATE);
  PARAMETER = "&PARAM";
  LCI = 100 * EXP(LOWER);

```

```

        UCI = 100 * EXP(UPPER);
    RUN;

    *** for scaled dataset***;
    DATA UNSC&PARAM;
        SET UNSC&NO;
    RUN;
%mend calc1;

*%calc1(LCMAX,1);
*%calc1(LAUCT,2);
*%calc1(LAUCINF,3);

*****;

**** ESTIMATES ****;
DATA LSMLAUCT;
    SET LSMLAUCT;
    PARAMETER = "LAUCT";
RUN;

DATA LSMLAUCINF;
    SET LSMLAUCINF;
    PARAMETER = "LAUCI";
RUN;

DATA LSMLCMAX;
    SET LSMLCMAX;
    PARAMETER = "LCMAX";
RUN;

DATA UESTIMATE;
    SET LSMLAUCT LSMLAUCINF LSMLCMAX;
RUN;

DATA UESTIMATE;
    SET UESTIMATE;

    GEOMEAN = EXP(ESTIMATE);
RUN;

PROC SORT
    DATA=UESTIMATE;
    BY PARAMETER;
RUN;

PROC TRANSPOSE
    DATA=UESTIMATE
    OUT=TRANSUEST(DROP=_NAME_);
    VAR GEOMEAN;
    BY PARAMETER;
    ID TRT;
RUN;

```

```

DATA UEST;
  SET TRANSUEST;

  RATIO = ROUND((A/B), .01);
RUN;

DATA UALL;
  SET UPARAM1 UPARAM2 UPARAM3;
RUN;

PROC SORT
  DATA=UALL;
  BY PARAMETER;
RUN;

PROC SORT
  DATA=UEST;
  BY PARAMETER;
RUN;

DATA UPARAMS;
  MERGE UEST
        UALL;
  BY PARAMETER;
RUN;

*** PROPER ORDER AUCTION, AUCTION, CMAX ***;
DATA UPARAMS;
  SET UPARAMS;

  IF PARAMETER = "LAUCTION" THEN ORDER=1;
  ELSE IF PARAMETER = "LAUCTION" THEN ORDER=2;
  ELSE IF PARAMETER = "LCMAX" THEN ORDER=3;
RUN;

PROC SORT
  DATA=UPARAMS;
  BY ORDER;
RUN;

proc template;
  define style mystyle1;
    parent = styles.rtf;
    REPLACE fonts /
      'headingFont' = ("Arial", 8pt, Bold)
      'docFont' = ("Arial", 8pt)
      'TitleFont2' = ("Arial", 8pt, Bold)
      'TitleFont' = ("Arial", 8pt, Bold)
      'StrongFont' = ("Arial", 8pt, Bold)
      'EmphasisFont' = ("Arial", 8pt)
      'FixedEmphasisFont' = ("Arial", 8pt)
      'FixedStrongFont' = ("Arial", 8pt, Bold)
      'FixedHeadingFont' = ("Arial", 8pt, Bold)

```

```

'BatchFixedFont' = ("Arial",8pt)
'FixedFont' = ("Arial",8pt)
'headingEmphasisFont' = ("Arial",8pt,Bold);

style SysTitleAndFooterContainer from Container /
outputwidth = 85%
cellpadding = 2
cellspacing = 2
borderwidth = 0;

REPLACE Body from Document /
bottommargin = 1.0in
topmargin = 1.0in
rightmargin = 1in
leftmargin = 1in;
END;
run;

/*
data unsc1; set unsc1; unscabe_lower=exp(lower); unscabe_upper=exp(upper);
keep unscabe_lower unscabe_upper; run;
*/

***** SCALED ANALYSIS *****;

%MACRO SCALE(parameter, ipar, dpar);

proc glm data=scavbe;
class seq;
model &ipar =seq/clparm alpha=0.1;
estimate 'average' intercept 1 seq 0.3333333333 0.3333333333
0.3333333333;
ods output overallanova=iglm&ipar.1;
ods output Estimates=iglm&ipar.2;
ods output NObs=iglm&ipar.3;
title1 'scaled average BE';
title2 'intermediate analysis - &ipar glm';
run;

title "dev iglm&ipar.1";
proc print data=iglm&ipar.1;
run;

proc glm data=scavbe;
class seq;
model &dpar =seq;
ods output overallanova=dglm&dpar.1;
ods output NObs=dglm&dpar.3;
title1 'scaled average BE';
title2 'intermediate analysis - &dpar glm';
run;

```



```

        data unsc&PARAMETER; set unsc&PARAMETER; unscae_lower=exp(lower);
        unscae_upper=exp(upper);
        keep unscae_lower unscae_upper;
        run;

        data iglm&ipar.1; set iglm&ipar.1; if _n_=2; dfi=df; s2i=ms; keep dfi
s2i param;
        param = "&parameter";
        run;

        data iglm&ipar.2; set iglm&ipar.2; pointest=exp(estimate);
x=(estimate**2)-(stderr**2);
        boundx=(max((abs(LowerCL)), (abs(UpperCL))))**2;
        keep pointest x boundx stderr param;
        param = "&parameter";
        run;

        data iglm&ipar.3; set iglm&ipar.3; if _n_ = 2; ni=NobsUsed; keep ni
param;
        param = "&parameter";
        run;

        data dglm&dpar.1; set dglm&dpar.1; if _n_=2; dfd=df; s2wr=ms/2; keep
dfd s2wr param;
        param = "&parameter";
        run;

        data dglm&dpar.3; set dglm&dpar.3; if _n_ = 2; nd=NobsUsed; keep nd
param;
        param = "&parameter";
        run;

        data idallglm&parameter;
        length method_used $15;
        merge unsc&parameter iglm&ipar.1 iglm&ipar.2 iglm&ipar.3 dglm&dpar.1
dglm&dpar.3;
        theta=((log(1.25))/0.25)**2; y=-theta*s2wr;
        boundy=y*dfd/cinv(0.95,dfd); sWR=sqrt(s2wr);
        critbound=(x+y)+sqrt(((boundx-x)**2)+((boundy-y)**2));
        outcome='FAIL';
        if (s2wr < 0.086436) then method_used='Unscaled'; else
method used='Scaled/PE';
        if ((s2wr < 0.086436) and (unscae_lower ge 0.8) and (unscae_upper le
1.25)) then outcome='PASS';
        if ((s2wr ge 0.086436) and (pointest ge 0.8) and (pointest le 1.25) and
(critbound le 0)) then outcome='PASS';
*       else outcome='FAIL';
        run;

        proc print data=idallglm&parameter;
        title1 'output needed for mixed scaled av. BE - using glm';
        run;

        data finalglm; set idallglm&parameter;
        keep param s2wr sWR unscae_lower unscae_upper pointest critbound
outcome method_used;

```

```

run;

proc print data=finalglm;
title1 'final output - &parameter - using glm';
run;

%mend scale;

%scale(LAUCT, ilat, dlat);
%scale(LAUCINF, ilai, dlai);
%scale(LCMAX, ilc, dlc);

data all;
set idallglmLAUCT
    idallglmLAUCINF
    idallglmLCMAX;

    unscabe_lower = round((unscabe_lower*100), .01);
    unscabe_upper = round((unscabe_upper*100), .01);

run;

ods rtf file="&studydir\&ANDA.-ANALYSIS.doc" style=mystyle1 bodytitle;

**** ARITHMETIC MEANS *****;
/*
footnote "* Tmax values are presented as median, range.";
TITLE "ARITHMETIC MEANS AND RATIOS - REPLICATE 1 (PERIODS 1 AND 2)";
proc report data=pkratio1 nowd split='\' box
    style(header)={background=lightorange
                    foreground=black}
    style(column)={background=white
                    foreground=black};

    column nname units ("Test" mean1 cv1 min1 max1)
              ("Reference" mean2 cv2 min2 max2)
              ("Ratio" rmean12);

    define nname /format=$12. spacing=2 "Parameter";
    define units /format=$12. spacing=2 "Unit";
    define mean1 /format=8.3 spacing=2 "Mean";
    define cv1 /format=8.2 spacing=2 "CV%";
    define min1 /format=8.2 spacing=2 "Min";
    define max1 /format=8.2 spacing=2 "Max";
    define mean2 /format=8.3 spacing=2 "Mean";
    define cv2 /format=8.2 spacing=2 "CV%";
    define min2 /format=8.2 spacing=2 "Min";
    define max2 /format=8.2 spacing=2 "Max";
    define rmean12 /format=8.2 spacing=2 "(T/R)";
run;
footnote;

footnote "* Tmax values are presented as median, range.";
TITLE "ARITHMETIC MEANS AND RATIOS - REPLICATE 2 (PERIODS 3 AND 4)";
proc report data=pkratio2 nowd split='\' box
    style(header)={background=lightorange
                    foreground=black}

```

```

style(column)={background=white
                foreground=black};

column nname units ("Test" mean1 cv1 min1 max1)
              ("Reference" mean2 cv2 min2 max2)
              ("Ratio" rmean12);

define nname /format=$12. spacing=2 "Parameter";
define units /format=$12. spacing=2 "Unit";
define mean1 /format=8.3 spacing=2 "Mean";
define cv1 /format=8.2 spacing=2 "CV%";
define min1 /format=8.2 spacing=2 "Min";
define max1 /format=8.2 spacing=2 "Max";
define mean2 /format=8.3 spacing=2 "Mean";
define cv2 /format=8.2 spacing=2 "CV%";
define min2 /format=8.2 spacing=2 "Min";
define max2 /format=8.2 spacing=2 "Max";
define rmean12 /format=8.2 spacing=2 "(T/R)";
run;
footnote;

footnote "* Tmax values are presented as median, range.";
TITLE "ARITHMETIC MEANS AND RATIOS - ALL PERIODS (PERIODS 1, 2, 3, AND 4)";
proc report data=pkratio3 nowd split='\' box
  style(header)={background=lightorange
                  foreground=black}
  style(column)={background=white
                  foreground=black};

column nname units ("Test" mean1 cv1 min1 max1)
              ("Reference" mean2 cv2 min2 max2)
              ("Ratio" rmean12);

define nname /format=$12. spacing=2 "Parameter";
define units /format=$12. spacing=2 "Unit";
define mean1 /format=8.3 spacing=2 "Mean";
define cv1 /format=8.2 spacing=2 "CV%";
define min1 /format=8.2 spacing=2 "Min";
define max1 /format=8.2 spacing=2 "Max";
define mean2 /format=8.3 spacing=2 "Mean";
define cv2 /format=8.2 spacing=2 "CV%";
define min2 /format=8.2 spacing=2 "Min";
define max2 /format=8.2 spacing=2 "Max";
define rmean12 /format=8.2 spacing=2 "(T/R)";
run;
footnote;

*/

*** UNSCALED ANALYSIS REPORT *****;
title1 "ANDA: &anda &drug STUDY TYPE: &STUDYTYPE";
title2 "SUMMARY OF STATISTICAL ANALYSIS - UNSCALED DATA";

proc report
  data=uparams
  headline
  headskip

```

```

        nowd
        split="|" box
style(header)={background=lightorange
                foreground=black}
style(column)={background=white
                foreground=black};

        column parameter ("Geometric Means|" a b) ratio ("90% CI|" lci uci);

        define parameter /display "Parameter" width=20 center;
        define a          /display "Test"      width=15 center
format=8.2;
        define b          /display "Reference" width=15 center
format=8.2;
        define ratio      /display "T/R Ratio" width=15 center
format=8.2;
        define lci        /display "Lower CI"  width=20 center format=8.2;
        define uci        /display "Upper CI"  width=20 center format=8.2;
run;

***** SCALED ANALYSIS REPORT *****;
title1 "SUMMARY OF STATISTICAL ANALYSIS - SCALED DATA";

proc report
data=all
headline
headskip
nowd
split="|" box
style(header)={background=lightorange
                foreground=black}
style(column)={background=white
                foreground=black};

        column param pointest unscale_lower unscale_upper s2wr swr critbound
method_used outcome;

        define param /display "Parameter" width=20 center;
        define pointest /display "T/R Ratio" width=15 center format=8.2;
        define unscale_lower /display "Lower|90% CI" width=20 center
format=8.2;
        define unscale_upper /display "Upper|90% CI" width=20 center
format=8.2;
        define s2wr /display "s2wr" width=15 center;
        define swr /display "swr" width=15 center;
        define critbound /display "Criteria Bound" width=15 center;
        define method used /display "Method Used" width=25 center;
        define outcome /display "OUTCOME" width=15 center;

run;

ods rtf close;

```


4.7.3 Fasting Study Output

Obs	subj	sequ	per	treat	C _{MAX}	T _{MAX}	AUC _I	AUC _T	KEL	THALF	SEQ	TRT
1	(b) (6)	ABB	1	A	5098.51	6.0000	15894.84	5208.39	.	.	1	A
2		BBA	3	A	463.23	13.0000	9331.16	8039.49	0.0726	9.5509	3	A
3		BAB	2	A	487.33	4.0000	6548.68	4701.40	0.0658	10.5357	2	A
4		BAB	2	A	206.50	12.0000	3229.36	3104.97	0.1093	6.3411	2	A
5		ABB	1	A	659.53	36.0000	12989.59	12815.25	.	.	1	A
6		BBA	3	A	3574.24	6.0000	18800.90	10953.45	0.0676	10.2584	3	A
7		ABB	1	A	968.97	10.0000	9898.08	8817.28	0.0681	10.1760	1	A
8		BAB	2	A	1301.49	10.0000	12478.31	10887.65	0.0722	9.6017	2	A
9		BBA	3	A	517.60	9.0000	12356.31	7160.50	.	.	3	A
10		ABB	1	A	869.58	26.0000	5715.72	5715.72	0.1446	4.7950	1	A
11		BAB	2	A	628.65	12.0000	7544.09	5929.16	0.0422	16.4450	2	A
12		BBA	3	A	811.93	10.0000	8001.26	6401.13	0.1330	5.2124	3	A
13		ABB	1	A	980.45	26.0000	16377.52	16348.24	0.2515	2.7559	1	A
14		BAB	2	A	491.95	14.1833	8990.68	7518.49	0.0713	9.7170	2	A
15		ABB	1	A	355.56	10.0000	4562.14	4460.85	0.1692	4.0971	1	A
16		BBA	3	A	811.29	11.0333	11966.18	9452.02	0.0995	6.9701	3	A
17		BBA	3	A	128.74	15.0000	4388.67	3569.00	0.0437	15.8656	3	A
18		ABB	1	A	486.43	9.0000	9699.81	8963.23	0.0541	12.8064	1	A
19		BAB	2	A	1201.85	8.0000	7101.16	5333.73	0.8069	0.8590	2	A
20		BBA	3	A	431.84	4.0000	5947.56	4421.30	0.3668	1.8897	3	A
21		ABB	1	A	818.49	10.0000	8950.59	7343.54	0.0572	12.1170	1	A
22		ABB	1	A	648.15	26.0000	14972.72	14972.72	0.0587	11.8005	1	A
23		BBA	3	A	767.66	10.0000	11393.79	9569.41	0.0966	7.1786	3	A
24		BAB	2	A	896.18	7.0000	8040.00	5718.94	0.0499	13.8814	2	A
25		BBA	3	A	889.94	16.0000	12096.40	10729.18	0.0763	9.0832	3	A
26		ABB	1	A	404.45	26.0000	8208.86	8208.86	0.0362	19.1570	1	A
27		BAB	2	A	487.00	26.0000	10365.11	9253.40	0.0895	7.7411	2	A
28		BBA	3	A	591.63	15.0000	9884.22	9740.25	0.0734	9.4376	3	A
29		BAB	2	A	1383.00	5.0000	7944.11	5485.29	0.0747	9.2810	2	A
30		ABB	1	A	4486.72	5.0000	13206.16	4802.77	.	.	1	A
31		BBA	3	A	804.78	14.0000	10585.82	9035.42	0.0382	18.1402	3	A

Obs	subj	sequ	per	treat	CMAX	TMAX	AUCI	AUCT	KEL	THALF	SEQ	TRT
32	(b) (6)	BAB	2	A	469.20	24.0000	13303.18	9862.82	0.0173	40.1317	2	A
33		ABB	1	A	163.41	36.0000	7175.48	4929.57	.	.	1	A
34		BBA	3	A	312.97	14.0000	8906.52	6567.59	0.0223	31.1504	3	A
35		ABB	1	A	1885.05	4.0000	11474.39	7023.05	.	.	1	A
36		BAB	2	A	502.03	6.0000	4490.71	3056.48	0.0814	8.5203	2	A
37		BAB	2	A	548.95	10.0000	6930.18	6249.54	0.1406	4.9293	2	A
38		BBA	3	A	665.46	13.0000	12200.75	10567.97	0.0515	13.4474	3	A
39		ABB	1	A	1826.01	4.0000	7298.82	3578.02	0.1205	5.7522	1	A
40		ABB	1	A	440.36	14.0000	6138.04	5627.03	0.0478	14.5108	1	A
41		BBA	3	A	583.12	12.0000	6239.99	4742.21	0.0303	22.9026	3	A
42		ABB	1	A	252.26	26.0000	1872.27	1865.08	0.0260	26.6583	1	A
43		BBA	3	A	3021.02	5.0000	12979.27	8062.42	.	.	3	A
44		BAB	2	A	992.35	7.0000	11471.67	9280.72	0.0797	8.6980	2	A
45		BBA	3	A	449.36	13.0000	6192.47	6189.07	0.1182	5.8629	3	A
46		BAB	2	A	1925.75	4.0000	16238.88	10616.09	0.1256	5.5187	2	A
47		ABB	1	A	1637.30	5.0000	8526.22	4752.32	0.0217	31.9441	1	A
48		BAB	2	A	1008.76	13.0000	16172.75	15836.89	0.0510	13.5930	2	A
49		ABB	1	A	1077.52	4.0000	10618.78	6546.38	0.1535	4.5160	1	A
50		BBA	3	A	379.81	12.0000	4930.18	4470.95	.	.	3	A
51		ABB	1	A	682.41	26.0000	16297.81	13585.93	0.0872	7.9535	1	A
52		BAB	2	A	2151.77	5.0500	10947.97	6839.60	0.1218	5.6914	2	A
53		BAB	2	A	2438.40	6.0000	8961.41	3660.66	0.1122	6.1790	2	A
54		BBA	3	A	623.94	15.0000	12642.85	11977.99	0.0437	15.8572	3	A
55		ABB	1	A	963.40	9.0000	7716.08	6002.72	0.0712	9.7331	1	A
56		ABB	1	A	488.52	26.0000	6963.60	6230.58	0.0794	8.7310	1	A
57		BBA	3	A	2163.25	11.0000	17942.10	16260.77	0.0494	14.0318	3	A
58		BAB	2	A	415.65	28.0000	9494.37	9387.01	0.1055	6.5675	2	A
59		ABB	2	B	5495.36	5.0000	17725.92	6813.58	.	.	1	B
60		BBA	1	B	702.37	5.0000	8641.03	7303.19	0.0884	7.8416	3	B
61		BAB	1	B	2877.55	5.0000	13556.76	4813.90	0.0297	23.3057	2	B
62		BAB	1	B	270.97	11.0000	3286.79	3004.60	0.1772	3.9108	2	B
63		ABB	2	B	443.52	26.0000	5391.26	5352.45	.	.	1	B
64		BBA	1	B	4582.53	8.0000	25872.46	16996.58	0.0238	29.1861	3	B

Obs	subj	sequ	per	treat	CMAX	TMAX	AUCI	AUCT	KEL	THALF	SEQ	TRT
65	(b) (6)	ABB	2	B	931.11	11.0000	13480.80	11986.93	0.0970	7.1480	1	B
66		BAB	1	B	1407.09	6.0000	9799.14	6840.96	0.0671	10.3382	2	B
67		BBA	1	B	224.49	48.0000	8909.20	4393.94	.	.	3	B
68		ABB	2	B	881.42	9.0000	10656.31	8145.27	0.0542	12.7924	1	B
69		BAB	1	B	5372.55	6.0333	12712.28	4935.15	0.0120	57.5490	2	B
70		BBA	1	B	1151.87	9.0000	7880.38	5997.24	0.0581	11.9220	3	B
71		ABB	2	B	3131.63	4.0000	18655.81	10568.20	0.0580	11.9428	1	B
72		BAB	1	B	788.52	5.0000	9062.26	6542.21	0.0876	7.9122	2	B
73		ABB	2	B	1210.58	10.0000	7200.34	6239.20	0.2644	2.6221	1	B
74		BBA	1	B	604.04	13.0000	9488.41	9110.08	0.1998	3.4696	3	B
75		BBA	1	B	354.12	11.0000	6425.48	5220.09	0.0759	9.1286	3	B
76		ABB	2	B	1097.64	7.0000	9362.88	6686.34	0.1454	4.7672	1	B
77		BAB	1	B	493.93	4.0000	1326.84	11.70	0.7743	0.8952	2	B
78		BBA	1	B	1842.76	4.0000	13229.57	8653.30	0.2179	3.1813	3	B
79		ABB	2	B	1928.30	6.0000	11375.70	7883.43	0.0529	13.1114	1	B
80		ABB	2	B	1211.30	11.0000	12055.87	10047.61	0.0661	10.4927	1	B
81		BBA	1	B	1654.68	4.0000	10716.33	6667.43	0.0516	13.4281	3	B
82		BAB	1	B	1970.21	7.0000	11839.24	7363.12	0.0742	9.3419	2	B
83		BBA	1	B	1023.07	9.0000	9027.26	7439.47	0.0702	9.8782	3	B
84		ABB	2	B	416.72	4.0000	8907.85	7722.06	0.0393	17.6536	1	B
85		BAB	1	B	843.58	11.0000	7340.30	6720.97	0.0621	11.1675	2	B
86		BBA	1	B	227.14	9.0000	6344.29	6243.38	0.0443	15.6613	3	B
87		BAB	1	B	691.12	5.0000	6656.54	5499.73	0.0443	15.6421	2	B
88		ABB	2	B	819.82	5.0000	9139.48	6575.57	.	.	1	B
89		BBA	1	B	376.55	18.0000	13109.04	9311.27	.	.	3	B
90		BAB	1	B	703.91	11.0000	9194.52	7914.86	0.0388	17.8775	2	B
91		ABB	2	B	1280.98	6.0000	9359.51	4608.49	.	.	1	B
92		BBA	1	B	310.66	12.0000	4782.56	3941.99	0.0424	16.3638	3	B
93		ABB	2	B	1132.88	10.0000	9763.52	7696.94	.	.	1	B
94		BAB	1	B	1667.77	8.0000	11611.48	10394.83	0.2016	3.4383	2	B
95		BAB	1	B	946.71	10.0000	9076.07	7504.13	0.0448	15.4875	2	B
96		BBA	1	B	813.35	10.0000	9990.88	7528.56	0.0202	34.3952	3	B
97		ABB	2	B	749.29	10.0000	6595.71	5430.02	0.1633	4.2449	1	B

Obs	subj	sequ	per	treat	CMAX	TMAX	AUCI	AUCT	KEL	THALF	SEQ	TRT
98	(b) (6)	ABB	2	B	364.25	11.0000	6889.17	6456.03	0.0949	7.3060	1	B
99		BBA	1	B	231.27	5.0000	8344.29	6105.39	0.0208	33.3987	3	B
100		ABB	2	B	396.83	12.0000	4434.11	4198.56	0.1360	5.0967	1	B
101		BBA	1	B	1161.55	10.0000	15470.72	11651.00	.	.	3	B
102		BAB	1	B	1022.49	12.0000	7886.15	7745.49	0.0777	8.9159	2	B
103		BBA	1	B	575.71	12.0000	4701.89	4446.36	0.3387	2.0463	3	B
104		BAB	1	B	787.45	12.0000	8458.61	7003.44	0.0641	10.8086	2	B
105		ABB	2	B	501.52	13.0000	5480.87	4867.52	0.0723	9.5822	1	B
106		BAB	1	B	305.41	13.0000	5128.41	4600.10	0.0844	8.2164	2	B
107		ABB	2	B	2903.83	4.0000	18175.03	10936.37	0.1092	6.3483	1	B
108		BBA	1	B	445.36	13.0000	11778.07	9835.16	.	.	3	B
109		ABB	2	B	408.27	13.0000	10706.36	9023.26	0.0581	11.9282	1	B
110		BAB	1	B	558.71	30.0000	15480.34	15263.76	.	.	2	B
111		BAB	1	B	380.96	12.0000	4151.96	3906.87	0.0600	11.5459	2	B
112		BBA	1	B	795.77	11.0000	11502.18	9960.42	0.0707	9.8073	3	B
113		ABB	2	B	661.03	9.0000	7006.72	5899.06	0.0507	13.6811	1	B
114		ABB	2	B	635.06	10.0000	4770.98	3931.72	0.0355	19.5347	1	B
115		BBA	1	B	1493.03	11.0000	13922.42	12582.78	0.0346	20.0114	3	B
116		BAB	1	B	233.94	18.0000	4870.73	4565.78	0.0838	8.2673	2	B
117		ABB	3	B	5404.78	6.0000	17809.48	7516.13	.	.	1	B
118		BBA	2	B	905.48	10.0000	8510.11	8281.63	0.0495	13.9989	3	B
119		BAB	3	B	1934.49	6.0000	10867.80	6038.78	0.0743	9.3266	2	B
120		BAB	3	B	552.67	5.0000	4557.08	3176.60	0.1375	5.0406	2	B
121		ABB	3	B	460.27	13.0000	7563.11	5668.63	.	.	1	B
122		BBA	2	B	4341.62	8.0000	24497.28	19989.18	0.0502	13.8157	3	B
123		ABB	3	B	1497.93	6.0000	11881.55	8743.20	0.0421	16.4618	1	B
124		BAB	3	B	1566.70	10.0000	20836.92	17243.04	0.0929	7.4620	2	B
125		BBA	2	B	176.40	36.0000	3144.06	3144.06	.	.	3	B
126		ABB	3	B	908.05	9.0000	9587.91	7757.61	0.0321	21.5690	1	B
127		BAB	3	B	796.48	10.0000	9455.29	6518.61	0.0625	11.0882	2	B
128		BBA	2	B	1007.09	11.0000	8638.12	6907.86	0.0802	8.6429	3	B
129		ABB	3	B	1862.91	5.0000	17706.74	14657.47	0.2055	3.3726	1	B
130		BAB	3	B	1348.81	10.0000	12919.02	11343.30	0.1151	6.0242	2	B

Obs	subj	sequ	per	treat	CMAX	TMAX	AUCI	AUCT	KEL	THALF	SEQ	TRT
131	(b) (6)	ABB	3	B	744.29	12.0000	7163.74	6583.21	0.1370	5.0604	1	B
132		BBA	2	B	487.41	10.0000	10243.27	9892.79	0.1077	6.4370	3	B
133		BBA	2	B	210.11	11.0000	4028.49	3758.16	.	.	3	B
134		ABB	3	B	1478.72	5.0000	16382.13	12579.87	0.0942	7.3617	1	B
135		BAB	3	B	236.99	11.0000	2337.82	2231.06	0.2225	3.1155	2	B
136		BBA	2	B	621.78	11.0000	9268.03	7696.96	0.4987	1.3899	3	B
137		ABB	3	B	936.53	12.0000	8348.74	7944.29	0.1259	5.5061	1	B
138		ABB	3	B	697.11	28.0000	14060.84	13694.90	0.0646	10.7385	1	B
139		BBA	2	B	841.72	11.0000	7137.93	6398.43	0.0289	23.9965	3	B
140		BAB	3	B	3193.33	8.0000	15034.16	9705.43	0.0706	9.8224	2	B
141		BBA	2	B	951.18	12.0000	10433.64	8739.20	0.0848	8.1711	3	B
142		ABB	3	B	425.67	13.0000	5825.22	5551.09	0.4788	1.4476	1	B
143		BAB	3	B	1151.38	11.0000	9084.40	8373.48	0.0726	9.5493	2	B
144		BBA	2	B	536.44	8.0000	4112.36	2480.90	0.0966	7.1762	3	B
145		BAB	3	B	888.44	5.0000	10499.71	7689.20	0.0635	10.9161	2	B
146		ABB	3	B	1445.81	11.0500	11926.17	11048.24	35.0000	.	1	B
147		BAB	3	B	421.11	8.0000	12849.16	8639.09	0.0434	15.9582	2	B
148		ABB	3	B	950.74	5.0000	10684.05	6235.44	.	.	1	B
149		BBA	2	B	1032.12	4.0000	8655.96	5463.56	0.0250	27.7284	3	B
150		ABB	3	B	560.84	30.0000	9952.40	9828.89	.	.	1	B
151		BAB	3	B	1466.03	7.0000	10966.71	8763.86	0.1607	4.3144	2	B
152		BAB	3	B	507.34	12.0000	5751.23	4915.27	0.1326	5.2272	2	B
153		BBA	2	B	1659.32	5.0000	14393.97	9608.70	0.0191	36.2865	3	B
154		ABB	3	B	749.88	8.0000	7401.00	6004.63	0.0294	23.5480	1	B
155		ABB	3	B	2413.34	5.0000	13887.12	9749.42	0.1045	6.6322	1	B
156		BBA	2	B	4501.98	8.0000	13121.35	9689.02	.	.	3	B
157		ABB	3	B	440.41	11.0000	5633.55	5346.66	0.0952	7.2837	1	B
158		BBA	2	B	3805.98	5.1500	20494.07	10075.62	.	.	3	B
159		BAB	3	B	1267.32	11.0000	12072.87	10194.13	0.0383	18.1098	2	B
160		BBA	2	B	111.03	9.0000	915.35	671.69	0.0917	7.5559	3	B
161		BAB	3	B	1418.23	9.0000	15792.33	11610.83	0.0728	9.5243	2	B
162		ABB	3	B	446.31	12.0000	5655.23	4763.52	0.0352	19.7079	1	B
163		BAB	3	B	1332.81	11.0000	12640.33	11418.30	0.1157	5.9922	2	B

Obs	subj	sequ	per	treat	C _{MAX}	T _{MAX}	AUC _I	AUC _T	KEL	THALF	SEQ	TRT
164	(b) (6)	ABB	3	B	1029.04	13.0000	11540.43	9913.44	0.1304	5.3168	1	B
165	(b) (6)	BBA	2	B	1201.41	8.0000	9715.75	7065.79	.	.	3	B
166	(b) (6)	ABB	3	B	683.53	26.0000	16598.28	16577.49	0.0303	22.8570	1	B
167	(b) (6)	BAB	3	B	572.71	28.0000	14922.61	13633.03	0.0665	10.4309	2	B
168	(b) (6)	BAB	3	B	293.26	13.0000	4387.39	3902.83	0.0938	7.3874	2	B
169	(b) (6)	BBA	2	B	1994.15	5.0000	9307.00	5507.37	0.0260	26.6695	3	B
170	(b) (6)	ABB	3	B	609.79	10.0000	5483.11	4935.36	0.0627	11.0548	1	B
171	(b) (6)	ABB	3	B	742.61	9.0000	6044.09	4654.89	0.0839	8.2623	1	B
172	(b) (6)	BBA	2	B	2926.11	10.0000	21735.98	19292.62	0.0376	18.4191	3	B
173	(b) (6)	BAB	3	B	746.32	13.0000	8616.59	7829.59	0.0516	13.4306	2	B

ref1

Obs	subj	sequ	per	treat	CMAX	TMAX	AUCI	AUCT	KEL	THALF	SEQ	TRT	LAUCT	LAUCINF	LCMAX	lat1r	lai1r	lc1r
1	(b) (6)	ABB	2	B	5495.36	5.0000	17725.92	6813.58	.	.	1	B	8.82667	9.7828	8.61166	8.82667	9.7828	8.61166
2		ABB	2	B	443.52	26.0000	5391.26	5352.45	.	.	1	B	8.58531	8.5925	6.09474	8.58531	8.5925	6.09474
3		ABB	2	B	931.11	11.0000	13480.80	11986.93	0.09697	7.1480	1	B	9.39157	9.5090	6.83638	9.39157	9.5090	6.83638
4		ABB	2	B	881.42	9.0000	10656.31	8145.27	0.05418	12.7924	1	B	9.00519	9.2739	6.78153	9.00519	9.2739	6.78153
5		ABB	2	B	3131.63	4.0000	18655.81	10568.20	0.05804	11.9428	1	B	9.26560	9.8339	8.04931	9.26560	9.8339	8.04931
6		ABB	2	B	1210.58	10.0000	7200.34	6239.20	0.26435	2.6221	1	B	8.73861	8.8819	7.09885	8.73861	8.8819	7.09885
7		ABB	2	B	1097.64	7.0000	9362.88	6686.34	0.14540	4.7672	1	B	8.80782	9.1445	7.00092	8.80782	9.1445	7.00092
8		ABB	2	B	1928.30	6.0000	11375.70	7883.43	0.05287	13.1114	1	B	8.97252	9.3392	7.56439	8.97252	9.3392	7.56439
9		ABB	2	B	1211.30	11.0000	12055.87	10047.61	0.06606	10.4927	1	B	9.21509	9.3973	7.09945	9.21509	9.3973	7.09945
10		ABB	2	B	416.72	4.0000	8907.85	7722.06	0.03926	17.6536	1	B	8.95184	9.0947	6.03241	8.95184	9.0947	6.03241
11		ABB	2	B	819.82	5.0000	9139.48	6575.57	.	.	1	B	8.79112	9.1204	6.70908	8.79112	9.1204	6.70908
12		ABB	2	B	1280.98	6.0000	9359.51	4608.49	.	.	1	B	8.43565	9.1441	7.15538	8.43565	9.1441	7.15538
13		ABB	2	B	1132.88	10.0000	9763.52	7696.94	.	.	1	B	8.94858	9.1864	7.03252	8.94858	9.1864	7.03252
14		ABB	2	B	749.29	10.0000	6595.71	5430.02	0.16329	4.2449	1	B	8.59970	8.7942	6.61913	8.59970	8.7942	6.61913
15		ABB	2	B	364.25	11.0000	6889.17	6456.03	0.09487	7.3060	1	B	8.77277	8.8377	5.89784	8.77277	8.8377	5.89784
16		ABB	2	B	396.83	12.0000	4434.11	4198.56	0.13600	5.0967	1	B	8.34250	8.3971	5.98351	8.34250	8.3971	5.98351
17		ABB	2	B	501.52	13.0000	5480.87	4867.52	0.07234	9.5822	1	B	8.49034	8.6090	6.21764	8.49034	8.6090	6.21764
18		ABB	2	B	2903.83	4.0000	18175.03	10936.37	0.10919	6.3483	1	B	9.29985	9.8078	7.97379	9.29985	9.8078	7.97379
19		ABB	2	B	408.27	13.0000	10706.36	9023.26	0.05811	11.9282	1	B	9.10756	9.2786	6.01193	9.10756	9.2786	6.01193
20		ABB	2	B	661.03	9.0000	7006.72	5899.06	0.05066	13.6811	1	B	8.68255	8.8546	6.49380	8.68255	8.8546	6.49380
21		ABB	2	B	635.06	10.0000	4770.98	3931.72	0.03548	19.5347	1	B	8.27683	8.4703	6.45372	8.27683	8.4703	6.45372
22		BAB	1	B	2877.55	5.0000	13556.76	4813.90	0.02974	23.3057	2	B	8.47926	9.5146	7.96469	8.47926	9.5146	7.96469

Obs	subj	sequ	per	treat	CMAX	TMAX	AUCI	AUCT	KEL	THALF	SEQ	TRT	LAUCT	LAUCINF	LCMAX	lat1r	lai1r	lc1r
23	(b) (6)	BAB	1	B	270.97	11.0000	3286.79	3004.60	0.17724	3.9108	2	B	8.00790	8.0977	5.60201	8.00790	8.0977	5.60201
24		BAB	1	B	1407.09	6.0000	9799.14	6840.96	0.06705	10.3382	2	B	8.83068	9.1900	7.24928	8.83068	9.1900	7.24928
25		BAB	1	B	5372.55	6.0333	12712.28	4935.15	0.01204	57.5490	2	B	8.50414	9.4503	8.58906	8.50414	9.4503	8.58906
26		BAB	1	B	788.52	5.0000	9062.26	6542.21	0.08760	7.9122	2	B	8.78603	9.1119	6.67016	8.78603	9.1119	6.67016
27		BAB	1	B	493.93	4.0000	1326.84	11.70	0.77426	0.8952	2	B	2.45959	7.1906	6.20239	2.45959	7.1906	6.20239
28		BAB	1	B	1970.21	7.0000	11839.24	7363.12	0.07420	9.3419	2	B	8.90424	9.3792	7.58590	8.90424	9.3792	7.58590
29		BAB	1	B	843.58	11.0000	7340.30	6720.97	0.06207	11.1675	2	B	8.81299	8.9011	6.73765	8.81299	8.9011	6.73765
30		BAB	1	B	691.12	5.0000	6656.54	5499.73	0.04431	15.6421	2	B	8.61245	8.8034	6.53831	8.61245	8.8034	6.53831
31		BAB	1	B	703.91	11.0000	9194.52	7914.86	0.03877	17.8775	2	B	8.97650	9.1264	6.55665	8.97650	9.1264	6.55665
32		BAB	1	B	1667.77	8.0000	11611.48	10394.83	0.20159	3.4383	2	B	9.24906	9.3597	7.41924	9.24906	9.3597	7.41924
33		BAB	1	B	946.71	10.0000	9076.07	7504.13	0.04476	15.4875	2	B	8.92321	9.1134	6.85299	8.92321	9.1134	6.85299
34		BAB	1	B	1022.49	12.0000	7886.15	7745.49	0.07774	8.9159	2	B	8.95487	8.9729	6.93000	8.95487	8.9729	6.93000
35		BAB	1	B	787.45	12.0000	8458.61	7003.44	0.06413	10.8086	2	B	8.85416	9.0429	6.66880	8.85416	9.0429	6.66880
36		BAB	1	B	305.41	13.0000	5128.41	4600.10	0.08436	8.2164	2	B	8.43383	8.5426	5.72166	8.43383	8.5426	5.72166
37		BAB	1	B	558.71	30.0000	15480.34	15263.76	.	.	2	B	9.63324	9.6473	6.32563	9.63324	9.6473	6.32563
38		BAB	1	B	380.96	12.0000	4151.96	3906.87	0.06003	11.5459	2	B	8.27049	8.3313	5.94269	8.27049	8.3313	5.94269
39		BAB	1	B	233.94	18.0000	4870.73	4565.78	0.08384	8.2673	2	B	8.42635	8.4910	5.45506	8.42635	8.4910	5.45506
40		BBA	1	B	702.37	5.0000	8641.03	7303.19	0.08839	7.8416	3	B	8.89607	9.0643	6.55446	8.89607	9.0643	6.55446
41		BBA	1	B	4582.53	8.0000	25872.46	16996.58	0.02375	29.1861	3	B	9.74077	10.1609	8.43001	9.74077	10.1609	8.43001
42		BBA	1	B	224.49	48.0000	8909.20	4393.94	.	.	3	B	8.38798	9.0948	5.41383	8.38798	9.0948	5.41383
43		BBA	1	B	1151.87	9.0000	7880.38	5997.24	0.05814	11.9220	3	B	8.69905	8.9721	7.04914	8.69905	8.9721	7.04914
44		BBA	1	B	604.04	13.0000	9488.41	9110.08	0.19978	3.4696	3	B	9.11714	9.1578	6.40364	9.11714	9.1578	6.40364
45		BBA	1	B	354.12	11.0000	6425.48	5220.09	0.07593	9.1286	3	B	8.56027	8.7680	5.86964	8.56027	8.7680	5.86964
46		BBA	1	B	1842.76	4.0000	13229.57	8653.30	0.21788	3.1813	3	B	9.06570	9.4902	7.51902	9.06570	9.4902	7.51902
47		BBA	1	B	1654.68	4.0000	10716.33	6667.43	0.05162	13.4281	3	B	8.80499	9.2795	7.41136	8.80499	9.2795	7.41136

Obs	subj	sequ	per	treat	CMAX	TMAX	AUCI	AUCT	KEL	THALF	SEQ	TRT	LAUCT	LAUCINF	LCMAX	lat1r	lai1r	lc1r
48	(b) (6)	BBA	1	B	1023.07	9.0000	9027.26	7439.47	0.07017	9.8782	3	B	8.91455	9.1080	6.93056	8.91455	9.1080	6.93056
49		BBA	1	B	227.14	9.0000	6344.29	6243.38	0.04426	15.6613	3	B	8.73928	8.7553	5.42557	8.73928	8.7553	5.42557
50		BBA	1	B	376.55	18.0000	13109.04	9311.27	.	.	3	B	9.13898	9.4811	5.93105	9.13898	9.4811	5.93105
51		BBA	1	B	310.66	12.0000	4782.56	3941.99	0.04236	16.3638	3	B	8.27944	8.4727	5.73870	8.27944	8.4727	5.73870
52		BBA	1	B	813.35	10.0000	9990.88	7528.56	0.02015	34.3952	3	B	8.92646	9.2094	6.70116	8.92646	9.2094	6.70116
53		BBA	1	B	231.27	5.0000	8344.29	6105.39	0.02075	33.3987	3	B	8.71693	9.0293	5.44359	8.71693	9.0293	5.44359
54		BBA	1	B	1161.55	10.0000	15470.72	11651.00	.	.	3	B	9.36315	9.6467	7.05751	9.36315	9.6467	7.05751
55		BBA	1	B	575.71	12.0000	4701.89	4446.36	0.33874	2.0463	3	B	8.39984	8.4557	6.35560	8.39984	8.4557	6.35560
56		BBA	1	B	445.36	13.0000	11778.07	9835.16	.	.	3	B	9.19372	9.3740	6.09888	9.19372	9.3740	6.09888
57		BBA	1	B	795.77	11.0000	11502.18	9960.42	0.07068	9.8073	3	B	9.20637	9.3503	6.67931	9.20637	9.3503	6.67931
58		BBA	1	B	1493.03	11.0000	13922.42	12582.78	0.03464	20.0114	3	B	9.44008	9.5413	7.30856	9.44008	9.5413	7.30856

ref2

Obs	subj	sequ	per	treat	CMAX	TMAX	AUCI	AUCT	KEL	THALF	SEQ	TRT	LAUCT	LAUCINF	LCMAX	lat2r	lai2r	lc2r
1	(b) (6)	ABB	3	B	5404.78	6.00	17809.48	7516.13	.	.	1	B	8.92481	9.7875	8.59504	8.92481	9.7875	8.59504
2		ABB	3	B	460.27	13.00	7563.11	5668.63	.	.	1	B	8.64270	8.9310	6.13181	8.64270	8.9310	6.13181
3		ABB	3	B	1497.93	6.00	11881.55	8743.20	0.0421	16.4618	1	B	9.07603	9.3827	7.31184	9.07603	9.3827	7.31184
4		ABB	3	B	908.05	9.00	9587.91	7757.61	0.0321	21.5690	1	B	8.95643	9.1683	6.81130	8.95643	9.1683	6.81130
5		ABB	3	B	1862.91	5.00	17706.74	14657.47	0.2055	3.3726	1	B	9.59271	9.7817	7.52990	9.59271	9.7817	7.52990
6		ABB	3	B	744.29	12.00	7163.74	6583.21	0.1370	5.0604	1	B	8.79228	8.8768	6.61243	8.79228	8.8768	6.61243
7		ABB	3	B	1478.72	5.00	16382.13	12579.87	0.0942	7.3617	1	B	9.43985	9.7039	7.29893	9.43985	9.7039	7.29893
8		ABB	3	B	936.53	12.00	8348.74	7944.29	0.1259	5.5061	1	B	8.98021	9.0299	6.84218	8.98021	9.0299	6.84218
9		ABB	3	B	697.11	28.00	14060.84	13694.90	0.0646	10.7385	1	B	9.52478	9.5511	6.54694	9.52478	9.5511	6.54694
10		ABB	3	B	425.67	13.00	5825.22	5551.09	0.4788	1.4476	1	B	8.62175	8.6700	6.05366	8.62175	8.6700	6.05366

Obs	subj	sequ	per	treat	CMAX	TMAX	AUCI	AUCT	KEL	THALF	SEQ	TRT	LAUCT	LAUCINF	LCMAX	lat2r	lai2r	lc2r
11	(b) (6)	ABB	3	B	1445.81	11.05	11926.17	11048.24	35.0000	.	1	B	9.31003	9.3865	7.27642	9.31003	9.3865	7.27642
12		ABB	3	B	950.74	5.00	10684.05	6235.44	.	.	1	B	8.73800	9.2765	6.85724	8.73800	9.2765	6.85724
13		ABB	3	B	560.84	30.00	9952.40	9828.89	.	.	1	B	9.19308	9.2056	6.32944	9.19308	9.2056	6.32944
14		ABB	3	B	749.88	8.00	7401.00	6004.63	0.0294	23.5480	1	B	8.70029	8.9094	6.61991	8.70029	8.9094	6.61991
15		ABB	3	B	2413.34	5.00	13887.12	9749.42	0.1045	6.6322	1	B	9.18496	9.5387	7.78877	9.18496	9.5387	7.78877
16		ABB	3	B	440.41	11.00	5633.55	5346.66	0.0952	7.2837	1	B	8.58423	8.6365	6.08771	8.58423	8.6365	6.08771
17		ABB	3	B	446.31	12.00	5655.23	4763.52	0.0352	19.7079	1	B	8.46874	8.6403	6.10101	8.46874	8.6403	6.10101
18		ABB	3	B	1029.04	13.00	11540.43	9913.44	0.1304	5.3168	1	B	9.20165	9.3536	6.93638	9.20165	9.3536	6.93638
19		ABB	3	B	683.53	26.00	16598.28	16577.49	0.0303	22.8570	1	B	9.71580	9.7171	6.52727	9.71580	9.7171	6.52727
20		ABB	3	B	609.79	10.00	5483.11	4935.36	0.0627	11.0548	1	B	8.50418	8.6094	6.41311	8.50418	8.6094	6.41311
21		ABB	3	B	742.61	9.00	6044.09	4654.89	0.0839	8.2623	1	B	8.44567	8.7068	6.61017	8.44567	8.7068	6.61017
22		BAB	3	B	1934.49	6.00	10867.80	6038.78	0.0743	9.3266	2	B	8.70596	9.2936	7.56760	8.70596	9.2936	7.56760
23		BAB	3	B	552.67	5.00	4557.08	3176.60	0.1375	5.0406	2	B	8.06357	8.4244	6.31476	8.06357	8.4244	6.31476
24		BAB	3	B	1566.70	10.00	20836.92	17243.04	0.0929	7.4620	2	B	9.75516	9.9445	7.35673	9.75516	9.9445	7.35673
25		BAB	3	B	796.48	10.00	9455.29	6518.61	0.0625	11.0882	2	B	8.78242	9.1543	6.68020	8.78242	9.1543	6.68020
26		BAB	3	B	1348.81	10.00	12919.02	11343.30	0.1151	6.0242	2	B	9.33638	9.4665	7.20698	9.33638	9.4665	7.20698
27		BAB	3	B	236.99	11.00	2337.82	2231.06	0.2225	3.1155	2	B	7.71023	7.7570	5.46802	7.71023	7.7570	5.46802
28		BAB	3	B	3193.33	8.00	15034.16	9705.43	0.0706	9.8224	2	B	9.18044	9.6181	8.06882	9.18044	9.6181	8.06882
29		BAB	3	B	1151.38	11.00	9084.40	8373.48	0.0726	9.5493	2	B	9.03283	9.1143	7.04872	9.03283	9.1143	7.04872
30		BAB	3	B	888.44	5.00	10499.71	7689.20	0.0635	10.9161	2	B	8.94757	9.2591	6.78947	8.94757	9.2591	6.78947
31		BAB	3	B	421.11	8.00	12849.16	8639.09	0.0434	15.9582	2	B	9.06405	9.4610	6.04289	9.06405	9.4610	6.04289
32		BAB	3	B	1466.03	7.00	10966.71	8763.86	0.1607	4.3144	2	B	9.07839	9.3026	7.29031	9.07839	9.3026	7.29031
33		BAB	3	B	507.34	12.00	5751.23	4915.27	0.1326	5.2272	2	B	8.50010	8.6572	6.22918	8.50010	8.6572	6.22918
34		BAB	3	B	1267.32	11.00	12072.87	10194.13	0.0383	18.1098	2	B	9.22957	9.3987	7.14466	9.22957	9.3987	7.14466
35		BAB	3	B	1418.23	9.00	15792.33	11610.83	0.0728	9.5243	2	B	9.35969	9.6673	7.25716	9.35969	9.6673	7.25716

Obs	subj	sequ	per	treat	CMAX	TMAX	AUCI	AUCT	KEL	THALF	SEQ	TRT	LAUCT	LAUCINF	LCMAX	lat2r	lai2r	lc2r
36	(b) (6)	BAB	3	B	1332.81	11.00	12640.33	11418.30	0.1157	5.9922	2	B	9.34297	9.4446	7.19504	9.34297	9.4446	7.19504
37		BAB	3	B	572.71	28.00	14922.61	13633.03	0.0665	10.4309	2	B	9.52025	9.6106	6.35038	9.52025	9.6106	6.35038
38		BAB	3	B	293.26	13.00	4387.39	3902.83	0.0938	7.3874	2	B	8.26946	8.3865	5.68106	8.26946	8.3865	5.68106
39		BAB	3	B	746.32	13.00	8616.59	7829.59	0.0516	13.4306	2	B	8.96567	9.0614	6.61515	8.96567	9.0614	6.61515
40		BBA	2	B	905.48	10.00	8510.11	8281.63	0.0495	13.9989	3	B	9.02180	9.0490	6.80847	9.02180	9.0490	6.80847
41		BBA	2	B	4341.62	8.00	24497.28	19989.18	0.0502	13.8157	3	B	9.90295	10.1063	8.37600	9.90295	10.1063	8.37600
42		BBA	2	B	176.40	36.00	3144.06	3144.06	.	.	3	B	8.05327	8.0533	5.17275	8.05327	8.0533	5.17275
43		BBA	2	B	1007.09	11.00	8638.12	6907.86	0.0802	8.6429	3	B	8.84041	9.0639	6.91482	8.84041	9.0639	6.91482
44		BBA	2	B	487.41	10.00	10243.27	9892.79	0.1077	6.4370	3	B	9.19956	9.2344	6.18911	9.19956	9.2344	6.18911
45		BBA	2	B	210.11	11.00	4028.49	3758.16	.	.	3	B	8.23168	8.3011	5.34763	8.23168	8.3011	5.34763
46		BBA	2	B	621.78	11.00	9268.03	7696.96	0.4987	1.3899	3	B	8.94858	9.1343	6.43259	8.94858	9.1343	6.43259
47		BBA	2	B	841.72	11.00	7137.93	6398.43	0.0289	23.9965	3	B	8.76381	8.8732	6.73545	8.76381	8.8732	6.73545
48		BBA	2	B	951.18	12.00	10433.64	8739.20	0.0848	8.1711	3	B	9.07557	9.2528	6.85770	9.07557	9.2528	6.85770
49		BBA	2	B	536.44	8.00	4112.36	2480.90	0.0966	7.1762	3	B	7.81638	8.3218	6.28495	7.81638	8.3218	6.28495
50		BBA	2	B	1032.12	4.00	8655.96	5463.56	0.0250	27.7284	3	B	8.60585	9.0660	6.93937	8.60585	9.0660	6.93937
51		BBA	2	B	1659.32	5.00	14393.97	9608.70	0.0191	36.2865	3	B	9.17042	9.5746	7.41416	9.17042	9.5746	7.41416
52		BBA	2	B	4501.98	8.00	13121.35	9689.02	.	.	3	B	9.17875	9.4820	8.41227	9.17875	9.4820	8.41227
53		BBA	2	B	3805.98	5.15	20494.07	10075.62	.	.	3	B	9.21787	9.9279	8.24433	9.21787	9.9279	8.24433
54		BBA	2	B	111.03	9.00	915.35	671.69	0.0917	7.5559	3	B	6.50980	6.8193	4.70980	6.50980	6.8193	4.70980
55		BBA	2	B	1201.41	8.00	9715.75	7065.79	.	.	3	B	8.86302	9.1815	7.09125	8.86302	9.1815	7.09125
56		BBA	2	B	1994.15	5.00	9307.00	5507.37	0.0260	26.6695	3	B	8.61384	9.1385	7.59797	8.61384	9.1385	7.59797
57		BBA	2	B	2926.11	10.00	21735.98	19292.62	0.0376	18.4191	3	B	9.86748	9.9867	7.98143	9.86748	9.9867	7.98143

dataset for scaled average BE

Obs	subj	per	SEQ	TRT	ilat	ilai	ilc	dlat	dlai	dlc
1	(b) (6)	3	1	B	-0.31771	-0.11139	-0.06665	-0.09813	-0.00470	0.01662
2		3	1	B	0.84438	0.71012	0.37825	-0.05739	-0.33850	-0.03707
3		3	1	B	-0.14933	-0.24579	-0.19787	0.31554	0.12628	-0.47546
4		3	1	B	-0.32984	-0.57011	-0.02841	0.04876	0.10565	-0.02977
5		3	1	B	0.27272	-0.10414	-0.90159	-0.32710	0.05221	0.51941
6		3	1	B	-0.36235	-0.45379	-0.98195	-0.05367	0.00510	0.48642
7		3	1	B	-0.02295	-0.24437	-0.96283	-0.63203	-0.55944	-0.29801
8		3	1	B	-0.07479	-0.08508	-0.49583	-0.00769	0.30937	0.72221
9		3	1	B	0.24405	0.13976	-0.34907	-0.30969	-0.15384	0.55251
10		3	1	B	0.22618	0.13065	-0.04051	0.33009	0.42474	-0.02125
11		3	1	B	-0.57362	0.23501	1.41612	-0.51891	-0.26613	-0.56734
12		3	1	B	-0.08382	-0.33190	-1.91005	-0.30235	-0.13236	0.29814
13		3	1	B	-0.21388	0.15188	0.86073	-0.24450	-0.01916	0.70308
14		3	1	B	-0.46743	0.04369	0.89037	-0.10059	-0.11520	-0.00079
15		3	1	B	-0.34353	-0.46595	-0.75571	-0.41219	-0.70101	-1.89093
16		3	1	B	-0.93230	-0.98188	-0.50515	-0.24173	-0.23941	-0.10420
17		3	1	B	-0.01315	0.42622	1.24148	0.02160	-0.03132	0.11663
18		3	1	B	-0.46408	-0.31033	-0.47267	0.09820	0.45419	1.03740
19		3	1	B	0.10511	0.20096	0.25603	-0.60824	-0.43846	-0.51534
20		3	1	B	0.10660	0.21904	0.41701	0.17837	0.24520	0.08068
21		3	1	B	0.37597	0.25988	-0.34056	-0.16884	-0.23653	-0.15645
22		3	2	B	-0.13699	-0.61708	-1.57721	-0.22669	0.22108	0.39710
23		3	2	B	0.00503	-0.18101	-0.62808	-0.05567	-0.32677	-0.71275
24		3	2	B	0.00246	-0.13552	-0.13174	-0.92448	-0.75443	-0.10745
25		3	2	B	0.04436	-0.37381	-1.19106	-0.27828	0.29599	1.90886
26		3	2	B	-0.13609	-0.18522	-0.74019	-0.55035	-0.35458	-0.53682
27		3	2	B	3.49690	1.39425	1.25641	-5.25064	-0.56642	0.73438
28		3	2	B	-0.39080	-0.50644	-1.02922	-0.27620	-0.23891	-0.48292
29		3	2	B	0.20984	0.23848	-0.70492	-0.21984	-0.21318	-0.31106

Obs	subj	per	SEQ	TRT	ilat	ilai	ilc	dlat	dlai	dlc
30	(b) (6)	3	2	B	-0.17019	-0.05104	0.56812	-0.33512	-0.45575	-0.25115
31		3	2	B	0.17625	0.20206	-0.14874	-0.08756	-0.33467	0.51376
32		3	2	B	-1.13871	-0.92142	-1.13612	0.17067	0.05713	0.12893
33		3	2	B	0.02861	-0.04164	-0.23308	0.42311	0.45623	0.62381
34		3	2	B	0.04348	0.16185	-0.13725	-0.27470	-0.42585	-0.21466
35		3	2	B	0.16320	0.34005	0.60009	-0.50554	-0.62434	-0.58837
36		3	2	B	0.78170	0.69748	0.45813	-0.90914	-0.90210	-1.47339
37		3	2	B	-0.74626	-0.32807	1.33604	0.11299	0.03669	-0.02475
38		3	2	B	-0.06458	0.74177	1.98722	0.00103	-0.05515	0.26163
39		3	2	B	0.45108	0.38223	-0.00527	-0.53932	-0.57044	-1.16009
40		2	3	B	0.03319	0.08447	-0.54324	-0.12573	0.01527	-0.25400
41		2	3	B	-0.52045	-0.29197	-0.22150	-0.16218	0.05462	0.05400
42		2	3	B	0.65571	0.84787	0.95591	0.33471	1.04157	0.24108
43		2	3	B	-0.00550	-0.03068	-0.28257	-0.14136	-0.09181	0.13432
44		2	3	B	-0.00437	0.19374	0.40225	-0.08242	-0.07655	0.21453
45		2	3	B	-0.21594	-0.14781	-0.75084	0.32859	0.46688	0.52200
46		2	3	B	-0.61295	-0.62153	-0.90775	0.11712	0.35588	1.08643
47		2	3	B	0.38193	0.26447	-0.43006	0.04118	0.40635	0.67592
48		2	3	B	0.28566	0.22027	-0.10298	-0.16102	-0.14479	0.07286
49		2	3	B	0.90619	0.66016	0.52762	0.92290	0.43356	-0.85939
50		1	3	B	.	.	.	.	.	.
51		2	3	B	0.34725	0.32517	-0.59293	-0.32641	-0.59327	-1.20067
52		2	3	B	0.21714	0.01726	-0.55718	-0.24396	-0.36514	-0.71300
53		2	3	B	-0.48358	-0.51693	-0.55954	-0.46182	-0.45266	-2.96869
54		2	3	B	-0.29554	-0.31619	0.36243	0.14527	-0.28119	-1.18682
55		2	3	B	1.27572	1.09358	0.57512	1.89005	1.63641	1.64580
56		2	3	B	-0.62301	-0.77462	-0.65540	0.33070	0.19249	-0.99237
57		2	3	B	0.48072	0.20044	-0.70259	0.59253	0.21177	-0.91866
58		2	3	B	0.04273	0.03092	0.03437	-0.42739	-0.44547	-0.67287

unscaled BE 90% CI - guidance version

The Mixed Procedure

Model Information	
Data Set	WORK.PKN
Dependent Variable	LCMAX
Covariance Structures	Factor Analytic, Variance Components
Subject Effects	subj, subj
Group Effect	TRT
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Satterthwaite

Class Level Information	
Class	Levels Values
SEQ	3 1 2 3
subj	58 1 2 3 4 5 6 7 8 9 10 11 13 14 15 16 18 19 21 22 23 24 25 26 27 28 29 30 32 33 34 35 36 37 40 41 42 43 44 45 46 47 49 50 51 52 53 54 55 56 57 58 59 61 62 63 64 65 66
per	3 1 2 3
TRT	2 A B

Dimensions	
Covariance Parameters	5
Columns in X	9
Columns in Z Per Subject	2
Subjects	58
Max Obs Per Subject	3

Number of Observations	
Number of Observations Read	173
Number of Observations Used	173
Number of Observations Not Used	0

Iteration History				
Iteration	Evaluations	-2 Res Log Like	Criterion	
0	1	416.67099342		
1	2	393.83834304	0.13853596	
2	1	391.01755730	0.00743303	
3	1	390.76410881	0.26193662	
4	1	390.74679921	0.00044553	
5	1	390.74676802	0.00000001	
6	1	390.74676802	0.00000000	

Convergence criteria met but final hessian is not positive definite.

Estimated G Matrix					
Row	Effect	TRT	subj	Col1	Col2
1	TRT	A	1	0.5015	0.2232
2	TRT	B	1	0.2232	0.3103

Covariance Parameter Estimates			
Cov Parm	Subject	Group	Estimate
FA(1,1)	subj		0.7082
FA(2,1)	subj		0.3152
FA(2,2)	subj		0.4593
Residual	subj	TRT A	0.09261
Residual	subj	TRT B	0.3275

Fit Statistics	
-2 Res Log Likelihood	390.7
AIC (smaller is better)	400.7
AICC (smaller is better)	401.1
BIC (smaller is better)	411.0

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
4	25.92	<.0001

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
SEQ	2	55.4	0.35	0.7083
per	2	111	0.74	0.4794
TRT	1	56.3	1.23	0.2725

Estimates								
Label	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
T vs. R	-0.1150	0.1038	56.3	-1.11	0.2725	0.1	-0.2886	0.05855

Least Squares Means						
Effect	TRT	Estimate	Standard Error	DF	t Value	Pr > t
TRT	A	6.6448	0.1014	55.5	65.55	<.0001
TRT	B	6.7598	0.09076	55.4	74.48	<.0001

unscaled BE 90% CI - guidance version

The Mixed Procedure

Model Information	
Data Set	WORK.PKN
Dependent Variable	LAUCT
Covariance Structures	Factor Analytic, Variance Components
Subject Effects	subj, subj
Group Effect	TRT
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Satterthwaite

Class Level Information

Class	Levels	Values
SEQ	3	1 2 3
subj	58	1 2 3 4 5 6 7 8 9 10 11 13 14 15 16 18 19 21 22 23 24 25 26 27 28 29 30 32 33 34 35 36 37 40 41 42 43 44 45 46 47 49 50 51 52 53 54 55 56 57 58 59 61 62 63 64 65 66
per	3	1 2 3
TRT	2	A B

Dimensions	
Covariance Parameters	5
Columns in X	9
Columns in Z Per Subject	2
Subjects	58
Max Obs Per Subject	3

Number of Observations	
Number of Observations Read	173
Number of Observations Used	173
Number of Observations Not Used	0

Iteration History			
Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	364.41562603	
1	2	334.79749995	3.05680818
2	1	327.73577400	0.07101400
3	1	327.25929342	28.09292324
4	1	327.14722131	0.37996779
5	1	327.14509155	0.00014580
6	1	327.14509034	0.00000000

Convergence criteria met but final hessian is not positive definite.

Estimated G Matrix

Row	Effect	TRT	subj	Col1	Col2
1	TRT	A	1	0.1288	0.1086
2	TRT	B	1	0.1086	0.2671

Covariance Parameter Estimates			
Cov Parm	Subject	Group	Estimate
FA(1,1)	subj		0.3589
FA(2,1)	subj		0.3025
FA(2,2)	subj		0.4190
Residual	subj	TRT A	0.08129
Residual	subj	TRT B	0.3122

Fit Statistics	
-2 Res Log Likelihood	327.1
AIC (smaller is better)	337.1
AICC (smaller is better)	337.5
BIC (smaller is better)	347.4

Null Model Likelihood Ratio Test		
DF	Chi-Square	Pr > ChiSq
4	37.27	<.0001

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
SEQ	2	64.9	0.29	0.7473
per	2	112	2.79	0.0660
TRT	1	55.4	0.29	0.5917

Estimates								
Label	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
T vs. R	0.04584	0.08497	55.4	0.54	0.5917	0.1	-0.09631	0.1880

Least Squares Means						
Effect	TRT	Estimate	Standard Error	DF	t Value	Pr > t
TRT	A	8.8562	0.06030	54.9	146.87	<.0001
TRT	B	8.8104	0.08573	55.1	102.77	<.0001

unscaled BE 90% CI - guidance version

The Mixed Procedure

Model Information	
Data Set	WORK.PKN
Dependent Variable	LAUCINF
Covariance Structures	Factor Analytic, Variance Components
Subject Effects	subj, subj
Group Effect	TRT
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Satterthwaite

Class Level Information		
Class	Levels	Values
SEQ	3	1 2 3
subj	58	1 2 3 4 5 6 7 8 9 10 11 13 14 15 16 18 19 21 22 23 24 25 26 27 28 29 30 32 33 34 35 36 37 40 41 42 43 44 45 46 47 49 50 51 52 53 54 55 56 57 58 59 61 62 63 64 65 66
per	3	1 2 3
TRT	2	A B

Dimensions	
Covariance Parameters	5
Columns in X	9
Columns in Z Per Subject	2

Dimensions	
Subjects	58
Max Obs Per Subject	3

Number of Observations	
Number of Observations Read	173
Number of Observations Used	173
Number of Observations Not Used	0

Iteration History				
Iteration	Evaluations	-2 Res	Log Like	Criterion
0	1	270.36886123		
1	2	222.29337905	0.51882390	
2	1	217.25797071	0.03582566	
3	1	216.11697477	0.00019281	
4	1	216.10837700	0.00070124	
5	1	216.10836868	0.00000002	
6	1	216.10836868	0.00000000	

Convergence criteria met but final hessian is not positive definite.

Estimated G Matrix					
Row	Effect	TRT	subj	Col1	Col2
1	TRT	A	1	0.1700	0.1117
2	TRT	B	1	0.1117	0.1993

Covariance Parameter Estimates			
Cov Parm	Subject	Group	Estimate
FA(1,1)	subj		0.4123
FA(2,1)	subj		0.2710
FA(2,2)	subj		0.3547
Residual	subj	TRT A	0.02979

Covariance Parameter Estimates

Cov Parm	Subject	Group	Estimate
Residual	subj	TRT B	0.09097

Fit Statistics

-2 Res Log Likelihood	216.1
AIC (smaller is better)	226.1
AICC (smaller is better)	226.5
BIC (smaller is better)	236.4

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
4	54.26	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
SEQ	2	57.6	0.08	0.9257
per	2	106	2.42	0.0936
TRT	1	56.2	0.03	0.8656

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
T vs. R	0.01052	0.06187	56.2	0.17	0.8656	0.1	-0.09295	0.1140

Least Squares Means

Effect	TRT	Estimate	Standard Error	DF	t Value	Pr > t
TRT	A	9.1107	0.05880	55.1	154.94	<.0001
TRT	B	9.1002	0.06514	55.4	139.70	<.0001

scaled average BE intermediate analysis - &ipar glm
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The GLM Procedure

Class Level Information

Class	Levels	Values
SEQ	3	1 2 3

Number of Observations Read	58
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Number of Observations Used	57
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scaled average BE intermediate analysis - &ipar glm
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The GLM Procedure

Dependent Variable: ilat

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	0.70572564	0.35286282	0.84	0.4355
Error	54	22.57132954	0.41798758		
Corrected Total	56	23.27705518			

R-Square	Coeff Var	Root MSE	ilat Mean
0.030319	1595.016	0.646520	0.040534

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	2	0.70572564	0.35286282	0.84	0.4355

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	2	0.70572564	0.35286282	0.84	0.4355

Parameter	Estimate	Standard Error	t Value	Pr > t 	90% Confidence Limits
average	0.04853633	0.08585986	0.57	0.5742	-0.09515572 0.19222837

dev iglmilat1

Obs	Dependent	Source	DF	SS	MS	FValue	ProbF
1	ilat	Model	2	0.70572564	0.35286282	0.84	0.4355
2	ilat	Error	54	22.57132954	0.41798758	—	—
3	ilat	Corrected Total	56	23.27705518	—	—	—

scaled average BE
intermediate analysis - &dpar glm

The GLM Procedure

Class Level Information

Class	Levels	Values
SEQ	3	1 2 3

Number of Observations Read 58

Number of Observations Used 57

scaled average BE
intermediate analysis - &dpar glm

The GLM Procedure

Dependent Variable: dlat

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	4.23537826	2.11768913	3.53	0.0363
Error	54	32.42195823	0.60040663		
Corrected Total	56	36.65733648			

R-Square	Coeff Var	Root MSE	dlat Mean
0.115540	-431.0866	0.774859	-0.179746

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	2	4.23537826	2.11768913	3.53	0.0363

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	2	4.23537826	2.11768913	3.53	0.0363

output needed for mixed scaled av. BE - using glm

Obs	method_used	unscale_lower	unscale_upper	dfi	s2i	param	StdErr	pointest
1	Scaled/PE	0.90819	1.20682	54	0.41799	LAUCT	0.08585986	1.04973

.005016

final output - ¶meter - using glm

Obs	method_used	unscale_lower	unscale_upper	param	pointest	s2wr	sWR	critbound	outc
1	Scaled/PE	0.90819	1.20682	LAUCT	1.04973	0.30020	0.54791	-0.17082	PAS

scaled average BE
intermediate analysis - &ipar glm

The GLM Procedure

Class Level Information

Class	Levels	Values
SEQ	3	1 2 3

Number of Observations Read 58

Number of Observations Used 57

scaled average BE
intermediate analysis - &ipar glm

The GLM Procedure

Dependent Variable: ilai

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	0.20615037	0.10307518	0.46	0.6343
Error	54	12.12604783	0.22455644		
Corrected Total	56	12.33219819			

R-Square	Coeff Var	Root MSE	ilai Mean
0.016716	4043.331	0.473874	0.011720

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	2	0.20615037	0.10307518	0.46	0.6343

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	2	0.20615037	0.10307518	0.46	0.6343

Parameter	Estimate	Standard Error	t Value	Pr > t	90% Confidence Limits
average	0.01604161	0.06293196	0.25	0.7998	-0.08927910 0.12136232

dev iglmilai1

Obs	Dependent	Source	DF	SS	MS	FValue	ProbF
1	ilai	Model	2	0.20615037	0.10307518	0.46	0.6343
2	ilai	Error	54	12.12604783	0.22455644	—	—
3	ilai	Corrected Total	56	12.33219819	—	—	—

scaled average BE
intermediate analysis - &dpar glm

The GLM Procedure

Class Level Information

Class	Levels	Values
SEQ	3	1 2 3

Number of Observations Read 58

Number of Observations Used 57

scaled average BE
intermediate analysis - &dpar glm

The GLM Procedure

Dependent Variable: dlai

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	1.40835658	0.70417829	4.04	0.0231
Error	54	9.40352362	0.17413933		

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Corrected Total	56	10.81188019			

R-Square	Coeff Var	Root MSE	dlai Mean
0.130260	-609.1376	0.417300	-0.068507

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	2	1.40835658	0.70417829	4.04	0.0231

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	2	1.40835658	0.70417829	4.04	0.0231

output needed for mixed scaled av. BE - using glm

Obs	method_used	unscale_lower	unscale_upper	dfi	s2i	param	StdErr	pointest
1	Scaled/PE	0.91124	1.12074	54	0.22456	LAUCINF	0.06293196	1.01617

.0037

final output - ¶meter - using glm

Obs	method_used	unscale_lower	unscale_upper	param	pointest	s2wr	sWR	critbound
1	Scaled/PE	0.91124	1.12074	LAUCINF	1.01617	0.087070	0.29508	-0.047687

scaled average BE
intermediate analysis - &ipar glm

The GLM Procedure

Class Level Information

Class	Levels	Values
SEQ	3	1 2 3

Number of Observations Read	58
Number of Observations Used	57

scaled average BE

intermediate analysis - &ipar glm

The GLM Procedure

Dependent Variable: ilc

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	0.11316566	0.05658283	0.09	0.9143
Error	54	34.04297048	0.63042538		
Corrected Total	56	34.15613615			

R-Square	Coeff Var	Root MSE	ilc Mean
0.003313	-607.1125	0.793993	-0.130782

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	2	0.11316566	0.05658283	0.09	0.9143

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	2	0.11316566	0.05658283	0.09	0.9143

Parameter	Estimate	Standard Error	t Value	Pr > t	90% Confidence Limits
average	-0.13130457	0.10544484	-1.25	0.2184	-0.30777334 0.04516421

dev iglmilc1

Obs	Dependent	Source	DF	SS	MS	FValue	ProbF
1	ilc	Model	2	0.11316566	0.05658283	0.09	0.9143
2	ilc	Error	54	34.04297048	0.63042538	—	—
3	ilc	Corrected Total	56	34.15613615	—	—	—

scaled average BE

intermediate analysis - &dpar glm

The GLM Procedure

Class Level Information

Class	Levels	Values
SEQ	3	1 2 3

Number of Observations Read 58

Number of Observations Used 57

scaled average BE

intermediate analysis - &dp ar glm

The GLM Procedure

Dependent Variable: dlc

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	0.93136685	0.46568342	0.70	0.5033
Error	54	36.16489551	0.66972029		
Corrected Total	56	37.09626236			

R-Square Coeff Var Root MSE dlc Mean

0.025107 -780.3124 0.818364 -0.104877

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	2	0.93136685	0.46568342	0.70	0.5033

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	2	0.93136685	0.46568342	0.70	0.5033

output needed for mixed scaled av. BE - using glm

Obs	method_used	unscape_lower	unscape_upper	dfi	s2i	param	StdErr	pointest	
1	Scaled/PE	0.74935	1.06030	54	0.63043	LCMAX	0.10544484	0.87695	.006122

final output - ¶meter - using glm

Obs	method_used	unscape_lower	unscape_upper	param	pointest	s2wr	sWR	critbound	out
1	Scaled/PE	0.74935	1.06030	LCMAX	0.87695	0.33486	0.57867	-0.14950	PA

ANDA: 091640-fasting STUDY TYPE: Fasting

SUMMARY OF STATISTICAL ANALYSIS - UNSCALED DATA

Parameter	Geometric Means			90% CI	
	Test	Reference	T/R Ratio	Lower CI	Upper CI
LAUCT	7017.89	6703.45	1.05	90.82	120.68
LAUCI	9051.89	8957.16	1.01	91.12	112.07
LCMAX	768.81	862.51	0.89	74.93	106.03

SUMMARY OF STATISTICAL ANALYSIS - SCALED DATA

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	1.05	90.82	120.68	0.3002033	0.5479081	-0.170822	Scaled/PE	PASS
LAUCI	1.02	91.12	112.07	0.0870697	0.2950757	-0.047687	Scaled/PE	PASS
LCMAX	0.88	74.93	106.03	0.3348601	0.578671	-0.149502	Scaled/PE	PASS

4.7.4 Fed Study Data

Fed CONCENTRATION DATASET

Obs	sub	sequ	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
1	(b) (6)	BAB	1	B1	0.00	0.00	0.00	0.00	990.02	392.87	176.51	172.37	142.04	122.54	118.70	112.51	119.97	132.03	128.40
2		BAB	2	A	0.00	0.00	0.00	0.00	118.21	89.33	86.87	140.08	138.63	170.49	175.36	192.56	216.31	218.74	195.87
3		BAB	3	B2	0.00	0.00	0.00	0.00	620.44	781.24	846.67	242.80	148.53	176.77	196.60	204.75	203.31	186.32	178.43
4		ABB	1	A	0.00	0.00	0.00	5.79	203.71	255.29	211.38	180.94	217.57	262.99	271.02	291.13	313.49	313.64	315.18
5		ABB	2	B1	0.00	0.00	0.00	3636.60	594.01	408.43	274.86	190.28	144.48	116.71	97.59	124.57	115.96	111.02	107.73
6		ABB	3	B2	0.00	0.00	0.00	0.00	409.55	165.22	142.41	149.73	163.76	151.13	175.68	182.75	233.86	210.87	224.72
7		BBA	1	B1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	3.38	13.23	14.68	9.95	23.33	20.82	21.31	28.77
8		BBA	2	B2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	9.82	21.74	34.10	61.22	137.11
9		BBA	3	A	0.00	0.00	0.00	727.55	159.64	205.06	214.31	170.65	97.28	72.06	72.40	73.27	82.81	94.61	43.09
10		BAB	1	B1	0.00	0.00	0.00	0.00	101.11	75.10	92.69	166.13	248.46	266.25	301.10	319.95	339.55	357.27	413.76
11		BAB	2	A	0.00	0.00	0.00	0.00	20.43	72.23	85.00	125.38	254.70	273.77	217.17	263.13	203.55	172.92	163.51
12		BAB	3	B2	0.00	0.00	0.00	668.23	254.81	280.23	277.61	275.77	276.74	261.51	238.42	257.09	178.13	179.47	157.95
13		BBA	1	B1	0.00	0.00	0.00	8.04	89.98	80.60	128.56	326.90	215.14	237.34	272.27	274.49	236.52	166.23	105.36
14		BBA	2	B2	0.00	0.00	0.00	58.48	60.13	54.79	45.10	49.47	60.01	81.04	107.09	104.88	95.03	87.50	88.22
15		BBA	3	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	3.47	12.83	23.81	40.42	67.42	147.11
16		ABB	1	A	0.00	0.00	0.00	0.00	27.22	22.81	34.51	55.32	118.34	145.40	185.63	224.04	274.26	275.39	260.03
17		ABB	2	B1	0.00	0.00	0.00	821.54	336.86	220.56	160.05	211.27	175.60	221.03	158.34	123.95	193.89	172.03	128.82
18		ABB	3	B2	0.00	0.00	0.00	0.00	262.49	89.79	107.29	132.81	132.70	98.28	112.75	126.38	113.37	110.82	115.58
19		BAB	1	B1	0.00	0.00	0.00	58.61	100.50	64.46	51.84	53.51	74.11	66.63	70.64	79.84	122.18	122.79	121.67
20		BAB	2	A	0.00	0.00	0.00	0.00	20.77	15.18	48.83	75.71	74.97	77.87	98.22	105.39	120.56	383.56	395.29
21		BAB	3	B2	0.00	0.00	0.00	0.00	2.71	0.00	2.61	3.79	5.25	5.97	6.51	9.37	27.84	66.75	108.92
22		ABB	1	A	0.00	0.00	0.00	0.00	1171.30	575.75	332.79	168.53	128.67	105.10	79.42	110.42	101.44	120.82	115.06
23		ABB	2	B1	0.00	0.00	0.00	0.00	179.81	81.11	52.74	49.51	52.10	40.56	39.69	47.68	60.44	66.00	114.81
24		ABB	3	B2	0.00	0.00	0.00	1224.48	1034.14	677.69	479.92	284.36	195.86	110.53	43.80	32.29	31.37	26.27	21.58
25		BBA	1	B1	0.00	0.00	0.00	0.00	0.00	0.00	3.45	5.71	4.61	9.43	6.29	180.58	1409.11	942.24	844.64

Obs	sub	sequ	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
26	(b) (6)	BBA	2	B2	0.00	0.00	0.00	0.00	2244.13	542.24	331.21	265.35	280.86	258.18	221.15	185.80	171.82	161.79	176.71
27		BBA	3	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	885.45	1829.01
28		BAB	1	B1	0.00	0.00	0.00	0.00	0.00	81.55	384.34	78.09	28.77	22.40	14.75	22.87	25.48	51.99	72.55
29		BAB	2	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	71.27	344.90	99.39
30		BAB	3	B2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	36.32	729.81	1091.88	249.00	49.91	27.09	69.30	73.30
31		ABB	1	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1252.99	469.23
32		ABB	2	B1	0.00	0.00	0.00	0.00	0.00	72.80	605.15	1250.75	1401.10	197.76	60.09	58.29	96.50	114.84	173.42
33		ABB	3	B2	0.00	0.00	0.00	0.00	0.00	0.00	52.85	626.47	883.35	957.85	127.39	54.45	68.10	87.17	135.18
34		BBA	1	B1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.75	370.11	800.38	1472.80	956.95	254.06
35		BBA	2	B2	0.00	0.00	0.00	0.00	0.00	0.00	5.31	8.16	12.38	9.55	4.69	8.27	51.44	72.18	135.87
36		BBA	3	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	10.87	639.37	91.42	48.40	44.51	76.22	111.76
37		ABB	1	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
38		ABB	2	B1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.88	13.13	13.41	22.93	9.32	151.20
39		ABB	3	B2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.89	7.25	5.10	197.04	327.53
40		BAB	1	B1	0.00	0.00	0.00	0.00	87.98	46.72	102.45	178.59	348.33	380.22	431.26	528.01	506.49	408.66	208.19
41		BAB	2	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	47.82	24.39	60.94	94.73	246.90
42		BAB	3	B2	0.00	0.00	0.00	981.55	313.73	292.43	420.79	514.05	549.65	559.21	608.10	516.09	524.38	460.15	374.40
43		BBA	1	B1	0.00	0.00	0.00	4.66	3099.66	3336.72	3389.05	1119.87	490.79	287.76	167.14	105.82	82.36	59.43	49.75
44		BBA	2	B2	0.00	0.00	0.00	33.35	4946.51	4200.24	3663.63	2981.15	1052.56	461.70	211.53	120.18	75.16	46.76	33.30
45		BBA	3	A	0.00	0.00	0.00	0.00	1816.32	1788.45	3526.11	4992.86	5115.32	4191.95	1849.09	766.90	326.66	172.41	89.98
46		ABB	1	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	529.64	1887.27	1397.52
47		ABB	2	B1	0.00	0.00	0.00	2864.24	498.61	406.69	318.22	249.71	131.81	78.22	40.65	22.20	16.47	18.65	16.41
48		ABB	3	B2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	683.12	138.31	30.54	21.44	46.63
49		BAB	1	B1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	3.65	6.96	26.38	221.28	222.57	1191.86	2101.38
50		BAB	2	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
51		BAB	3	B2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.66	7.75	10.77	27.91	556.89	1237.74	814.66
52		BAB	1	B1	0.00	0.00	0.00	96.94	278.54	179.32	166.79	146.41	145.29	138.25	184.88	154.32	132.32	151.91	154.64
53		BAB	2	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	41.84	946.50	189.75
54		BAB	3	B2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	5.50	20.37	5.57	316.82	795.03	900.77

Obs	sub	sequ	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
55	(b) (6)	BBA	1	B1	0.00	0.00	0.00	0.00	0.00	0.00	16.83	103.25	1788.72	2436.40	592.80	243.78	114.61	67.95	61.75
56		BBA	2	B2	0.00	0.00	0.00	0.00	4.19	363.08	142.77	60.72	38.02	20.94	15.96	23.96	23.17	32.78	43.90
57		BBA	3	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	274.38	2663.21	2756.02	771.51
58		BBA	1	B1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	3.32	6.90	2.93	104.84	588.88	2461.12	1471.10
59		BBA	2	B2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	3.35	12.68	2.99	17.44	357.32	455.19
60		BBA	3	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
61		ABB	1	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	6.35	539.59	970.22
62		ABB	2	B1	0.00	0.00	0.00	0.00	5702.82	3323.01	953.91	450.82	257.14	221.99	228.07	180.61	137.84	136.58	106.80
63		ABB	3	B2	0.00	0.00	0.00	0.00	40.62	741.51	523.37	108.47	29.51	30.18	19.75	25.56	28.39	25.99	43.05
64		BAB	1	B1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	37.26	76.31	558.64	821.59	1102.23	1820.37
65		BAB	2	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	5.96	1222.06	2083.86	1736.92	369.24	163.30	110.15
66		BAB	3	B2	0.00	0.00	0.00	0.00	2357.36	837.92	375.34	203.45	102.63	94.87	85.82	87.73	92.72	92.66	87.47
67		ABB	1	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	874.45
68		ABB	2	B1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	6.16	6.44	6.16	169.84	194.73	529.33	2917.40
69		ABB	3	B2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	3.59	110.26	435.30	641.64	331.91	123.73
70		BBA	1	B1	0.00	0.00	0.00	0.00	7.71	27.83	55.16	57.64	71.22	95.14	126.96	117.82	131.56	119.90	118.45
71		BBA	2	B2	0.00	0.00	0.00	0.00	0.00	0.00	3.08	5.73	11.09	15.97	18.25	17.54	19.79	28.04	48.70
72		BBA	3	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	9.83
73		BAB	1	B1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	30.44	102.78	83.28	543.80	1239.60	2478.61
74		BAB	2	A	4.79	3.33	3.32	2.78	4.01	4.05	3.52	3.62	3.17	3.43	2.91	3.54	3.27	45.98	1843.50
75		BAB	3	B2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.71	22.06	273.70	372.44	527.56	1235.17
76		BAB	1	B1	0.00	0.00	0.00	0.00	1246.54	3340.17	1363.83	460.44	210.71	158.67	127.20	92.58	88.71	71.49	68.02
77		BAB	2	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	80.54	3359.33	2759.55
78		BAB	3	B2	0.00	0.00	0.00	0.00	87.67	1279.26	3212.96	1713.10	514.36	230.53	168.29	100.07	104.85	87.53	95.23
79		BBA	1	B1	0.00	0.00	0.00	0.00	258.44	1029.76	697.56	188.58	140.99	172.68	207.43	191.90	182.58	194.68	195.81
80		BBA	2	B2	0.00	0.00	0.00	0.00	1928.97	2623.52	734.74	369.62	349.48	305.62	242.87	203.25	139.18	130.85	118.20
81		BBA	3	A	0.00	0.00	0.00	0.00	307.05	1759.42	463.48	267.41	196.03	181.66	136.43	120.50	108.49	83.00	147.59
82		ABB	1	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	58.81	2124.03	1405.29	301.03
83		ABB	2	B1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	5.47	166.07

Obs	sub	sequ	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
84	(b) (6)	ABB	3	B2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	4.57	2.90	10.34	32.07	272.29	483.37
85		ABB	1	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	154.23
86		ABB	2	B1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.60	139.05	991.91
87		ABB	3	B2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	3.63	233.89
88		BAB	1	B1	0.00	0.00	0.00	19.21	280.27	110.11	73.03	60.56	64.93	91.70	86.25	75.72	66.11	49.91	54.89
89		BAB	2	A	0.00	0.00	0.00	0.00	446.11	46.52	28.10	25.92	39.50	60.50	79.73	65.19	75.28	77.04	128.38
90		BAB	3	B2	0.00	0.00	0.00	0.00	142.23	92.58	22.02	10.93	8.14	6.20	4.33	3.45	2.93	5.77	16.69
91		ABB	1	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	20.67	328.59
92		ABB	2	B1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	18.35	256.04	1206.93	2700.94
93		ABB	3	B2	0.00	0.00	0.00	0.00	1689.38	529.22	458.08	374.61	388.38	330.58	270.50	246.31	199.30	184.40	155.70
94		BBA	1	B1	0.00	0.00	0.00	0.00	3463.88	880.53	538.95	325.40	175.64	144.46	153.86	146.73	190.65	237.06	237.70
95		BBA	2	B2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	13.45	406.11	1966.61	4019.97	1236.64	508.72
96		BBA	3	A	0.00	0.00	0.00	0.00	799.55	316.32	180.69	143.39	113.06	113.78	138.80	148.61	148.64	156.80	148.65
97		BAB	1	B1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	8.88	782.50	2780.63	3547.15
98		BAB	2	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	382.70
99		BAB	3	B2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.99	6.31	272.00	759.93	2154.62	1960.30
100		BAB	1	B1	0.00	0.00	0.00	0.00	3578.29	5005.96	4433.86	1321.36	497.60	223.45	126.22	82.85	72.36	59.97	49.50
101		BAB	2	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	149.86	1786.09	1084.88	283.92	119.55	108.18	148.39
102		BAB	3	B2	0.00	0.00	0.00	9.22	6737.43	4726.01	1401.11	557.29	243.34	118.28	81.78	53.66	55.65	51.76	41.79
103		ABB	1	A	0.00	0.00	0.00	0.00	3106.88	2652.52	750.29	543.71	457.31	312.79	260.36	159.77	126.59	113.10	109.33
104		ABB	2	B1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	343.73	726.58	952.79	242.30	120.46	112.27	97.82
105		ABB	3	B2	0.00	0.00	0.00	7.67	834.98	504.26	351.54	269.75	207.99	138.09	180.12	161.53	146.97	129.75	136.04
106		BBA	1	B1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	5.16	18.25	10.43	10.61	22.39	276.60	1450.49	2491.41
107		BBA	2	B2	0.00	0.00	0.00	1224.12	496.11	427.02	373.19	323.95	254.22	224.58	182.20	174.33	169.95	199.73	242.11
108		BBA	3	A	0.00	0.00	0.00	2929.88	533.53	360.82	324.67	226.09	201.29	149.99	127.68	127.53	117.42	111.07	132.19
109		BAB	1	B1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	7.68	10.69	719.67	663.13	933.14	210.67	98.80
110		BAB	2	A	0.00	0.00	0.00	0.00	2670.44	546.25	278.52	223.89	161.26	185.21	210.80	152.48	149.09	98.14	97.08
111		BAB	3	B2	0.00	0.00	0.00	0.00	489.07	179.32	140.39	189.28	186.78	166.96	192.83	155.22	167.00	160.63	143.03
112		ABB	1	A	0.00	0.00	0.00	0.00	22.80	19.08	24.81	38.60	60.20	83.72	100.23	108.26	129.63	164.38	187.14

Obs	sub	sequ	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
113	(b) (6)	ABB	2	B1	0.00	0.00	0.00	0.00	790.42	261.36	133.78	111.74	80.54	90.44	72.86	71.55	91.08	110.28	138.53
114		ABB	3	B2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	18.29	10.33	47.68	176.64
115		BAB	1	B1	0.00	0.00	0.00	0.00	257.65	310.46	326.96	261.08	212.49	145.70	125.59	108.74	106.62	102.03	78.07
116		BAB	2	A	0.00	0.00	0.00	0.00	3925.96	1870.54	579.21	455.63	202.27	127.80	69.50	41.10	33.30	22.84	23.04
117		BAB	3	B2	0.00	0.00	0.00	0.00	0.00	9.10	231.56	40.82	56.71	61.53	72.11	94.98	97.91	152.52	204.71
118		BBA	1	B1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.66	89.59	172.98	1436.80	1157.20	349.84	182.34	123.34
119		BBA	2	B2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	5.24	277.12	1198.78	2016.29	410.29	163.28
120		BBA	3	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	518.80	95.82
121		ABB	1	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	28.47	1125.23	271.38	110.63	76.77
122		ABB	2	B1	0.00	0.00	0.00	0.00	2384.97	4564.96	2151.61	839.18	655.73	511.06	409.34	287.82	158.39	149.52	130.01
123		ABB	3	B2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	13.38	46.60	112.36	704.89	3606.15	4981.23	2103.51
124		BAB	1	B1	0.00	0.00	0.00	0.00	805.51	1349.72	248.22	75.04	44.83	33.91	29.48	27.47	30.11	69.37	138.82
125		BAB	2	A	0.00	0.00	0.00	0.00	36.22	1158.83	1892.96	1914.80	559.79	194.79	114.59	77.53	72.46	88.14	84.25
126		BAB	3	B2	0.00	0.00	0.00	0.00	513.19	1436.05	1441.74	1668.25	1449.55	347.12	146.86	88.60	87.65	92.68	96.16
127		BBA	1	B1	0.00	0.00	0.00	0.00	1477.54	486.25	176.85	83.35	63.42	53.81	39.61	38.13	49.57	51.43	43.70
128		BBA	2	B2	0.00	0.00	0.00	0.00	3000.19	1490.96	339.00	154.46	131.59	151.11	143.58	124.22	99.20	98.66	113.26
129		BBA	3	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	170.30	1208.67	1549.73	436.11	295.50	192.28
130		ABB	1	A	0.00	0.00	0.00	0.00	558.32	316.29	198.14	120.50	83.37	59.83	51.85	74.62	71.78	66.81	60.08
131		ABB	2	B1	0.00	0.00	0.00	0.00	3222.73	768.03	330.31	242.63	207.67	156.27	121.53	88.84	77.20	57.62	60.07
132		ABB	3	B2	0.00	0.00	0.00	0.00	3225.30	765.42	307.74	163.94	122.78	82.13	62.40	51.45	39.57	36.29	36.29
133		BAB	1	B1	0.00	0.00	0.00	0.00	594.25	1260.48	589.50	269.92	232.18	177.51	152.11	107.03	111.01	66.41	46.74
134		BAB	2	A	0.00	0.00	0.00	0.00	3408.73	2082.83	528.47	289.40	209.36	174.79	120.60	89.01	78.08	56.63	50.52
135		BAB	3	B2	0.00	0.00	0.00	0.00	397.99	2577.63	2821.71	726.01	352.05	250.59	154.88	120.63	99.33	89.79	55.92
136		ABB	1	A	0.00	0.00	0.00	0.00	157.50	102.95	73.84	60.08	44.42	47.45	69.06	65.50	60.99	60.25	60.27
137		ABB	2	B1	0.00	0.00	0.00	0.00	2016.89	497.60	191.48	92.30	56.06	43.75	33.19	34.63	38.67	41.49	53.01
138		ABB	3	B2	0.00	0.00	0.00	0.00	2167.00	992.34	267.62	191.07	126.17	76.52	75.61	60.39	60.26	64.64	62.68
139		BBA	1	B1	0.00	0.00	0.00	0.00	5123.11	4621.58	2526.09	622.55	236.62	130.55	77.97	56.45	39.33	39.13	25.34
140		BBA	2	B2	0.00	0.00	0.00	0.00	1015.31	1331.24	1568.33	1977.41	422.75	211.98	156.43	120.97	111.59	79.37	72.63
141		BBA	3	A	0.00	0.00	0.00	0.00	1917.50	2348.47	2009.34	1561.30	1466.63	1253.70	248.97	149.08	125.11	97.79	97.77

Obs	sub	sequ	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
142	(b) (6)	ABB	1	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	326.11	3180.24	2891.24
143		ABB	2	B1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	217.40	1866.67	3165.83	2784.39
144		ABB	3	B2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	5.64	341.64	1071.66	2589.35	2188.71	1256.68	484.39
145		BBA	1	B1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	24.22	119.49	136.23	351.26	993.39	1494.59	1711.39	1195.57
146		BBA	2	B2	0.00	0.00	0.00	0.00	0.00	4.54	0.00	5.86	8.35	421.35	509.36	568.45	2539.25	3465.70	3213.44
147		BBA	3	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	3.40	803.65	2866.12	1831.77
148		ABB	1	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	147.85	1962.38	3224.55	1177.28	429.08
149		ABB	2	B1	0.00	0.00	0.00	0.00	591.31	2667.06	624.40	239.38	263.62	252.34	200.18	164.46	238.85	260.51	256.64
150		ABB	3	B2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	19.17	398.33	1477.11	708.96	1944.62	6514.46	4889.50
151		BAB	1	B1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
152		BAB	2	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	25.35	502.98	110.24
153		BAB	3	B2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	3.26	200.86	387.60	322.29	44.15	26.33	25.82
154		BBA	1	B1	0.00	0.00	0.00	346.22	147.01	119.62	97.28	87.52	76.90	61.89	52.57	81.52	76.78	83.71	83.29
155		BBA	2	B2	0.00	0.00	0.00	1714.61	297.47	203.24	135.05	126.29	108.96	106.01	92.55	83.00	80.55	94.13	99.37
156		BBA	3	A	0.00	0.00	0.00	0.00	733.20	314.86	143.71	88.38	97.18	97.24	108.50	106.67	130.81	148.67	148.03
157		BAB	1	B1	0.00	0.00	0.00	0.00	1122.46	906.11	344.82	160.52	229.69	219.15	187.55	127.42	99.06	97.25	115.35
158		BAB	2	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	75.36	2152.36	3646.02	2092.26
159		BAB	3	B2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	3.71	43.43	126.49	109.78	220.36	574.29	174.28
160		BBA	1	B1	0.00	0.00	0.00	0.00	2858.15	766.56	330.19	158.07	77.92	53.58	36.69	29.77	25.46	24.60	23.31
161		BBA	2	B2	0.00	0.00	0.00	3064.47	914.12	367.66	141.95	68.74	36.44	26.03	21.82	19.30	18.17	16.07	15.26
162		BBA	3	A	0.00	0.00	0.00	0.00	1641.95	295.49	101.28	50.75	29.67	19.62	21.00	25.25	21.32	20.13	20.57
163		ABB	1	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
164		ABB	2	B1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	148.95	388.17	225.59	28.25
165		ABB	3	B2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	4.27	98.41	7.08	0.00	2.67	3.85
166		BBA	1	B1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	15.47	86.33	797.05
167		BBA	2	B2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	7.46	47.80	57.47	343.44	131.36	43.58
168		BBA	3	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	5.61	110.69	21.38	39.10
169		ABB	1	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	704.62	1833.70	449.77	327.43	227.64
170		ABB	2	B1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	6.14	13.85	150.50	302.65	1615.78	4664.94	1337.70

Obs	sub	sequ	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
171	(b) (6)	ABB	3	B2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.64	3.85	38.77	197.11	767.58	735.67	283.79
172		BAB	1	B1	0.00	0.00	0.00	0.00	0.00	0.00	214.69	1197.73	1371.38	2805.98	559.86	182.44	92.96	77.00	89.75
173		BAB	2	A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	5.18	2749.21	3309.97	6799.85
174		BAB	3	B2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	9.65	33.68	466.77	2470.89	2320.92

Obs	c16	c17	c18	c19	c20	c21	c22	c23	c24	trt	seq
1	189.57	203.86	192.44	161.92	173.60	8.38	0.00	0.00	0.00	2	2
2	247.48	248.30	331.91	303.68	357.03	130.55	93.57	154.06	0.00	1	2
3	157.11	183.82	139.51	106.46	101.23	81.77	57.87	40.61	0.00	3	2
4	357.70	434.32	552.22	547.55	467.44	306.40	222.08	97.87	0.00	1	1
5	132.15	125.27	146.18	138.69	125.50	76.39	65.37	26.24	0.00	2	1
6	234.80	238.52	271.65	236.43	264.60	188.00	107.21	51.15	3.64	3	1
7	40.41	66.43	6.59	0.00	0.00	0.00	0.00	0.00	0.00	2	3
8	144.34	192.54	155.95	103.18	126.66	47.47	72.51	0.00	0.00	3	3
9	29.37	23.84	19.52	19.07	17.69	0.00	0.00	0.00	0.00	1	3
10	435.22	451.24	496.27	552.24	240.04	195.56	140.99	52.56	0.00	2	2
11	145.56	129.61	135.47	144.63	100.32	6.47	8.68	4.72	3.89	1	2
12	150.79	163.05	185.81	95.42	153.16	128.44	78.56	84.31	0.00	3	2
13	110.70	138.80	129.53	138.44	111.11	102.64	67.75	86.38	8.46	2	3
14	130.80	93.09	242.80	307.27	234.97	109.11	54.26	63.59	12.34	3	3
15	232.57	386.00	372.03	313.63	410.56	257.48	186.34	176.93	64.97	1	3
16	242.87	228.57	195.95	239.09	248.15	137.74	102.36	62.23	0.00	1	1
17	106.69	88.90	139.85	91.91	96.84	61.32	37.53	44.19	4.04	2	1
18	127.81	131.04	164.98	117.13	133.63	160.55	102.62	122.19	0.00	3	1
19	112.28	131.91	111.10	79.03	98.62	58.32	33.76	6.21	0.00	2	2
20	341.04	169.74	89.14	55.85	33.88	37.79	19.34	0.00	0.00	1	2
21	251.94	354.49	280.31	194.12	160.33	156.15	92.35	3.21	0.00	3	2
22	130.85	161.13	147.66	102.46	99.62	2.86	0.00	0.00	0.00	1	1
23	194.03	257.24	266.32	189.80	68.40	0.00	0.00	0.00	0.00	2	1
24	31.93	40.52	53.38	55.31	56.68	5.70	3.71	0.00	0.00	3	1
25	3062.64	2805.21	342.95	128.66	68.42	119.97	66.29	53.07	38.63	2	3
26	164.46	221.52	178.22	177.31	182.87	134.75	88.58	94.03	33.14	3	3
27	1119.21	563.12	376.79	201.21	319.96	139.36	43.74	58.74	14.66	1	3
28	89.33	197.08	312.70	249.16	232.95	0.00	0.00	0.00	0.00	2	2
29	86.03	93.25	137.74	141.41	307.84	257.74	134.00	119.90	145.22	1	2
30	68.47	98.42	147.62	178.93	346.10	326.39	177.21	338.18	2.95	3	2
31	142.85	75.35	77.24	61.83	111.60	240.80	108.27	143.97	25.71	1	1
32	226.09	252.42	322.22	297.94	259.78	157.23	85.33	105.03	3.25	2	1
33	217.17	315.16	336.16	377.46	289.24	188.25	138.43	141.12	2.70	3	1
34	188.66	228.16	234.75	112.74	193.03	244.70	148.11	157.29	157.15	2	3
35	184.80	302.44	337.67	267.48	266.72	197.25	140.74	193.78	44.24	3	3
36	148.53	223.26	270.46	279.80	316.88	225.68	116.36	180.16	235.78	1	3
37	0.00	19.29	2037.31	815.78	380.65	364.04	136.67	206.02	43.05	1	1
38	1559.46	1041.99	203.75	153.84	49.82	57.49	60.28	4.74	0.00	2	1
39	654.06	2398.63	757.56	328.61	353.02	539.18	155.33	48.71	0.00	3	1
40	150.76	160.72	138.34	156.27	121.51	5.95	2.84	2.64	0.00	2	2

Obs	c16	c17	c18	c19	c20	c21	c22	c23	c24	trt	seq
41	355.61	522.57	489.84	408.08	313.80	44.28	22.19	25.35	0.00	1	2
42	131.23	70.80	43.65	9.71	7.38	0.00	0.00	0.00	0.00	3	2
43	36.10	37.20	41.34	25.67	26.08	24.81	13.35	11.77	9.18	2	3
44	24.02	24.64	22.68	13.95	15.64	10.93	6.76	6.11	3.74	3	3
45	60.31	44.50	33.16	20.75	21.68	19.34	15.14	12.78	7.69	1	3
46	484.11	361.26	364.93	330.19	184.59	37.00	20.49	10.87	0.00	1	1
47	20.09	26.84	30.59	24.30	19.87	16.14	14.68	6.54	0.00	2	1
48	119.08	267.11	340.05	254.06	291.08	213.85	112.08	25.22	0.00	3	1
49	2231.24	992.02	202.57	253.51	341.95	253.89	151.92	161.95	7.05	2	2
50	167.86	2160.57	256.25	437.59	544.00	327.54	177.32	192.12	0.00	1	2
51	1739.37	1414.21	284.53	290.07	366.96	276.48	172.47	160.34	9.52	3	2
52	160.03	170.93	182.09	139.19	123.19	113.22	85.83	48.61	0.00	2	2
53	99.26	127.84	194.67	135.51	103.13	211.83	206.08	71.28	0.00	1	2
54	1827.09	3802.20	1278.95	388.99	309.40	244.86	133.57	145.35	0.00	3	2
55	106.54	109.66	79.97	62.57	106.07	57.16	33.74	41.54	7.71	2	3
56	47.93	181.79	212.87	174.94	192.35	119.60	54.32	65.38	11.44	3	3
57	328.98	202.43	161.07	143.73	160.97	96.76	65.67	71.22	3.32	1	3
58	499.68	274.88	99.70	149.28	202.61	252.34	167.54	71.85	0.00	2	3
59	235.60	168.95	118.64	268.99	356.59	267.67	111.42	28.20	0.00	3	3
60	0.00	0.00	0.00	4.66	24.33	258.03	219.80	3.69	0.00	1	3
61	1063.45	363.57	135.44	92.66	181.60	126.01	158.89	106.16	5.46	1	1
62	117.37	146.97	157.07	105.79	114.67	77.31	34.49	57.12	0.00	2	1
63	61.52	84.46	103.83	119.03	118.91	95.52	96.19	143.68	0.00	3	1
64	1602.92	7689.70	3374.81	943.41	175.45	27.45	11.49	10.53	5.38	2	2
65	127.40	155.44	181.30	173.99	188.80	109.92	82.09	71.35	67.66	1	2
66	95.44	103.96	103.11	102.23	93.36	58.99	43.39	86.51	65.25	3	2
67	599.55	367.44	280.83	172.91	198.04	85.33	66.01	92.77	10.33	1	1
68	1846.05	2004.29	797.60	336.92	179.13	54.70	20.07	32.80	9.64	2	1
69	144.87	190.18	358.11	310.95	305.44	174.78	114.07	160.49	21.23	3	1
70	158.90	240.15	253.96	724.08	701.54	402.19	203.99	282.56	6.30	2	3
71	84.90	295.55	818.84	1037.80	749.25	335.08	173.31	192.64	3.94	3	3
72	68.48	152.36	908.91	837.09	595.88	334.38	218.15	68.90	0.00	1	3
73	931.44	528.43	229.02	134.81	192.19	140.41	42.43	34.75	18.60	2	2
74	3477.32	2828.76	484.67	139.56	225.23	68.84	21.28	20.12	12.78	1	2
75	1564.73	916.11	443.82	162.80	165.56	106.79	20.53	16.44	9.70	3	2
76	70.60	99.65	76.64	79.43	101.55	81.51	45.91	40.88	5.35	2	2
77	1132.12	439.20	155.89	126.54	144.99	170.61	58.48	58.59	29.70	1	2
78	110.56	134.99	131.27	145.42	115.34	84.58	54.62	42.69	0.00	3	2
79	197.53	181.92	212.71	151.98	151.54	101.36	55.55	47.41	4.88	2	3
80	117.28	114.13	125.65	70.41	60.77	54.07	33.04	24.82	0.00	3	3

Obs	c16	c17	c18	c19	c20	c21	c22	c23	c24	trt	seq
81	198.92	213.22	242.34	114.50	137.92	97.78	78.44	46.65	24.79	1	3
82	116.01	254.06	267.94	164.08	371.15	248.24	120.21	282.22	0.00	1	1
83	849.42	721.63	308.67	247.64	460.96	248.82	122.11	82.71	0.00	2	1
84	986.12	511.07	142.52	133.48	64.33	175.23	185.82	101.36	0.00	3	1
85	1375.16	474.72	181.91	129.18	373.65	293.48	100.35	65.27	33.38	1	1
86	434.41	317.83	255.12	674.19	699.94	268.71	167.66	166.69	3.97	2	1
87	159.43	157.69	123.89	103.76	81.55	187.35	195.46	282.94	146.39	3	1
88	61.34	53.64	56.78	51.27	70.14	26.74	18.55	12.21	0.00	2	2
89	143.73	164.43	145.47	271.00	255.37	218.26	170.45	218.61	77.68	1	2
90	40.77	38.37	87.72	98.51	70.01	25.26	19.61	26.57	26.23	3	2
91	121.91	96.66	80.86	156.67	353.96	331.92	112.23	104.84	9.75	1	1
92	3328.73	2515.26	876.90	228.32	123.04	159.66	79.77	67.65	19.43	2	1
93	150.77	148.05	143.15	117.82	132.12	70.63	47.49	30.22	0.00	3	1
94	186.65	157.96	133.55	88.87	102.63	67.82	47.40	41.51	20.76	2	3
95	304.19	223.05	184.87	213.07	195.97	212.29	94.08	114.30	39.12	3	3
96	195.69	274.13	255.26	197.40	190.69	140.65	79.46	63.12	28.48	1	3
97	2350.76	694.56	211.17	106.34	338.44	169.60	55.66	68.47	65.64	2	2
98	1795.05	513.27	287.08	295.77	321.61	475.96	324.99	578.62	8.68	1	2
99	665.46	263.26	123.99	80.70	128.28	164.11	101.60	141.95	45.46	3	2
100	48.72	47.77	38.38	36.81	36.28	31.92	19.22	14.53	0.00	2	2
101	192.96	203.81	148.50	97.58	164.92	70.13	38.38	30.81	0.00	1	2
102	40.43	31.32	28.57	26.65	21.86	12.86	8.11	6.23	0.00	3	2
103	100.69	101.40	96.68	118.09	105.43	72.45	48.04	19.36	3.01	1	1
104	153.97	254.39	302.26	308.38	271.09	172.75	114.28	56.58	21.47	2	1
105	164.35	159.07	147.02	149.51	153.87	127.92	78.37	111.57	49.43	3	1
106	1924.93	568.09	452.22	360.06	358.32	167.80	124.83	124.92	0.00	2	3
107	231.46	255.56	262.64	182.40	181.06	151.96	96.52	27.58	4.53	3	3
108	161.78	148.42	95.82	27.35	16.40	8.51	4.18	8.87	3.34	1	3
109	136.72	227.93	261.09	229.79	236.85	157.58	59.15	40.82	2.95	2	2
110	114.77	106.41	120.60	117.99	75.87	64.03	26.44	32.20	14.99	1	2
111	148.24	160.73	184.07	139.57	117.10	96.63	64.39	10.38	3.69	3	2
112	247.01	380.51	413.69	303.45	292.08	255.81	149.77	105.15	0.00	1	1
113	186.91	197.49	249.89	193.11	207.14	170.37	52.57	44.29	0.00	2	1
114	88.24	80.14	138.46	132.79	268.19	256.91	137.32	123.83	7.51	3	1
115	96.95	104.54	63.10	25.12	20.72	10.14	3.50	3.89	0.00	2	2
116	23.13	20.46	18.36	13.58	9.91	4.71	3.52	4.62	0.00	1	2
117	253.04	366.84	269.14	274.22	174.59	3.42	0.00	0.00	0.00	3	2
118	110.75	166.79	160.35	134.33	198.94	219.27	164.70	76.75	0.00	2	3
119	79.91	67.81	114.33	53.49	68.78	104.30	101.34	42.90	0.00	3	3
120	107.44	164.74	140.04	190.66	346.39	250.92	121.51	20.06	0.00	1	3

Obs	c16	c17	c18	c19	c20	c21	c22	c23	c24	trt	seq
121	124.44	169.07	312.94	346.33	455.13	147.03	50.82	66.51	15.07	1	1
122	124.15	146.99	194.18	97.44	65.96	37.24	29.18	21.01	5.77	2	1
123	1403.29	711.33	594.69	445.77	479.00	116.50	80.17	64.58	37.02	3	1
124	172.01	171.75	114.62	59.10	79.36	74.65	55.56	16.45	0.00	2	2
125	101.76	175.79	166.11	107.22	122.21	98.93	49.56	34.82	0.00	1	2
126	113.34	102.84	74.89	48.87	70.29	26.35	16.14	20.95	0.00	3	2
127	60.35	76.61	49.93	35.08	36.70	22.25	14.76	0.00	0.00	2	3
128	129.10	92.72	65.03	58.37	26.55	26.07	20.15	0.00	0.00	3	3
129	266.43	285.57	256.28	253.45	173.70	48.75	24.79	13.94	0.00	1	3
130	104.62	141.85	86.56	112.52	84.99	18.74	0.00	0.00	0.00	1	1
131	61.54	121.40	120.85	72.18	80.71	39.12	26.26	15.24	0.00	2	1
132	67.14	76.25	90.17	65.69	186.73	45.35	11.94	9.91	0.00	3	1
133	38.07	62.20	50.30	42.74	43.52	20.55	12.85	6.30	0.00	2	2
134	42.82	61.58	48.99	33.83	24.96	14.78	7.65	10.96	0.00	1	2
135	54.08	63.27	72.55	46.45	53.03	12.94	6.45	7.92	3.86	3	2
136	69.09	71.47	67.03	67.91	71.21	61.68	43.34	49.67	42.24	1	1
137	59.79	93.59	100.29	98.80	99.24	115.03	74.69	87.60	104.11	2	1
138	72.23	103.08	131.73	135.96	124.55	103.43	68.70	79.70	34.51	3	1
139	22.57	22.52	29.11	19.59	16.38	11.90	8.44	10.56	0.00	2	3
140	64.66	64.85	46.13	39.80	51.99	35.88	21.19	13.41	0.00	3	3
141	110.66	114.57	106.70	61.62	54.20	34.76	24.39	16.53	0.00	1	3
142	1132.42	447.86	204.08	283.01	275.09	111.52	35.06	30.17	35.65	1	1
143	2630.93	629.43	214.82	195.15	186.65	57.18	29.81	28.57	13.62	2	1
144	315.07	324.05	308.33	289.88	255.55	162.92	65.27	63.76	22.54	3	1
145	469.55	278.74	287.69	261.64	303.77	286.68	80.81	100.34	55.26	2	3
146	3395.22	1196.38	422.57	188.04	175.05	112.27	33.06	33.37	14.01	3	3
147	654.74	427.20	355.47	348.01	364.59	177.98	95.95	99.22	15.33	1	3
148	315.22	193.78	232.56	539.53	623.39	232.63	191.51	26.04	0.00	1	1
149	247.63	360.60	437.76	434.01	364.34	342.78	195.30	97.51	0.00	2	1
150	5140.62	2757.62	791.53	453.89	332.62	103.64	62.90	3.37	0.00	3	1
151	34.78	130.18	61.41	46.53	96.05	170.33	76.12	42.81	0.00	2	2
152	75.92	198.18	53.06	16.03	6.71	0.00	0.00	0.00	0.00	1	2
153	110.86	117.61	211.41	43.48	56.27	0.00	0.00	0.00	0.00	3	2
154	84.78	107.49	140.14	166.27	129.84	92.95	71.87	11.80	0.00	2	3
155	110.32	151.74	124.45	120.73	121.91	85.67	68.74	11.41	0.00	3	3
156	146.46	174.83	182.05	133.44	133.61	59.10	46.85	6.69	0.00	1	3
157	116.47	110.40	85.08	59.72	59.63	31.36	27.25	23.37	6.13	2	2
158	810.34	516.20	367.41	245.60	189.06	101.07	12.55	11.09	3.38	1	2
159	237.34	244.86	177.67	218.32	416.91	326.53	24.99	12.37	3.23	3	2
160	23.22	29.01	23.88	20.31	19.77	15.21	11.56	18.26	0.00	2	3

Obs	c16	c17	c18	c19	c20	c21	c22	c23	c24	trt	seq
161	15.45	18.24	17.19	13.76	13.62	11.72	9.60	10.65	3.26	3	3
162	29.45	50.79	49.06	106.40	113.47	35.06	16.26	25.57	0.00	1	3
163	0.00	0.00	6.54	7.33	39.77	129.10	88.74	91.84	0.00	1	1
164	18.41	46.74	145.35	184.20	285.61	215.34	329.60	285.61	179.78	2	1
165	8.95	51.72	203.45	57.26	56.77	214.67	100.09	135.67	151.80	3	1
166	1718.51	561.53	97.76	120.92	219.90	189.35	67.62	55.64	7.50	2	3
167	28.51	67.53	201.61	244.55	348.40	321.90	189.79	222.25	4.62	3	3
168	72.02	115.76	254.33	196.26	211.03	283.52	100.55	150.98	2.96	1	3
169	301.87	238.58	179.24	178.58	415.21	372.99	253.68	88.39	0.00	1	1
170	970.13	873.42	614.58	386.33	425.23	295.86	185.17	150.70	0.00	2	1
171	262.27	283.09	277.67	159.52	213.59	156.10	220.84	213.47	2.70	3	1
172	152.68	153.00	181.84	187.03	187.96	265.64	127.39	140.81	22.88	2	2
173	3350.59	979.89	247.01	92.18	91.19	35.71	23.18	14.64	19.23	1	2
174	4372.18	4335.71	425.58	165.92	114.98	56.78	18.71	17.03	15.58	3	2

Fed PHARMACOKINETIC DATASET

Obs	sub	sequ	per	treat	CMAX	TMAX	AUCT	AUC ₀₋₄₈	THALF	KE	trt	seq
1	(b) (6)	BAB	1	B1	990.02	12.0000	6016.61	6016.61	.	.	2	2
2		BAB	2	A	357.03	30.0000	7043.78	7043.78	.	.	1	2
3		BAB	3	B2	846.67	14.0000	7005.89	7005.89	.	.	3	2
4		ABB	1	A	552.22	26.1167	11713.41	11701.83	0.08132	8.5232	1	1
5		ABB	2	B1	3636.60	8.0000	20044.13	12770.93	0.07348	9.4337	2	1
6		ABB	3	B2	409.55	12.0000	8073.34	7415.86	0.11200	6.1886	3	1
7		BBA	1	B1	66.43	24.0000	282.12	282.12	.	.	2	3
8		BBA	2	B2	192.54	24.0000	2224.39	2224.39	.	.	3	3
9		BBA	3	A	727.55	8.0000	4594.84	3139.74	.	.	1	3
10		BAB	1	B1	552.24	28.0000	9179.28	9179.28	.	.	2	2
11		BAB	2	A	273.77	17.0000	3392.27	3288.95	.	.	1	2
12		BAB	3	B2	668.23	8.0000	8758.26	7421.80	.	.	3	2
13		BBA	1	B1	326.90	15.0000	6019.36	4865.20	0.07719	8.9792	2	3
14		BBA	2	B2	307.27	28.0000	5548.52	4521.86	0.05755	12.0443	3	3
15		BBA	3	A	410.56	30.0000	10218.72	7319.95	0.03747	18.4963	1	3
16		ABB	1	A	275.39	21.0000	5740.02	5740.02	0.07411	9.3532	1	1
17		ABB	2	B1	821.54	8.0000	8293.21	6071.37	0.07190	9.6406	2	1
18		ABB	3	B2	262.49	12.0000	5164.44	5164.44	.	.	3	1
19		BAB	1	B1	131.91	24.0000	2970.40	2853.18	0.18647	3.7172	2	2
20		BAB	2	A	395.29	22.0000	2753.42	2753.42	0.07815	8.8692	1	2
21		BAB	3	B2	354.49	24.0000	4118.27	4118.27	0.32371	2.1413	3	2
22		ABB	1	A	1171.30	12.0000	6046.10	6046.10	0.48066	1.4421	1	1
23		ABB	2	B1	266.32	26.0000	2613.35	2613.35	.	.	2	1

Obs	sub (b) (6)	sequ	per	treat	CMAX	TMAX	AUCT	AUC ₀₋₄₈	THALF	KE	trt	seq
24		ABB	3	B2	1224.48	8.0000	9973.81	7524.85	0.21882	3.1677	3	1
25		BBA	1	B1	3062.64	23.0000	14270.59	13170.19	0.01664	41.6602	2	3
26		BBA	2	B2	2244.13	12.0000	13292.83	11766.79	0.03836	18.0692	3	3
27		BBA	3	A	1829.01	22.0000	9269.81	8389.01	0.07388	9.3816	1	3
28		BAB	1	B1	384.34	14.0000	2524.41	2524.41	.	.	2	2
29		BAB	2	A	344.90	21.0000	8422.71	5241.27	.	.	1	2
30		BAB	3	B2	1091.88	17.0000	12709.91	8616.35	.	.	3	2
31		ABB	1	A	1252.99	21.0000	7269.37	5228.97	0.05824	11.9019	1	1
32		ABB	2	B1	1401.10	16.0000	9983.39	8684.03	0.09723	7.1293	2	1
33		ABB	3	B2	957.85	17.0000	10376.20	8650.36	0.14084	4.9215	3	1
34		BBA	1	B1	1472.80	20.0000	12458.52	8685.24	.	.	2	3
35		BBA	2	B2	337.67	26.0000	8681.54	5835.21	.	.	3	3
36		BBA	3	A	639.37	17.0000	11460.05	6475.70	.	.	1	3
37		ABB	1	A	2037.31	26.0000	13882.63	10887.56	0.05219	13.2823	1	1
38		ABB	2	B1	1559.46	23.0000	4975.70	4975.70	.	.	2	1
39		ABB	3	B2	2398.63	24.1333	12682.53	12682.53	0.20035	3.4597	3	1
40		BAB	1	B1	528.01	19.0000	4886.63	4886.63	0.20329	3.4097	2	2
41		BAB	2	A	522.57	24.0000	5140.16	5140.16	0.15791	4.3896	1	2
42		BAB	3	B2	981.55	8.0000	9881.31	7918.21	0.47263	1.4666	3	2
43		BBA	1	B1	3389.05	14.0000	17702.66	17441.94	0.01188	58.3700	2	3
44		BBA	2	B2	4946.51	12.0000	25851.10	25666.53	0.01995	34.7417	3	3
45		BBA	3	A	5115.32	16.0000	28172.99	27927.35	0.02218	31.2564	1	3
46		ABB	1	A	1887.27	21.0000	7346.58	7346.58	0.10208	6.7905	1	1
47		ABB	2	B1	2864.24	8.0000	14459.19	8730.71	0.05888	11.7724	2	1
48		ABB	3	B2	683.12	18.0000	5823.57	5823.57	0.17814	3.8911	3	1
49		BAB	1	B1	2231.24	23.0000	14722.02	12694.02	0.11042	6.2776	2	2
50		BAB	2	A	2160.57	24.0000	10577.92	10577.92	0.06227	11.1315	1	2
51		BAB	3	B2	1739.37	23.0000	14349.15	12310.83	0.10259	6.7565	3	2
52		BAB	1	B1	278.54	12.0000	5529.98	5336.10	.	.	2	2
53		BAB	2	A	946.50	21.0000	5261.38	5261.38	.	.	1	2
54		BAB	3	B2	3802.20	24.0000	16854.56	16854.56	.	.	3	2
55		BBA	1	B1	2436.40	17.1167	7737.35	7146.35	0.05843	11.8620	2	3
56		BBA	2	B2	363.08	13.0500	4799.45	3877.61	0.06349	10.9179	3	3
57		BBA	3	A	2756.02	21.0000	10448.17	9553.69	0.10756	6.4442	1	3
58		BBA	1	B1	2461.12	21.0000	9594.32	9594.32	.	.	2	3
59		BBA	2	B2	455.19	22.0000	5908.24	5908.24	.	.	3	3
60		BBA	3	A	258.03	36.0000	2980.47	2980.47	.	.	1	3
61		ABB	1	A	1063.45	23.0000	7674.89	6335.45	0.11558	5.9969	1	1
62		ABB	2	B1	5702.82	12.0000	22420.50	22420.50	0.05108	13.5694	2	1
63		ABB	3	B2	741.51	13.0000	4370.80	4370.80	.	.	3	1

Obs	sub	sequ	per	treat	CMAX	TMAX	AUCT	AUC ₀₋₄₈	THALF	KE	trt	seq
64	(b) (6)	BAB	1	B1	7689.70	24.0000	27323.29	27132.37	.	.	2	2
65		BAB	2	A	2083.86	18.0500	10542.66	8871.07	.	.	1	2
66		BAB	3	B2	2357.36	12.0000	11683.71	9867.65	.	.	3	2
67		ABB	1	A	874.45	22.0000	6148.35	4911.15	0.06799	10.1945	1	1
68		ABB	2	B1	2917.40	22.0000	12724.41	12215.13	.	.	2	1
69		ABB	3	B2	641.64	20.0000	9031.66	6851.02	0.05901	11.7463	3	1
70		BBA	1	B1	724.08	28.0333	14165.94	10699.62	0.11112	6.2378	2	3
71		BBA	2	B2	1037.80	28.0000	13392.02	11033.06	0.12253	5.6567	3	3
72		BBA	3	A	908.91	26.0000	9704.25	9704.25	0.11531	6.0114	1	3
73		BAB	1	B1	2478.61	22.0500	9559.62	8919.42	0.02708	25.5998	2	2
74		BAB	2	A	3477.32	23.0000	12829.59	12407.82	0.01754	39.5115	1	2
75		BAB	3	B2	1564.73	23.0000	8374.94	8061.26	0.02413	28.7228	3	2
76		BAB	1	B1	3340.17	13.0000	11478.51	10923.75	0.07489	9.2558	2	2
77		BAB	2	A	3359.33	21.0000	11744.95	10685.47	0.02422	28.6186	1	2
78		BAB	3	B2	3212.96	14.0000	10016.41	10016.41	0.05698	12.1638	3	2
79		BBA	1	B1	1029.76	13.0000	7365.80	6738.32	0.08183	8.4708	2	3
80		BBA	2	B2	2623.52	13.0000	11563.90	11563.90	0.06505	10.6556	3	3
81		BBA	3	A	1759.42	13.0000	8070.30	7213.02	0.04050	17.1135	1	3
82		ABB	1	A	2124.03	20.0000	9792.26	9792.26	.	.	1	1
83		ABB	2	B1	849.42	23.0000	7556.11	7556.11	.	.	2	1
84		ABB	3	B2	986.12	23.0000	5826.07	5826.07	.	.	3	1
85		ABB	1	A	1375.16	23.0000	8100.84	6917.04	0.03419	20.2732	1	1
86		ABB	2	B1	991.91	22.0000	11869.31	9821.39	0.13362	5.1876	2	1
87		ABB	3	B2	282.94	48.0000	9712.63	4560.67	.	.	3	1
88		BAB	1	B1	280.27	12.0000	2457.63	2419.21	0.06533	10.6107	2	2
89		BAB	2	A	446.11	12.0000	10529.22	6973.74	0.02696	25.7144	1	2
90		BAB	3	B2	142.23	12.0000	2263.19	1629.59	.	.	3	2
91		ABB	1	A	353.96	30.0000	6861.56	5486.48	0.09305	7.4490	1	1
92		ABB	2	B1	3328.73	23.0000	16696.10	15651.14	0.04848	14.2981	2	1
93		ABB	3	B2	1689.38	12.0000	9583.18	9583.18	0.07075	9.7977	3	1
94		BBA	1	B1	3463.88	12.0000	14541.19	13793.95	0.02791	24.8387	2	3
95		BBA	2	B2	4019.97	20.0000	14392.00	12550.96	0.03928	17.6457	3	3
96		BBA	3	A	799.55	12.0000	8492.88	7393.68	0.03390	20.4444	1	3
97		BAB	1	B1	3547.15	22.0000	15666.83	14057.51	.	.	2	2
98		BAB	2	A	1795.05	23.0000	18988.96	11941.36	0.13625	5.0872	1	2
99		BAB	3	B2	2154.62	21.0000	11405.94	9157.02	0.03356	20.6538	3	2
100		BAB	1	B1	5005.96	13.0000	21585.62	21585.62	0.06558	10.5687	2	2
101		BAB	2	A	1786.09	17.0000	6074.88	6074.88	0.09393	7.3796	1	2
102		BAB	3	B2	6737.43	12.0000	24640.93	24622.49	0.07245	9.5676	3	2
103		ABB	1	A	3106.88	12.0000	15408.41	15139.97	0.08556	8.1013	1	1

Obs	sub	sequ	per	treat	CMAX	TMAX	AUCT	AUC ₀₋₄₈	THALF	KE	trt	seq
104	(b) (6)	ABB	2	B1	952.79	18.0000	8292.58	7335.17	0.06079	11.4022	2	1
105		ABB	3	B2	834.98	12.0000	9460.12	7512.78	0.02421	28.6331	3	1
106		BBA	1	B1	2491.41	22.0000	12147.81	12147.81	0.06792	10.2060	2	3
107		BBA	2	B2	1224.12	8.0000	12897.75	10064.19	0.08867	7.8170	3	3
108		BBA	3	A	2929.88	8.0000	15804.77	9871.74	0.09491	7.3030	1	3
109		BAB	1	B1	933.14	20.0000	6999.51	6474.27	0.10267	6.7515	2	2
110		BAB	2	A	2670.44	12.0000	11039.57	10473.29	0.04907	14.1248	1	2
111		BAB	3	B2	489.07	12.0000	5575.23	5406.39	0.08653	8.0107	3	2
112		ABB	1	A	413.69	26.0000	7142.36	7142.36	0.07409	9.3558	1	1
113		ABB	2	B1	790.42	12.0000	6805.38	6805.38	0.08301	8.3501	2	1
114		ABB	3	B2	268.19	30.0000	6388.72	4812.64	0.09865	7.0266	3	1
115		BAB	1	B1	326.96	14.0000	3043.89	3043.89	0.13808	5.0199	2	2
116		BAB	2	A	3925.96	12.0000	13468.86	13468.86	0.08376	8.2758	1	2
117		BAB	3	B2	366.84	24.0500	3629.19	3629.19	0.57246	1.2108	3	2
118		BBA	1	B1	1436.80	18.0000	7794.88	7794.88	0.08748	7.9236	2	3
119		BBA	2	B2	2016.29	20.0000	6225.93	6225.93	.	.	3	3
120		BBA	3	A	518.80	21.0000	5310.89	5310.89	0.21053	3.2923	1	3
121		ABB	1	A	1125.23	19.0000	7501.82	6522.86	0.07311	9.4805	1	1
122		ABB	2	B1	4564.96	13.0000	17845.48	17524.12	0.05412	12.8064	2	1
123		ABB	3	B2	4981.23	21.0000	20558.45	19342.64	0.02505	27.6746	3	1
124		BAB	1	B1	1349.72	13.0000	5980.90	5980.90	0.12604	5.4994	2	2
125		BAB	2	A	1914.80	15.0000	8645.31	8645.31	0.08702	7.9655	1	2
126		BAB	3	B2	1668.25	15.0000	9251.71	9251.71	0.07358	9.4199	3	2
127		BBA	1	B1	1477.54	12.0000	5449.29	5449.29	0.07590	9.1318	2	3
128		BBA	2	B2	3000.19	12.0000	11184.57	11184.57	0.08570	8.0885	3	3
129		BBA	3	A	1549.73	19.0000	6746.07	6746.07	0.10433	6.6439	1	3
130		ABB	1	A	558.32	12.0000	3609.86	3609.86	0.23050	3.0071	1	1
131		ABB	2	B1	3222.73	12.0000	11558.16	11558.16	0.07856	8.8233	2	1
132		ABB	3	B2	3225.30	12.0000	11345.76	11345.76	0.16905	4.1003	3	1
133		BAB	1	B1	1260.48	13.0000	5200.88	5200.88	0.10439	6.6401	2	2
134		BAB	2	A	3408.73	12.0000	12780.66	12780.66	0.08142	8.5132	1	2
135		BAB	3	B2	2821.71	14.0000	9135.91	8993.27	0.07276	9.5269	3	2
136		ABB	1	A	157.50	12.0000	3651.43	2548.51	.	.	1	1
137		ABB	2	B1	2016.89	12.0000	10821.48	8524.16	.	.	2	1
138		ABB	3	B2	2167.00	12.0000	11234.52	9877.33	.	.	3	1
139		BBA	1	B1	5123.11	12.0000	21556.95	21556.95	0.05058	13.7050	2	3
140		BBA	2	B2	1977.41	15.0000	9515.38	9515.38	0.08201	8.4515	3	3
141		BBA	3	A	2348.47	13.0000	15397.47	15397.47	0.06069	11.4216	1	3
142		ABB	1	A	3180.24	21.0000	11930.16	11140.32	.	.	1	1
143		ABB	2	B1	3165.83	21.0000	14344.30	13838.02	.	.	2	1

Obs	sub	sequ	per	treat	CMAX	TMAX	AUCT	AUC ₀₋₄₈	THALF	KE	trt	seq
144	(b) (6)	ABB	3	B2	2589.35	19.0000	13569.53	12518.82	.	.	3	1
145		BBA	1	B1	1711.39	21.0333	13579.88	11712.68	0.04190	16.5411	2	3
146		BBA	2	B2	3465.70	21.0000	19391.32	18822.76	0.03077	22.5240	3	3
147		BBA	3	A	2866.12	21.0000	12995.00	11607.04	0.06966	9.9507	1	3
148		ABB	1	A	3224.55	20.0000	14011.49	14011.49	0.16202	4.2782	1	1
149		ABB	2	B1	2667.06	13.0000	14155.94	14155.94	0.10476	6.6165	2	1
150		ABB	3	B2	6514.46	21.0000	30067.52	30067.52	0.25366	2.7326	3	1
151		BAB	1	B1	170.33	36.0000	2437.26	2437.26	.	.	2	2
152		BAB	2	A	502.98	21.0000	1161.78	1161.78	.	.	1	2
153		BAB	3	B2	387.60	18.0000	1869.36	1869.36	.	.	3	2
154		BBA	1	B1	346.22	8.0000	4980.80	4288.36	0.17472	3.9673	2	3
155		BBA	2	B2	1714.61	8.0000	11010.75	7581.53	0.16766	4.1343	3	3
156		BBA	3	A	733.20	12.0000	5448.16	5448.16	0.13344	5.1943	1	3
157		BAB	1	B1	1122.46	12.0000	6879.78	6525.78	0.05145	13.4717	2	2
158		BAB	2	A	3646.02	21.0000	12421.53	12247.89	0.04538	15.2745	1	2
159		BAB	3	B2	574.29	21.0000	6650.02	6462.82	0.06470	10.7133	3	2
160		BBA	1	B1	2858.15	12.0000	9121.94	9121.94	.	.	2	3
161		BBA	2	B2	3064.47	8.0000	15765.58	9469.72	.	.	3	3
162		BBA	3	A	1641.95	12.0000	5965.02	5965.02	.	.	1	3
163		ABB	1	A	129.10	36.0000	1770.51	1770.51	.	.	1	1
164		ABB	2	B1	388.17	20.0000	12378.03	6801.11	.	.	2	1
165		ABB	3	B2	214.67	36.0000	6696.52	3246.88	.	.	3	1
166		BBA	1	B1	1718.51	23.0667	7247.62	6489.94	0.07621	9.0947	2	3
167		BBA	2	B2	348.40	30.0000	9506.17	6783.73	0.13458	5.1506	3	3
168		BBA	3	A	283.52	36.0000	6766.85	4919.57	0.13075	5.3014	1	3
169		ABB	1	A	1833.70	19.0000	10548.15	10548.15	0.11998	5.7771	1	1
170		ABB	2	B1	4664.94	21.0000	17561.22	17561.22	0.05957	11.6364	2	1
171		ABB	3	B2	767.58	20.0000	9943.76	7349.72	0.15689	4.4181	3	1
172		BAB	1	B1	2805.98	17.0000	13221.49	11257.21	.	.	2	2
173		BAB	2	A	6799.85	22.0000	19418.65	19012.21	.	.	1	2
174		BAB	3	B2	4372.18	23.0000	18710.63	18319.85	.	.	3	2

4.7.5 Fed Study Codes

```

/*=====
=====
/ Program   : HVScale3Period.SAS
/ SubMacros :
/ Updated   : 15 Aug 2009
/ Purpose   : To analyze three period reference-scaled bioequivalence
studies.
/
/ Notes     : EXCEL DATA FILE MUST BE OPEN WHEN RUNNING THIS PROGRAM.

```

```

/                               : OUTPUT FILE (WORD DOCUMENT) CONTAINING SUMMARY TABLES IS
CREATED.
/
/=====
====
/ PARAMETERS:  THE FOLLOWING COLUMNS SHOULD BE IN THE INPUT DATASET (EXCEL
FILE).
/-----name-----description-----
----
NAME OF VARIABLE
      SUBJ          SUBJECT NUMBER
      TRT            TREATMENT - CHARACTER (EITHER A OR B) A=TEST; B=REF
      SEQ            SEQUENCE NUMBER - NUMERIC (EITHER 1, 2, OR 3)
      PER            PERIOD NUMBER - NUMERIC (EITHER 1, 2, 3, OR 4)
      AUCT           AREA UNDER CURVE 0-T
      AUCI           AREA UNDER CURVE 0-INF
      CMAX           CMAX
      TMAX           TMAX
      KEL            ELIMINATION RATE CONSTANT
      THALF          HALF LIFE

      sequence 1      T      R      R
      sequence 2      R      T      R
      sequence 3      R      R      T

/=====
====
/ AMENDMENT HISTORY:
/ Init --Date-- -----Description-----
/
/=====
====*/
options nofmterr nocenter nodate symbolgen mlogic macrogen mprint ps=65
ls=80;

*****STEP 1: ENTER ANDA INFORMATION *****;
%let drug= ;
%let anda=091640-Fed;
%let studytype=Fed;

*****STEP 2: ENTER UNITS FOR PK PARAMETERS *****;
%let aucunit = ng hr/mL;
%let cmaxunit = ng/mL;
%let timeunit = hr;

***** STEP 3: ENTER LOCATION OF DATASETS AND LOCATION FOR SAVING OUTPUT
REPORTS *****;
%let studydir=M:\BE\Mesalamine 091640\Fed\Scaled;

***** STEP 4:  ENTER THE NAME OF THE DATASET FILE (EXCEL FILE) *****;
%let excelfile = Drpscale.xls;

***** STEP 5:  ENTER THE NAME OF THE EXCEL WORKSHEET NAME CONTAINING STUDY
DATA *****;
FILENAME ORGPK DDE 'EXCEL|pk!R2C2:R175C11';

```

```

*%let sheetname = pk;

/*
proc import datafile="&excelfile"
    out=base
    dbms=excel replace;
        sheet="&sheetname";
        getnames=yes;
        mixed=yes;
run;
*/

libname studylib "&studydir";

***** STEP 5:  PROVIDE NAMES OF THE VARIABLES TO READ IN FROM EXCEL FILE
*****;
***** PROVIDE STANDARD VARIABLE NAMES FROM THE PARAMETER LIST ABOVE *****;
***** VARIABLE NAMES: SUBJ TRT(A,B) SEQ(1,2) PER(1,2,3) AUCT AUCINF CMAX TMAX
KEL THALF *****;

data base;
*   set base;
    infile orgpk;
    input subj sequ $   per treat $   CMAX TMAX AUCI AUCT KEL THALF;

/*sequence 1           T       R       R
   sequence 2           R       T       R
   sequence 3           R       R       T
*/

IF SEQU="ABB" THEN SEQ=1;
ELSE IF SEQU="BAB" THEN SEQ=2;
ELSE IF SEQU="BBA" THEN SEQ=3;

IF TREAT="B" THEN TRT="B";
ELSE IF TREAT="A" THEN TRT="A";

run;

proc print data=base;
run;

*****
;
        ***** DO NOT CHANGE ANYTHING BELOW THIS LINE *****;
*****
;

data pk;

```



```

    set base;

    LAUCT=log(auct);
    LAUCINF=log(auci);
    LCMAX=log(cmax);

run;

data pkn;
    set pk;
run;

data full;
    set pkn;

run;

proc sort
    data=pkn;
    by seq subj per;
run;

data test; set pkn; if trt='A'; latt=LAUCT; lait=LAUCINF; lct=LCMAX;
run;

data ref; set pkn; if trt='B';
run;

    /*sequence 1          T      R      R
       sequence 2          R      T      R
       sequence 3          R      R      T
    */
    /** ORIGINAL DON'S CODE **
data ref1; set ref; if (seq=1 and per=1) or (seq=2 and per=2) or (seq=3 and
per=1); lat1r=LAUCT; lai1r=LAUCINF; lc1r=LCMAX;
run;
**/
data ref1; set ref; if (seq=1 and per=2) or (seq=2 and per=1) or (seq=3 and
per=1); lat1r=LAUCT; lai1r=LAUCINF; lc1r=LCMAX;
run;

data ref2; set ref; if (seq=1 and per=3) or (seq=2 and per=3) or (seq=3 and
per=2); lat2r=LAUCT; lai2r=LAUCINF; lc2r=LCMAX;
run;

title "ref1";
proc print data=ref1;
run;

title "ref2";
proc print data=ref2;
run;

```

```

title;

data scavbe; merge test ref1 ref2; by seq subj;
ilat=latt-(0.5*(lat1r+lat2r)); *auct;
ilai=lait-(0.5*(lai1r+lai2r)); *auci;
ilc=lct-(0.5*(lc1r+lc2r)); *cmax;

dlat=lat1r-lat2r; *auct;
dlai=lai1r-lai2r; *auci;
dlc=lc1r-lc2r; *cmax;
keep seq subj per trt ilat dlat ilai dlai ilc dlc;
run;

proc print data=scavbe;
title1 'dataset for scaled average BE';
run;

%macro calc(param,no);

PROC MIXED data=pkn;
CLASSES SEQ SUBJ PER TRT;
MODEL &param = SEQ PER TRT/ DDFM=SATTERTH;
RANDOM TRT/TYPE=FA0(2) SUB=SUBJ G;
REPEATED/GRP=TRT SUB=SUBJ;
ESTIMATE 'T vs. R' TRT 1 -1/CL ALPHA=0.1;
lsmeans trt; /* DEV */
ods output lsmeans=lsm&param(keep=trt estimate); /* DEV */
ods output Estimates=unsc&no;
title1 'unscaled BE 90% CI - guidance version';
run;

DATA UPARAM&NO(KEEP=PARAMETER LCI UCI);
SET UNSC&NO;

ESTIMATE = 100 * EXP(ESTIMATE);
PARAMETER = "&PARAM";
LCI = 100 * EXP(LOWER);
UCI = 100 * EXP(UPPER);
RUN;

*** for scaled dataset***;
DATA UNSC&PARAM;
SET UNSC&NO;
RUN;

%mend calc;

%calc(LCMAX,1);
%calc(LAUCT,2);
%calc(LAUCINF,3);

*****;
* LAUCT DOES NOT CONVERGE. SET INITIAL PARAMTERS;

**** without the repeated statement to get a starting point for the PARMS
statement as follows;

```

```

%macro calc1(param,no);

PROC MIXED data=pkn;
  CLASS SEQ SUBJ PER TRT;
  MODEL &param = SEQ PER TRT/ DDFM=SATTERTH;
  RANDOM TRT/TYPE=FA0(2) SUB=SUBJ G;
  ESTIMATE 'T vs. R' TRT 1 -1/CL ALPHA=0.1;
/* ods output Estimates=unsc&param; */
  title1 'unscaled BE 90% CI - guidance version';
  title2 '&param';
  title4 'without repeated';
run;
quit;

/*
Covariance Parameter Estimates

Cov Parm      Subject      Estimate

FA(1,1)       subj         0.5596
FA(2,1)       subj         0.2676
FA(2,2)       subj         0.2540
Residual                               0.1214

*/

**** NORMAL MODEL WITH INITIAL PARAMETERS ****;
PROC MIXED data=pkn;
  CLASS SEQ SUBJ PER TRT;
  MODEL &param = SEQ PER TRT/ DDFM=SATTERTH;
  RANDOM TRT/TYPE=FA0(2) SUB=SUBJ G;
  REPEATED/GRP=TRT SUB=SUBJ;
  PARMS (0.5596) (0.2676) (0.01) (0.01) (0.1214);
  ESTIMATE 'T vs. R' TRT 1 -1/CL ALPHA=0.1;
  lsmeans trt;

  ods output lsmeans=lsmean&param(keep=trt estimate); /* DEV */
  ods output Estimates=unsc&no;

  title1 'unscaled BE 90% CI - guidance version';
  title2 '&param';
  title4 'with repeated WITH INITIAL PARAMETERS';
run;
QUIT;

DATA UPARAM&NO(KEEP=PARAMETER LCI UCI);
  SET UNSC&NO;

  ESTIMATE = 100 * EXP(ESTIMATE);
  PARAMETER = "&PARAM";
  LCI = 100 * EXP(LOWER);

```

```

        UCI = 100 * EXP(UPPER);
    RUN;

    *** for scaled dataset***;
    DATA UNSC&PARAM;
        SET UNSC&NO;
    RUN;
%mend calc1;

*%calc1(LCMAX,1);
*%calc1(LAUCT,2);
*%calc1(LAUCINF,3);

*****;

**** ESTIMATES ****;
DATA LSMLAUCT;
    SET LSMLAUCT;
    PARAMETER = "LAUCT";
RUN;

DATA LSMLAUCINF;
    SET LSMLAUCINF;
    PARAMETER = "LAUCI";
RUN;

DATA LSMLCMAX;
    SET LSMLCMAX;
    PARAMETER = "LCMAX";
RUN;

DATA UESTIMATE;
    SET LSMLAUCT LSMLAUCINF LSMLCMAX;
RUN;

DATA UESTIMATE;
    SET UESTIMATE;

    GEOMEAN = EXP(ESTIMATE);
RUN;

PROC SORT
    DATA=UESTIMATE;
    BY PARAMETER;
RUN;

PROC TRANSPOSE
    DATA=UESTIMATE
    OUT=TRANSUEST(DROP=_NAME_);
    VAR GEOMEAN;
    BY PARAMETER;
    ID TRT;
RUN;

```



```

DATA UEST;
  SET TRANSUEST;

  RATIO = ROUND((A/B), .01);
RUN;

DATA UALL;
  SET UPARAM1 UPARAM2 UPARAM3;
RUN;

PROC SORT
  DATA=UALL;
  BY PARAMETER;
RUN;

PROC SORT
  DATA=UEST;
  BY PARAMETER;
RUN;

DATA UPARAMS;
  MERGE UEST
        UALL;
  BY PARAMETER;
RUN;

*** PROPER ORDER AUCTION, AUCTION, CMAX ***;
DATA UPARAMS;
  SET UPARAMS;

  IF PARAMETER = "LAUCTION" THEN ORDER=1;
  ELSE IF PARAMETER = "LAUCTION" THEN ORDER=2;
  ELSE IF PARAMETER = "LCMAX" THEN ORDER=3;
RUN;

PROC SORT
  DATA=UPARAMS;
  BY ORDER;
RUN;

proc template;
  define style mystyle1;
    parent = styles.rtf;
    REPLACE fonts /
      'headingFont' = ("Arial", 8pt, Bold)
      'docFont' = ("Arial", 8pt)
      'TitleFont2' = ("Arial", 8pt, Bold)
      'TitleFont' = ("Arial", 8pt, Bold)
      'StrongFont' = ("Arial", 8pt, Bold)
      'EmphasisFont' = ("Arial", 8pt)
      'FixedEmphasisFont' = ("Arial", 8pt)
      'FixedStrongFont' = ("Arial", 8pt, Bold)
      'FixedHeadingFont' = ("Arial", 8pt, Bold)

```

```

'BatchFixedFont' = ("Arial",8pt)
'FixedFont' = ("Arial",8pt)
'headingEmphasisFont' = ("Arial",8pt,Bold);

style SysTitleAndFooterContainer from Container /
outputwidth = 85%
cellpadding = 2
cellspacing = 2
borderwidth = 0;

REPLACE Body from Document /
bottommargin = 1.0in
topmargin = 1.0in
rightmargin = 1in
leftmargin = 1in;
END;
run;

/*
data unsc1; set unsc1; unscabe_lower=exp(lower); unscabe_upper=exp(upper);
keep unscabe_lower unscabe_upper; run;
*/

***** SCALED ANALYSIS *****;

%MACRO SCALE(parameter, ipar, dpar);

proc glm data=scavbe;
class seq;
model &ipar =seq/clparm alpha=0.1;
estimate 'average' intercept 1 seq 0.3333333333 0.3333333333
0.3333333333;
ods output overallanova=iglm&ipar.1;
ods output Estimates=iglm&ipar.2;
ods output NObs=iglm&ipar.3;
title1 'scaled average BE';
title2 'intermediate analysis - &ipar glm';
run;

title "dev iglm&ipar.1";
proc print data=iglm&ipar.1;
run;

proc glm data=scavbe;
class seq;
model &dpar =seq;
ods output overallanova=dglm&dpar.1;
ods output NObs=dglm&dpar.3;
title1 'scaled average BE';
title2 'intermediate analysis - &dpar glm';
run;

```

```

        data unsc&PARAMETER; set unsc&PARAMETER; unscae_lower=exp(lower);
        unscae_upper=exp(upper);
        keep unscae_lower unscae_upper;
        run;

        data iglm&ipar.1; set iglm&ipar.1; if _n_=2; dfi=df; s2i=ms; keep dfi
s2i param;
        param = "&parameter";
        run;

        data iglm&ipar.2; set iglm&ipar.2; pointest=exp(estimate);
x=(estimate**2)-(stderr**2);
        boundx=(max((abs(LowerCL)), (abs(UpperCL))))**2;
        keep pointest x boundx stderr param;
        param = "&parameter";
        run;

        data iglm&ipar.3; set iglm&ipar.3; if _n_ = 2; ni=NobsUsed; keep ni
param;
        param = "&parameter";
        run;

        data dglm&dpar.1; set dglm&dpar.1; if _n_=2; dfd=df; s2wr=ms/2; keep
dfd s2wr param;
        param = "&parameter";
        run;

        data dglm&dpar.3; set dglm&dpar.3; if _n_ = 2; nd=NobsUsed; keep nd
param;
        param = "&parameter";
        run;

        data idallglm&parameter;
        length method_used $15;
        merge unsc&parameter iglm&ipar.1 iglm&ipar.2 iglm&ipar.3 dglm&dpar.1
dglm&dpar.3;
        theta=((log(1.25))/0.25)**2; y=-theta*s2wr;
        boundy=y*dfd/cinv(0.95,dfd); sWR=sqrt(s2wr);
        critbound=(x+y)+sqrt(((boundx-x)**2)+((boundy-y)**2));
        outcome='FAIL';
        if (s2wr < 0.086436) then method_used='Unscaled'; else
method used='Scaled/PE';
        if ((s2wr < 0.086436) and (unscae_lower ge 0.8) and (unscae_upper le
1.25)) then outcome='PASS';
        if ((s2wr ge 0.086436) and (pointest ge 0.8) and (pointest le 1.25) and
(critbound le 0)) then outcome='PASS';
*       else outcome='FAIL';
        run;

        proc print data=idallglm&parameter;
        title1 'output needed for mixed scaled av. BE - using glm';
        run;

        data finalglm; set idallglm&parameter;
        keep param s2wr sWR unscae_lower unscae_upper pointest critbound
outcome method_used;

```

```

run;

proc print data=finalglm;
title1 'final output - &parameter - using glm';
run;

%mend scale;

%scale(LAUCT, ilat, dlat);
%scale(LAUCINF, ilai, dlai);
%scale(LCMAX, ilc, dlc);

data all;
set idallglmLAUCT
    idallglmLAUCINF
    idallglmLCMAX;

    unscabe_lower = round((unscabe_lower*100), .01);
    unscabe_upper = round((unscabe_upper*100), .01);

run;

ods rtf file="&studydir\&ANDA.-ANALYSIS.doc" style=mystyle1 bodytitle;

**** ARITHMETIC MEANS *****;
/*
footnote "* Tmax values are presented as median, range.";
TITLE "ARITHMETIC MEANS AND RATIOS - REPLICATE 1 (PERIODS 1 AND 2)";
proc report data=pkratio1 nowd split='\' box
    style(header)={background=lightorange
                    foreground=black}
    style(column)={background=white
                    foreground=black};

    column nname units ("Test" mean1 cv1 min1 max1)
              ("Reference" mean2 cv2 min2 max2)
              ("Ratio" rmean12);

    define nname /format=$12. spacing=2 "Parameter";
    define units /format=$12. spacing=2 "Unit";
    define mean1 /format=8.3 spacing=2 "Mean";
    define cv1 /format=8.2 spacing=2 "CV%";
    define min1 /format=8.2 spacing=2 "Min";
    define max1 /format=8.2 spacing=2 "Max";
    define mean2 /format=8.3 spacing=2 "Mean";
    define cv2 /format=8.2 spacing=2 "CV%";
    define min2 /format=8.2 spacing=2 "Min";
    define max2 /format=8.2 spacing=2 "Max";
    define rmean12 /format=8.2 spacing=2 "(T/R)";
run;
footnote;

footnote "* Tmax values are presented as median, range.";
TITLE "ARITHMETIC MEANS AND RATIOS - REPLICATE 2 (PERIODS 3 AND 4)";
proc report data=pkratio2 nowd split='\' box
    style(header)={background=lightorange
                    foreground=black}

```



```

style(column)={background=white
                foreground=black};

column nname units ("Test" mean1 cv1 min1 max1)
              ("Reference" mean2 cv2 min2 max2)
              ("Ratio" rmean12);

define nname /format=$12. spacing=2 "Parameter";
define units /format=$12. spacing=2 "Unit";
define mean1 /format=8.3 spacing=2 "Mean";
define cv1 /format=8.2 spacing=2 "CV%";
define min1 /format=8.2 spacing=2 "Min";
define max1 /format=8.2 spacing=2 "Max";
define mean2 /format=8.3 spacing=2 "Mean";
define cv2 /format=8.2 spacing=2 "CV%";
define min2 /format=8.2 spacing=2 "Min";
define max2 /format=8.2 spacing=2 "Max";
define rmean12 /format=8.2 spacing=2 "(T/R)";
run;
footnote;

footnote "* Tmax values are presented as median, range.";
TITLE "ARITHMETIC MEANS AND RATIOS - ALL PERIODS (PERIODS 1, 2, 3, AND 4)";
proc report data=pkratio3 nowd split='\' box
  style(header)={background=lightorange
                  foreground=black}
  style(column)={background=white
                  foreground=black};

column nname units ("Test" mean1 cv1 min1 max1)
              ("Reference" mean2 cv2 min2 max2)
              ("Ratio" rmean12);

define nname /format=$12. spacing=2 "Parameter";
define units /format=$12. spacing=2 "Unit";
define mean1 /format=8.3 spacing=2 "Mean";
define cv1 /format=8.2 spacing=2 "CV%";
define min1 /format=8.2 spacing=2 "Min";
define max1 /format=8.2 spacing=2 "Max";
define mean2 /format=8.3 spacing=2 "Mean";
define cv2 /format=8.2 spacing=2 "CV%";
define min2 /format=8.2 spacing=2 "Min";
define max2 /format=8.2 spacing=2 "Max";
define rmean12 /format=8.2 spacing=2 "(T/R)";
run;
footnote;

*/

*** UNSCALED ANALYSIS REPORT *****;
title1 "ANDA: &anda &drug STUDY TYPE: &STUDYTYPE";
title2 "SUMMARY OF STATISTICAL ANALYSIS - UNSCALED DATA";

proc report
  data=uparams
  headline
  headskip

```

```

        nowd
        split="|" box
style(header)={background=lightorange
               foreground=black}
style(column)={background=white
               foreground=black};

        column parameter ("Geometric Means|" a b) ratio ("90% CI|" lci uci);

        define parameter /display "Parameter" width=20 center;
        define a          /display "Test"      width=15 center
format=8.2;
        define b          /display "Reference" width=15 center
format=8.2;
        define ratio      /display "T/R Ratio" width=15 center
format=8.2;
        define lci        /display "Lower CI"  width=20 center format=8.2;
        define uci        /display "Upper CI"  width=20 center format=8.2;
run;

***** SCALED ANALYSIS REPORT *****;
title1 "SUMMARY OF STATISTICAL ANALYSIS - SCALED DATA";

proc report
data=all
headline
headskip
nowd
split="|" box
style(header)={background=lightorange
               foreground=black}
style(column)={background=white
               foreground=black};

        column param pointest unscafe_lower unscafe_upper s2wr swr critbound
method_used outcome;

        define param /display "Parameter" width=20 center;
        define pointest /display "T/R Ratio" width=15 center format=8.2;
        define unscafe_lower /display "Lower|90% CI" width=20 center
format=8.2;
        define unscafe_upper /display "Upper|90% CI" width=20 center
format=8.2;
        define s2wr /display "s2wr" width=15 center;
        define swr /display "swr" width=15 center;
        define critbound /display "Criteria Bound" width=15 center;
        define method used /display "Method Used" width=25 center;
        define outcome /display "OUTCOME" width=15 center;

run;

ods rtf close;

```

4.7.6 Fed Study Output

Please note: In this SAS output, AUC_i is AUT_{0-t} and AUC_t is AUC_{8-48}

Obs	subj	sequ	per	treat	CMAX	TMAX	AUCI	AUCT	KEL	THALF	SEQ	TRT
1	(b) (6)	BAB	2	A	357.03	30.0000	7043.78	7043.78	.	.	2	A
2		ABB	1	A	552.22	26.1167	11713.41	11701.83	0.08132	8.5232	1	A
3		BBA	3	A	727.55	8.0000	4594.84	3139.74	.	.	3	A
4		BAB	2	A	273.77	17.0000	3392.27	3288.95	.	.	2	A
5		BBA	3	A	410.56	30.0000	10218.72	7319.95	0.03747	18.4963	3	A
6		ABB	1	A	275.39	21.0000	5740.02	5740.02	0.07411	9.3532	1	A
7		BAB	2	A	395.29	22.0000	2753.42	2753.42	0.07815	8.8692	2	A
8		ABB	1	A	1171.30	12.0000	6046.10	6046.10	0.48066	1.4421	1	A
9		BBA	3	A	1829.01	22.0000	9269.81	8389.01	0.07388	9.3816	3	A
10		BAB	2	A	344.90	21.0000	8422.71	5241.27	.	.	2	A
11		ABB	1	A	1252.99	21.0000	7269.37	5228.97	0.05824	11.9019	1	A
12		BBA	3	A	639.37	17.0000	11460.05	6475.70	.	.	3	A
13		ABB	1	A	2037.31	26.0000	13882.63	10887.56	0.05219	13.2823	1	A
14		BAB	2	A	522.57	24.0000	5140.16	5140.16	0.15791	4.3896	2	A
15		BBA	3	A	5115.32	16.0000	28172.99	27927.35	0.02218	31.2564	3	A
16		ABB	1	A	1887.27	21.0000	7346.58	7346.58	0.10208	6.7905	1	A
17		BAB	2	A	2160.57	24.0000	10577.92	10577.92	0.06227	11.1315	2	A
18		BAB	2	A	946.50	21.0000	5261.38	5261.38	.	.	2	A
19		BBA	3	A	2756.02	21.0000	10448.17	9553.69	0.10756	6.4442	3	A
20		BBA	3	A	258.03	36.0000	2980.47	2980.47	.	.	3	A
21		ABB	1	A	1063.45	23.0000	7674.89	6335.45	0.11558	5.9969	1	A
22		BAB	2	A	2083.86	18.0500	10542.66	8871.07	.	.	2	A
23		ABB	1	A	874.45	22.0000	6148.35	4911.15	0.06799	10.1945	1	A
24		BBA	3	A	908.91	26.0000	9704.25	9704.25	0.11531	6.0114	3	A
25		BAB	2	A	3477.32	23.0000	12829.59	12407.82	0.01754	39.5115	2	A
26		BAB	2	A	3359.33	21.0000	11744.95	10685.47	0.02422	28.6186	2	A
27		BBA	3	A	1759.42	13.0000	8070.30	7213.02	0.04050	17.1135	3	A
28		ABB	1	A	2124.03	20.0000	9792.26	9792.26	.	.	1	A
29		ABB	1	A	1375.16	23.0000	8100.84	6917.04	0.03419	20.2732	1	A
30		BAB	2	A	446.11	12.0000	10529.22	6973.74	0.02696	25.7144	2	A
31		ABB	1	A	353.96	30.0000	6861.56	5486.48	0.09305	7.4490	1	A
32		BBA	3	A	799.55	12.0000	8492.88	7393.68	0.03390	20.4444	3	A
33		BAB	2	A	1795.05	23.0000	18988.96	11941.36	0.13625	5.0872	2	A
34		BAB	2	A	1786.09	17.0000	6074.88	6074.88	0.09393	7.3796	2	A
35		ABB	1	A	3106.88	12.0000	15408.41	15139.97	0.08556	8.1013	1	A

Obs	subj	sequ	per	treat	CMAX	TMAX	AUCI	AUCT	KEL	THALF	SEQ	TRT
36	(b) (6)	BBA	3	A	2929.88	8.0000	15804.77	9871.74	0.09491	7.3030	3	A
37		BAB	2	A	2670.44	12.0000	11039.57	10473.29	0.04907	14.1248	2	A
38		ABB	1	A	413.69	26.0000	7142.36	7142.36	0.07409	9.3558	1	A
39		BAB	2	A	3925.96	12.0000	13468.86	13468.86	0.08376	8.2758	2	A
40		BBA	3	A	518.80	21.0000	5310.89	5310.89	0.21053	3.2923	3	A
41		ABB	1	A	1125.23	19.0000	7501.82	6522.86	0.07311	9.4805	1	A
42		BAB	2	A	1914.80	15.0000	8645.31	8645.31	0.08702	7.9655	2	A
43		BBA	3	A	1549.73	19.0000	6746.07	6746.07	0.10433	6.6439	3	A
44		ABB	1	A	558.32	12.0000	3609.86	3609.86	0.23050	3.0071	1	A
45		BAB	2	A	3408.73	12.0000	12780.66	12780.66	0.08142	8.5132	2	A
46		ABB	1	A	157.50	12.0000	3651.43	2548.51	.	.	1	A
47		BBA	3	A	2348.47	13.0000	15397.47	15397.47	0.06069	11.4216	3	A
48		ABB	1	A	3180.24	21.0000	11930.16	11140.32	.	.	1	A
49		BBA	3	A	2866.12	21.0000	12995.00	11607.04	0.06966	9.9507	3	A
50		ABB	1	A	3224.55	20.0000	14011.49	14011.49	0.16202	4.2782	1	A
51		BAB	2	A	502.98	21.0000	1161.78	1161.78	.	.	2	A
52		BBA	3	A	733.20	12.0000	5448.16	5448.16	0.13344	5.1943	3	A
53		BAB	2	A	3646.02	21.0000	12421.53	12247.89	0.04538	15.2745	2	A
54		BBA	3	A	1641.95	12.0000	5965.02	5965.02	.	.	3	A
55		ABB	1	A	129.10	36.0000	1770.51	1770.51	.	.	1	A
56		BBA	3	A	283.52	36.0000	6766.85	4919.57	0.13075	5.3014	3	A
57		ABB	1	A	1833.70	19.0000	10548.15	10548.15	0.11998	5.7771	1	A
58		BAB	2	A	6799.85	22.0000	19418.65	19012.21	.	.	2	A
59		BAB	1	B	990.02	12.0000	6016.61	6016.61	.	.	2	B
60		ABB	2	B	3636.60	8.0000	20044.13	12770.93	0.07348	9.4337	1	B
61		BBA	1	B	66.43	24.0000	282.12	282.12	.	.	3	B
62		BAB	1	B	552.24	28.0000	9179.28	9179.28	.	.	2	B
63		BBA	1	B	326.90	15.0000	6019.36	4865.20	0.07719	8.9792	3	B
64		ABB	2	B	821.54	8.0000	8293.21	6071.37	0.07190	9.6406	1	B
65		BAB	1	B	131.91	24.0000	2970.40	2853.18	0.18647	3.7172	2	B
66		ABB	2	B	266.32	26.0000	2613.35	2613.35	.	.	1	B
67		BBA	1	B	3062.64	23.0000	14270.59	13170.19	0.01664	41.6602	3	B
68		BAB	1	B	384.34	14.0000	2524.41	2524.41	.	.	2	B
69		ABB	2	B	1401.10	16.0000	9983.39	8684.03	0.09723	7.1293	1	B
70		BBA	1	B	1472.80	20.0000	12458.52	8685.24	.	.	3	B
71		ABB	2	B	1559.46	23.0000	4975.70	4975.70	.	.	1	B
72		BAB	1	B	528.01	19.0000	4886.63	4886.63	0.20329	3.4097	2	B

Obs	subj	sequ	per	treat	CMAX	TMAX	AUCI	AUCT	KEL	THALF	SEQ	TRT
73	(b) (6)	BBA	1	B	3389.05	14.0000	17702.66	17441.94	0.01188	58.3700	3	B
74		ABB	2	B	2864.24	8.0000	14459.19	8730.71	0.05888	11.7724	1	B
75		BAB	1	B	2231.24	23.0000	14722.02	12694.02	0.11042	6.2776	2	B
76		BAB	1	B	278.54	12.0000	5529.98	5336.10	.	.	2	B
77		BBA	1	B	2436.40	17.1167	7737.35	7146.35	0.05843	11.8620	3	B
78		BBA	1	B	2461.12	21.0000	9594.32	9594.32	.	.	3	B
79		ABB	2	B	5702.82	12.0000	22420.50	22420.50	0.05108	13.5694	1	B
80		BAB	1	B	7689.70	24.0000	27323.29	27132.37	.	.	2	B
81		ABB	2	B	2917.40	22.0000	12724.41	12215.13	.	.	1	B
82		BBA	1	B	724.08	28.0333	14165.94	10699.62	0.11112	6.2378	3	B
83		BAB	1	B	2478.61	22.0500	9559.62	8919.42	0.02708	25.5998	2	B
84		BAB	1	B	3340.17	13.0000	11478.51	10923.75	0.07489	9.2558	2	B
85		BBA	1	B	1029.76	13.0000	7365.80	6738.32	0.08183	8.4708	3	B
86		ABB	2	B	849.42	23.0000	7556.11	7556.11	.	.	1	B
87		ABB	2	B	991.91	22.0000	11869.31	9821.39	0.13362	5.1876	1	B
88		BAB	1	B	280.27	12.0000	2457.63	2419.21	0.06533	10.6107	2	B
89		ABB	2	B	3328.73	23.0000	16696.10	15651.14	0.04848	14.2981	1	B
90		BBA	1	B	3463.88	12.0000	14541.19	13793.95	0.02791	24.8387	3	B
91		BAB	1	B	3547.15	22.0000	15666.83	14057.51	.	.	2	B
92		BAB	1	B	5005.96	13.0000	21585.62	21585.62	0.06558	10.5687	2	B
93		ABB	2	B	952.79	18.0000	8292.58	7335.17	0.06079	11.4022	1	B
94		BBA	1	B	2491.41	22.0000	12147.81	12147.81	0.06792	10.2060	3	B
95		BAB	1	B	933.14	20.0000	6999.51	6474.27	0.10267	6.7515	2	B
96		ABB	2	B	790.42	12.0000	6805.38	6805.38	0.08301	8.3501	1	B
97		BAB	1	B	326.96	14.0000	3043.89	3043.89	0.13808	5.0199	2	B
98		BBA	1	B	1436.80	18.0000	7794.88	7794.88	0.08748	7.9236	3	B
99		ABB	2	B	4564.96	13.0000	17845.48	17524.12	0.05412	12.8064	1	B
100		BAB	1	B	1349.72	13.0000	5980.90	5980.90	0.12604	5.4994	2	B
101		BBA	1	B	1477.54	12.0000	5449.29	5449.29	0.07590	9.1318	3	B
102		ABB	2	B	3222.73	12.0000	11558.16	11558.16	0.07856	8.8233	1	B
103		BAB	1	B	1260.48	13.0000	5200.88	5200.88	0.10439	6.6401	2	B
104		ABB	2	B	2016.89	12.0000	10821.48	8524.16	.	.	1	B
105		BBA	1	B	5123.11	12.0000	21556.95	21556.95	0.05058	13.7050	3	B
106		ABB	2	B	3165.83	21.0000	14344.30	13838.02	.	.	1	B
107		BBA	1	B	1711.39	21.0333	13579.88	11712.68	0.04190	16.5411	3	B
108		ABB	2	B	2667.06	13.0000	14155.94	14155.94	0.10476	6.6165	1	B
109		BAB	1	B	170.33	36.0000	2437.26	2437.26	.	.	2	B

Obs	subj	sequ	per	treat	CMAX	TMAX	AUCI	AUCT	KEL	THALF	SEQ	TRT
110	(b) (6)	BBA	1	B	346.22	8.0000	4980.80	4288.36	0.17472	3.9673	3	B
111		BAB	1	B	1122.46	12.0000	6879.78	6525.78	0.05145	13.4717	2	B
112		BBA	1	B	2858.15	12.0000	9121.94	9121.94	.	.	3	B
113		ABB	2	B	388.17	20.0000	12378.03	6801.11	.	.	1	B
114		BBA	1	B	1718.51	23.0667	7247.62	6489.94	0.07621	9.0947	3	B
115		ABB	2	B	4664.94	21.0000	17561.22	17561.22	0.05957	11.6364	1	B
116		BAB	1	B	2805.98	17.0000	13221.49	11257.21	.	.	2	B
117		BAB	3	B	846.67	14.0000	7005.89	7005.89	.	.	2	B
118		ABB	3	B	409.55	12.0000	8073.34	7415.86	0.11200	6.1886	1	B
119		BBA	2	B	192.54	24.0000	2224.39	2224.39	.	.	3	B
120		BAB	3	B	668.23	8.0000	8758.26	7421.80	.	.	2	B
121		BBA	2	B	307.27	28.0000	5548.52	4521.86	0.05755	12.0443	3	B
122		ABB	3	B	262.49	12.0000	5164.44	5164.44	.	.	1	B
123		BAB	3	B	354.49	24.0000	4118.27	4118.27	0.32371	2.1413	2	B
124		ABB	3	B	1224.48	8.0000	9973.81	7524.85	0.21882	3.1677	1	B
125		BBA	2	B	2244.13	12.0000	13292.83	11766.79	0.03836	18.0692	3	B
126		BAB	3	B	1091.88	17.0000	12709.91	8616.35	.	.	2	B
127		ABB	3	B	957.85	17.0000	10376.20	8650.36	0.14084	4.9215	1	B
128		BBA	2	B	337.67	26.0000	8681.54	5835.21	.	.	3	B
129		ABB	3	B	2398.63	24.1333	12682.53	12682.53	0.20035	3.4597	1	B
130		BAB	3	B	981.55	8.0000	9881.31	7918.21	0.47263	1.4666	2	B
131		BBA	2	B	4946.51	12.0000	25851.10	25666.53	0.01995	34.7417	3	B
132		ABB	3	B	683.12	18.0000	5823.57	5823.57	0.17814	3.8911	1	B
133		BAB	3	B	1739.37	23.0000	14349.15	12310.83	0.10259	6.7565	2	B
134		BAB	3	B	3802.20	24.0000	16854.56	16854.56	.	.	2	B
135		BBA	2	B	363.08	13.0500	4799.45	3877.61	0.06349	10.9179	3	B
136		BBA	2	B	455.19	22.0000	5908.24	5908.24	.	.	3	B
137		ABB	3	B	741.51	13.0000	4370.80	4370.80	.	.	1	B
138		BAB	3	B	2357.36	12.0000	11683.71	9867.65	.	.	2	B
139		ABB	3	B	641.64	20.0000	9031.66	6851.02	0.05901	11.7463	1	B
140		BBA	2	B	1037.80	28.0000	13392.02	11033.06	0.12253	5.6567	3	B
141		BAB	3	B	1564.73	23.0000	8374.94	8061.26	0.02413	28.7228	2	B
142		BAB	3	B	3212.96	14.0000	10016.41	10016.41	0.05698	12.1638	2	B
143		BBA	2	B	2623.52	13.0000	11563.90	11563.90	0.06505	10.6556	3	B
144		ABB	3	B	986.12	23.0000	5826.07	5826.07	.	.	1	B
145		ABB	3	B	282.94	48.0000	9712.63	4560.67	.	.	1	B
146		BAB	3	B	142.23	12.0000	2263.19	1629.59	.	.	2	B

Obs	subj	sequ	per	treat	CMAX	TMAX	AUCI	AUCT	KEL	THALF	SEQ	TRT
147	(b) (6)	ABB	3	B	1689.38	12.0000	9583.18	9583.18	0.07075	9.7977	1	B
148		BBA	2	B	4019.97	20.0000	14392.00	12550.96	0.03928	17.6457	3	B
149		BAB	3	B	2154.62	21.0000	11405.94	9157.02	0.03356	20.6538	2	B
150		BAB	3	B	6737.43	12.0000	24640.93	24622.49	0.07245	9.5676	2	B
151		ABB	3	B	834.98	12.0000	9460.12	7512.78	0.02421	28.6331	1	B
152		BBA	2	B	1224.12	8.0000	12897.75	10064.19	0.08867	7.8170	3	B
153		BAB	3	B	489.07	12.0000	5575.23	5406.39	0.08653	8.0107	2	B
154		ABB	3	B	268.19	30.0000	6388.72	4812.64	0.09865	7.0266	1	B
155		BAB	3	B	366.84	24.0500	3629.19	3629.19	0.57246	1.2108	2	B
156		BBA	2	B	2016.29	20.0000	6225.93	6225.93	.	.	3	B
157		ABB	3	B	4981.23	21.0000	20558.45	19342.64	0.02505	27.6746	1	B
158		BAB	3	B	1668.25	15.0000	9251.71	9251.71	0.07358	9.4199	2	B
159		BBA	2	B	3000.19	12.0000	11184.57	11184.57	0.08570	8.0885	3	B
160		ABB	3	B	3225.30	12.0000	11345.76	11345.76	0.16905	4.1003	1	B
161		BAB	3	B	2821.71	14.0000	9135.91	8993.27	0.07276	9.5269	2	B
162		ABB	3	B	2167.00	12.0000	11234.52	9877.33	.	.	1	B
163		BBA	2	B	1977.41	15.0000	9515.38	9515.38	0.08201	8.4515	3	B
164		ABB	3	B	2589.35	19.0000	13569.53	12518.82	.	.	1	B
165		BBA	2	B	3465.70	21.0000	19391.32	18822.76	0.03077	22.5240	3	B
166		ABB	3	B	6514.46	21.0000	30067.52	30067.52	0.25366	2.7326	1	B
167		BAB	3	B	387.60	18.0000	1869.36	1869.36	.	.	2	B
168		BBA	2	B	1714.61	8.0000	11010.75	7581.53	0.16766	4.1343	3	B
169		BAB	3	B	574.29	21.0000	6650.02	6462.82	0.06470	10.7133	2	B
170		BBA	2	B	3064.47	8.0000	15765.58	9469.72	.	.	3	B
171		ABB	3	B	214.67	36.0000	6696.52	3246.88	.	.	1	B
172		BBA	2	B	348.40	30.0000	9506.17	6783.73	0.13458	5.1506	3	B
173		ABB	3	B	767.58	20.0000	9943.76	7349.72	0.15689	4.4181	1	B
174		BAB	3	B	4372.18	23.0000	18710.63	18319.85	.	.	2	B

ref1

Obs	subj	sequ	per	treat	CMAX	TMAX	AUCI	AUCT	KEL	THALF	SEQ	TRT	LAUCT	LAUCINF	LCMAX	latlr	lailr	lclr
1	(b) (6)	ABB	2	B	3636.60	8.0000	20044.13	12770.93	0.07348	9.4337	1	B	9.4549	9.9057	8.19880	9.4549	9.9057	8.19880
2		ABB	2	B	821.54	8.0000	8293.21	6071.37	0.07190	9.6406	1	B	8.7113	9.0232	6.71118	8.7113	9.0232	6.71118
3		ABB	2	B	266.32	26.0000	2613.35	2613.35	.	.	1	B	7.8684	7.8684	5.58470	7.8684	7.8684	5.58470
4		ABB	2	B	1401.10	16.0000	9983.39	8684.03	0.09723	7.1293	1	B	9.0692	9.2087	7.24501	9.0692	9.2087	7.24501
5		ABB	2	B	1559.46	23.0000	4975.70	4975.70	.	.	1	B	8.5123	8.5123	7.35209	8.5123	8.5123	7.35209
6		ABB	2	B	2864.24	8.0000	14459.19	8730.71	0.05888	11.7724	1	B	9.0746	9.5791	7.96006	9.0746	9.5791	7.96006
7		ABB	2	B	5702.82	12.0000	22420.50	22420.50	0.05108	13.5694	1	B	10.0177	10.0177	8.64872	10.0177	10.0177	8.64872
8		ABB	2	B	2917.40	22.0000	12724.41	12215.13	.	.	1	B	9.4104	9.4513	7.97845	9.4104	9.4513	7.97845
9		ABB	2	B	849.42	23.0000	7556.11	7556.11	.	.	1	B	8.9301	8.9301	6.74455	8.9301	8.9301	6.74455
10		ABB	2	B	991.91	22.0000	11869.31	9821.39	0.13362	5.1876	1	B	9.1923	9.3817	6.89963	9.1923	9.3817	6.89963
11		ABB	2	B	3328.73	23.0000	16696.10	15651.14	0.04848	14.2981	1	B	9.6583	9.7229	8.11035	9.6583	9.7229	8.11035
12		ABB	2	B	952.79	18.0000	8292.58	7335.17	0.06079	11.4022	1	B	8.9004	9.0231	6.85939	8.9004	9.0231	6.85939
13		ABB	2	B	790.42	12.0000	6805.38	6805.38	0.08301	8.3501	1	B	8.8255	8.8255	6.67256	8.8255	8.8255	6.67256
14		ABB	2	B	4564.96	13.0000	17845.48	17524.12	0.05412	12.8064	1	B	9.7713	9.7895	8.42617	9.7713	9.7895	8.42617
15		ABB	2	B	3222.73	12.0000	11558.16	11558.16	0.07856	8.8233	1	B	9.3551	9.3551	8.07798	9.3551	9.3551	8.07798
16		ABB	2	B	2016.89	12.0000	10821.48	8524.16	.	.	1	B	9.0507	9.2893	7.60931	9.0507	9.2893	7.60931
17		ABB	2	B	3165.83	21.0000	14344.30	13838.02	.	.	1	B	9.5352	9.5711	8.06017	9.5352	9.5711	8.06017
18		ABB	2	B	2667.06	13.0000	14155.94	14155.94	0.10476	6.6165	1	B	9.5579	9.5579	7.88873	9.5579	9.5579	7.88873
19		ABB	2	B	388.17	20.0000	12378.03	6801.11	.	.	1	B	8.8248	9.4237	5.96144	8.8248	9.4237	5.96144
20		ABB	2	B	4664.94	21.0000	17561.22	17561.22	0.05957	11.6364	1	B	9.7734	9.7734	8.44783	9.7734	9.7734	8.44783
21		BAB	1	B	990.02	12.0000	6016.61	6016.61	.	.	2	B	8.7023	8.7023	6.89773	8.7023	8.7023	6.89773
22		BAB	1	B	552.24	28.0000	9179.28	9179.28	.	.	2	B	9.1247	9.1247	6.31398	9.1247	9.1247	6.31398
23		BAB	1	B	131.91	24.0000	2970.40	2853.18	0.18647	3.7172	2	B	7.9562	7.9965	4.88212	7.9562	7.9965	4.88212
24		BAB	1	B	384.34	14.0000	2524.41	2524.41	.	.	2	B	7.8338	7.8338	5.95153	7.8338	7.8338	5.95153

Obs	subj	sequ	per	treat	CMAX	TMAX	AUCI	AUCT	KEL	THALF	SEQ	TRT	LAUCT	LAUCINF	LCMAX	lat1r	lai1r	lc1r
25	(b) (6)	BAB	1	B	528.01	19.0000	4886.63	4886.63	0.20329	3.4097	2	B	8.4943	8.4943	6.26912	8.4943	8.4943	6.26912
26		BAB	1	B	2231.24	23.0000	14722.02	12694.02	0.11042	6.2776	2	B	9.4489	9.5971	7.71031	9.4489	9.5971	7.71031
27		BAB	1	B	278.54	12.0000	5529.98	5336.10	.	.	2	B	8.5823	8.6179	5.62956	8.5823	8.6179	5.62956
28		BAB	1	B	7689.70	24.0000	27323.29	27132.37	.	.	2	B	10.2085	10.2155	8.94764	10.2085	10.2155	8.94764
29		BAB	1	B	2478.61	22.0500	9559.62	8919.42	0.02708	25.5998	2	B	9.0960	9.1653	7.81545	9.0960	9.1653	7.81545
30		BAB	1	B	3340.17	13.0000	11478.51	10923.75	0.07489	9.2558	2	B	9.2987	9.3482	8.11378	9.2987	9.3482	8.11378
31		BAB	1	B	280.27	12.0000	2457.63	2419.21	0.06533	10.6107	2	B	7.7912	7.8070	5.63575	7.7912	7.8070	5.63575
32		BAB	1	B	3547.15	22.0000	15666.83	14057.51	.	.	2	B	9.5509	9.6593	8.17390	9.5509	9.6593	8.17390
33		BAB	1	B	5005.96	13.0000	21585.62	21585.62	0.06558	10.5687	2	B	9.9798	9.9798	8.51838	9.9798	9.9798	8.51838
34		BAB	1	B	933.14	20.0000	6999.51	6474.27	0.10267	6.7515	2	B	8.7756	8.8536	6.83856	8.7756	8.8536	6.83856
35		BAB	1	B	326.96	14.0000	3043.89	3043.89	0.13808	5.0199	2	B	8.0209	8.0209	5.78984	8.0209	8.0209	5.78984
36		BAB	1	B	1349.72	13.0000	5980.90	5980.90	0.12604	5.4994	2	B	8.6963	8.6963	7.20765	8.6963	8.6963	7.20765
37		BAB	1	B	1260.48	13.0000	5200.88	5200.88	0.10439	6.6401	2	B	8.5566	8.5566	7.13925	8.5566	8.5566	7.13925
38		BAB	1	B	170.33	36.0000	2437.26	2437.26	.	.	2	B	7.7986	7.7986	5.13774	7.7986	7.7986	5.13774
39		BAB	1	B	1122.46	12.0000	6879.78	6525.78	0.05145	13.4717	2	B	8.7835	8.8363	7.02328	8.7835	8.8363	7.02328
40		BAB	1	B	2805.98	17.0000	13221.49	11257.21	.	.	2	B	9.3288	9.4896	7.93951	9.3288	9.4896	7.93951
41		BBA	1	B	66.43	24.0000	282.12	282.12	.	.	3	B	5.6423	5.6423	4.19615	5.6423	5.6423	4.19615
42		BBA	1	B	326.90	15.0000	6019.36	4865.20	0.07719	8.9792	3	B	8.4899	8.7027	5.78965	8.4899	8.7027	5.78965
43		BBA	1	B	3062.64	23.0000	14270.59	13170.19	0.01664	41.6602	3	B	9.4857	9.5660	8.02703	9.4857	9.5660	8.02703
44		BBA	1	B	1472.80	20.0000	12458.52	8685.24	.	.	3	B	9.0694	9.4302	7.29492	9.0694	9.4302	7.29492
45		BBA	1	B	3389.05	14.0000	17702.66	17441.94	0.01188	58.3700	3	B	9.7666	9.7815	8.12830	9.7666	9.7815	8.12830
46		BBA	1	B	2436.40	17.1167	7737.35	7146.35	0.05843	11.8620	3	B	8.8744	8.9538	7.79828	8.8744	8.9538	7.79828
47		BBA	1	B	2461.12	21.0000	9594.32	9594.32	.	.	3	B	9.1689	9.1689	7.80837	9.1689	9.1689	7.80837
48		BBA	1	B	724.08	28.0333	14165.94	10699.62	0.11112	6.2378	3	B	9.2780	9.5586	6.58490	9.2780	9.5586	6.58490
49		BBA	1	B	1029.76	13.0000	7365.80	6738.32	0.08183	8.4708	3	B	8.8156	8.9046	6.93708	8.8156	8.9046	6.93708
50		BBA	1	B	3463.88	12.0000	14541.19	13793.95	0.02791	24.8387	3	B	9.5320	9.5847	8.15014	9.5320	9.5847	8.15014

Obs	subj	sequ	per	treat	CMAX	TMAX	AUCI	AUCT	KEL	THALF	SEQ	TRT	LAUCT	LAUCINF	LCMAX	lat1r	lai1r	lc1r
51	(b) (6)	BBA	1	B	2491.41	22.0000	12147.81	12147.81	0.06792	10.2060	3	B	9.4049	9.4049	7.82060	9.4049	9.4049	7.82060
52		BBA	1	B	1436.80	18.0000	7794.88	7794.88	0.08748	7.9236	3	B	8.9612	8.9612	7.27017	8.9612	8.9612	7.27017
53		BBA	1	B	1477.54	12.0000	5449.29	5449.29	0.07590	9.1318	3	B	8.6032	8.6032	7.29813	8.6032	8.6032	7.29813
54		BBA	1	B	5123.11	12.0000	21556.95	21556.95	0.05058	13.7050	3	B	9.9785	9.9785	8.54152	9.9785	9.9785	8.54152
55		BBA	1	B	1711.39	21.0333	13579.88	11712.68	0.04190	16.5411	3	B	9.3684	9.5163	7.44506	9.3684	9.5163	7.44506
56		BBA	1	B	346.22	8.0000	4980.80	4288.36	0.17472	3.9673	3	B	8.3637	8.5133	5.84707	8.3637	8.5133	5.84707
57		BBA	1	B	2858.15	12.0000	9121.94	9121.94	.	.	3	B	9.1184	9.1184	7.95793	9.1184	9.1184	7.95793
58		BBA	1	B	1718.51	23.0667	7247.62	6489.94	0.07621	9.0947	3	B	8.7780	8.8884	7.44921	8.7780	8.8884	7.44921

ref2

Obs	subj	sequ	per	treat	CMAX	TMAX	AUCI	AUCT	KEL	THALF	SEQ	TRT	LAUCT	LAUCINF	LCMAX	lat2r	lai2r	lc2r
1	(b) (6)	ABB	3	B	409.55	12.0000	8073.34	7415.86	0.11200	6.1886	1	B	8.9114	8.9963	6.01506	8.9114	8.9963	6.01506
2		ABB	3	B	262.49	12.0000	5164.44	5164.44	.	.	1	B	8.5496	8.5496	5.57021	8.5496	8.5496	5.57021
3		ABB	3	B	1224.48	8.0000	9973.81	7524.85	0.21882	3.1677	1	B	8.9260	9.2077	7.11027	8.9260	9.2077	7.11027
4		ABB	3	B	957.85	17.0000	10376.20	8650.36	0.14084	4.9215	1	B	9.0654	9.2473	6.86469	9.0654	9.2473	6.86469
5		ABB	3	B	2398.63	24.1333	12682.53	12682.53	0.20035	3.4597	1	B	9.4480	9.4480	7.78265	9.4480	9.4480	7.78265
6		ABB	3	B	683.12	18.0000	5823.57	5823.57	0.17814	3.8911	1	B	8.6697	8.6697	6.52667	8.6697	8.6697	6.52667
7		ABB	3	B	741.51	13.0000	4370.80	4370.80	.	.	1	B	8.3827	8.3827	6.60869	8.3827	8.3827	6.60869
8		ABB	3	B	641.64	20.0000	9031.66	6851.02	0.05901	11.7463	1	B	8.8322	9.1085	6.46403	8.8322	9.1085	6.46403
9		ABB	3	B	986.12	23.0000	5826.07	5826.07	.	.	1	B	8.6701	8.6701	6.89378	8.6701	8.6701	6.89378
10		ABB	3	B	282.94	48.0000	9712.63	4560.67	.	.	1	B	8.4252	9.1812	5.64523	8.4252	9.1812	5.64523
11		ABB	3	B	1689.38	12.0000	9583.18	9583.18	0.07075	9.7977	1	B	9.1678	9.1678	7.43212	9.1678	9.1678	7.43212
12		ABB	3	B	834.98	12.0000	9460.12	7512.78	0.02421	28.6331	1	B	8.9244	9.1548	6.72741	8.9244	9.1548	6.72741
13		ABB	3	B	268.19	30.0000	6388.72	4812.64	0.09865	7.0266	1	B	8.4790	8.7623	5.59170	8.4790	8.7623	5.59170
14		ABB	3	B	4981.23	21.0000	20558.45	19342.64	0.02505	27.6746	1	B	9.8701	9.9310	8.51343	9.8701	9.9310	8.51343

Obs	subj	sequ	per	treat	CMAX	TMAX	AUCI	AUCT	KEL	THALF	SEQ	TRT	LAUCT	LAUCINF	LCMAX	lat2r	lai2r	lc2r
15	(b) (6)	ABB	3	B	3225.30	12.0000	11345.76	11345.76	0.16905	4.1003	1	B	9.3366	9.3366	8.07878	9.3366	9.3366	8.07878
16		ABB	3	B	2167.00	12.0000	11234.52	9877.33	.	.	1	B	9.1980	9.3267	7.68110	9.1980	9.3267	7.68110
17		ABB	3	B	2589.35	19.0000	13569.53	12518.82	.	.	1	B	9.4350	9.5156	7.85916	9.4350	9.5156	7.85916
18		ABB	3	B	6514.46	21.0000	30067.52	30067.52	0.25366	2.7326	1	B	10.3112	10.3112	8.78178	10.3112	10.3112	8.78178
19		ABB	3	B	214.67	36.0000	6696.52	3246.88	.	.	1	B	8.0854	8.8093	5.36910	8.0854	8.8093	5.36910
20		ABB	3	B	767.58	20.0000	9943.76	7349.72	0.15689	4.4181	1	B	8.9024	9.2047	6.64324	8.9024	9.2047	6.64324
21		BAB	3	B	846.67	14.0000	7005.89	7005.89	.	.	2	B	8.8545	8.8545	6.74131	8.8545	8.8545	6.74131
22		BAB	3	B	668.23	8.0000	8758.26	7421.80	.	.	2	B	8.9122	9.0778	6.50463	8.9122	9.0778	6.50463
23		BAB	3	B	354.49	24.0000	4118.27	4118.27	0.32371	2.1413	2	B	8.3232	8.3232	5.87068	8.3232	8.3232	5.87068
24		BAB	3	B	1091.88	17.0000	12709.91	8616.35	.	.	2	B	9.0614	9.4501	6.99566	9.0614	9.4501	6.99566
25		BAB	3	B	981.55	8.0000	9881.31	7918.21	0.47263	1.4666	2	B	8.9769	9.1984	6.88913	8.9769	9.1984	6.88913
26		BAB	3	B	1739.37	23.0000	14349.15	12310.83	0.10259	6.7565	2	B	9.4182	9.5714	7.46128	9.4182	9.5714	7.46128
27		BAB	3	B	3802.20	24.0000	16854.56	16854.56	.	.	2	B	9.7324	9.7324	8.24334	9.7324	9.7324	8.24334
28		BAB	3	B	2357.36	12.0000	11683.71	9867.65	.	.	2	B	9.1970	9.3660	7.76530	9.1970	9.3660	7.76530
29		BAB	3	B	1564.73	23.0000	8374.94	8061.26	0.02413	28.7228	2	B	8.9948	9.0330	7.35547	8.9948	9.0330	7.35547
30		BAB	3	B	3212.96	14.0000	10016.41	10016.41	0.05698	12.1638	2	B	9.2120	9.2120	8.07495	9.2120	9.2120	8.07495
31		BAB	3	B	142.23	12.0000	2263.19	1629.59	.	.	2	B	7.3961	7.7245	4.95745	7.3961	7.7245	4.95745
32		BAB	3	B	2154.62	21.0000	11405.94	9157.02	0.03356	20.6538	2	B	9.1223	9.3419	7.67537	9.1223	9.3419	7.67537
33		BAB	3	B	6737.43	12.0000	24640.93	24622.49	0.07245	9.5676	2	B	10.1114	10.1122	8.81543	10.1114	10.1122	8.81543
34		BAB	3	B	489.07	12.0000	5575.23	5406.39	0.08653	8.0107	2	B	8.5953	8.6261	6.19251	8.5953	8.6261	6.19251
35		BAB	3	B	366.84	24.0500	3629.19	3629.19	0.57246	1.2108	2	B	8.1968	8.1968	5.90493	8.1968	8.1968	5.90493
36		BAB	3	B	1668.25	15.0000	9251.71	9251.71	0.07358	9.4199	2	B	9.1326	9.1326	7.41953	9.1326	9.1326	7.41953
37		BAB	3	B	2821.71	14.0000	9135.91	8993.27	0.07276	9.5269	2	B	9.1042	9.1200	7.94510	9.1042	9.1200	7.94510
38		BAB	3	B	387.60	18.0000	1869.36	1869.36	.	.	2	B	7.5334	7.5334	5.95997	7.5334	7.5334	5.95997
39		BAB	3	B	574.29	21.0000	6650.02	6462.82	0.06470	10.7133	2	B	8.7738	8.8024	6.35313	8.7738	8.8024	6.35313
40		BAB	3	B	4372.18	23.0000	18710.63	18319.85	.	.	2	B	9.8157	9.8368	8.38302	9.8157	9.8368	8.38302

Obs	subj	sequ	per	treat	CMAX	TMAX	AUCI	AUCT	KEL	THALF	SEQ	TRT	LAUCT	LAUCINF	LCMAX	lat2r	lai2r	lc2r
41	(b) (6)	BBA	2	B	192.54	24.0000	2224.39	2224.39	.	.	3	B	7.7072	7.7072	5.26030	7.7072	7.7072	5.26030
42		BBA	2	B	307.27	28.0000	5548.52	4521.86	0.05755	12.0443	3	B	8.4167	8.6213	5.72773	8.4167	8.6213	5.72773
43		BBA	2	B	2244.13	12.0000	13292.83	11766.79	0.03836	18.0692	3	B	9.3730	9.4950	7.71607	9.3730	9.4950	7.71607
44		BBA	2	B	337.67	26.0000	8681.54	5835.21	.	.	3	B	8.6717	9.0690	5.82207	8.6717	9.0690	5.82207
45		BBA	2	B	4946.51	12.0000	25851.10	25666.53	0.01995	34.7417	3	B	10.1529	10.1601	8.50644	10.1529	10.1601	8.50644
46		BBA	2	B	363.08	13.0500	4799.45	3877.61	0.06349	10.9179	3	B	8.2630	8.4763	5.89462	8.2630	8.4763	5.89462
47		BBA	2	B	455.19	22.0000	5908.24	5908.24	.	.	3	B	8.6841	8.6841	6.12071	8.6841	8.6841	6.12071
48		BBA	2	B	1037.80	28.0000	13392.02	11033.06	0.12253	5.6567	3	B	9.3087	9.5024	6.94486	9.3087	9.5024	6.94486
49		BBA	2	B	2623.52	13.0000	11563.90	11563.90	0.06505	10.6556	3	B	9.3556	9.3556	7.87227	9.3556	9.3556	7.87227
50		BBA	2	B	4019.97	20.0000	14392.00	12550.96	0.03928	17.6457	3	B	9.4376	9.5744	8.29903	9.4376	9.5744	8.29903
51		BBA	2	B	1224.12	8.0000	12897.75	10064.19	0.08867	7.8170	3	B	9.2167	9.4648	7.10998	9.2167	9.4648	7.10998
52		BBA	2	B	2016.29	20.0000	6225.93	6225.93	.	.	3	B	8.7365	8.7365	7.60901	8.7365	8.7365	7.60901
53		BBA	2	B	3000.19	12.0000	11184.57	11184.57	0.08570	8.0885	3	B	9.3223	9.3223	8.00643	9.3223	9.3223	8.00643
54		BBA	2	B	1977.41	15.0000	9515.38	9515.38	0.08201	8.4515	3	B	9.1607	9.1607	7.58954	9.1607	9.1607	7.58954
55		BBA	2	B	3465.70	21.0000	19391.32	18822.76	0.03077	22.5240	3	B	9.8428	9.8726	8.15067	9.8428	9.8726	8.15067
56		BBA	2	B	1714.61	8.0000	11010.75	7581.53	0.16766	4.1343	3	B	8.9335	9.3066	7.44694	8.9335	9.3066	7.44694
57		BBA	2	B	3064.47	8.0000	15765.58	9469.72	.	.	3	B	9.1559	9.6656	8.02763	9.1559	9.6656	8.02763
58		BBA	2	B	348.40	30.0000	9506.17	6783.73	0.13458	5.1506	3	B	8.8223	9.1597	5.85335	8.8223	9.1597	5.85335

dataset for scaled average BE

Obs	subj	per	SEQ	TRT	ilat	ilai	ilc	dlat	dlai	dlc
1	(b) (6)	3	1	B	0.18435	-0.08252	-0.79299	0.54355	0.90937	2.18375
2		3	1	B	0.02477	-0.13115	-0.52251	0.16179	0.47364	1.14097
3		3	1	B	0.30999	0.16911	0.71838	-1.05758	-1.33933	-1.52557
4		3	1	B	-0.50533	-0.33655	0.07844	0.00388	-0.03859	0.38032
5		3	1	B	0.31523	0.55824	0.05201	-0.93566	-0.93566	-0.43056
6		3	1	B	0.02986	-0.22239	0.29952	0.40493	0.90942	1.43339
7		3	1	B	-0.44630	-0.25451	-0.65943	1.63503	1.63503	2.04003
8		3	1	B	-0.62203	-0.55595	-0.44764	0.57828	0.34279	1.51442
9		3	1	B	0.38924	0.38924	0.84190	0.26001	0.26001	-0.14922
10		3	1	B	0.03297	-0.28172	0.95389	0.76709	0.20053	1.25440
11		3	1	B	-0.80299	-0.61166	-1.90205	0.49053	0.55517	0.67823
12		3	1	B	0.71270	0.55369	1.24797	-0.02392	-0.13172	0.13199
13		3	1	B	0.22156	0.07992	-0.10701	0.34647	0.06318	1.08087
14		3	1	B	-1.03763	-0.93737	-1.44406	-0.09873	-0.14152	-0.08727
15		3	1	B	-1.15445	-1.15445	-1.75345	0.01855	0.01855	-0.00080
16		3	1	B	-1.28106	-1.10514	-2.58578	-0.14734	-0.03746	-0.07179
17		3	1	B	-0.16676	-0.15652	0.10505	0.10019	0.05553	0.20101
18		3	1	B	-0.38691	-0.38691	-0.25671	-0.75331	-0.75331	-0.89305
19		3	1	B	-0.97612	-1.63749	-0.80469	0.73939	0.61434	0.59234
20		3	1	B	-0.07423	-0.22537	-0.03145	0.87103	0.56875	1.80459
21		3	2	B	0.08151	0.08151	-0.94170	-0.15223	-0.15223	0.15641
22		3	2	B	-0.92012	-0.97197	-0.79702	0.21253	0.04695	-0.19065
23		3	2	B	-0.21909	-0.23922	0.60322	-0.36700	-0.32674	-0.98856
24		3	2	B	0.11673	0.39674	-0.63034	-1.22765	-1.61637	-1.04413
25		3	2	B	-0.19075	-0.30149	-0.32037	-0.48266	-0.70414	-0.62002
26		3	2	B	-0.16704	-0.31775	0.09233	0.03065	0.02565	0.24903
27		3	2	B	-0.58916	-0.60701	-0.08368	-1.15013	-1.11444	-2.61377
28		3	2	B	-0.61220	-0.52754	-0.71449	1.01147	0.84954	1.18234
29		3	2	B	0.38068	0.36036	0.56856	0.10116	0.13230	0.45998

Obs	subj	per	SEQ	TRT	ilat	ilai	ilc	dlat	dlai	dlc
30	(b) (6)	3	2	B	0.02130	0.09107	0.02513	0.08671	0.13625	0.03883
31		3	2	B	1.25627	1.49617	0.80397	0.39511	0.08242	0.67831
32		3	2	B	0.05117	0.35102	-0.43185	0.42864	0.31741	0.49853
33		3	2	B	-1.33368	-1.33406	-1.17913	-0.13163	-0.13238	-0.29705
34		3	2	B	0.57112	0.56940	1.37447	0.18025	0.22751	0.64605
35		3	2	B	1.39931	1.39931	2.42798	-0.17587	-0.17587	-0.11509
36		3	2	B	0.15033	0.15033	0.24378	-0.43624	-0.43624	-0.21188
37		3	2	B	0.62528	0.61741	0.59192	-0.54765	-0.56339	-0.80585
38		3	2	B	-0.60829	-0.60829	0.67169	0.26528	0.26528	-0.82224
39		3	2	B	0.63444	0.60783	1.51319	0.00970	0.03397	0.67014
40		3	2	B	0.28058	0.21077	0.66339	-0.48698	-0.34725	-0.44351
41		2	3	B	1.37712	1.75791	1.86146	-2.06492	-2.06492	-1.06416
42		2	3	B	0.44509	0.56997	0.25883	0.07318	0.08145	0.06193
43		2	3	B	-0.39470	-0.39595	-0.36002	0.11267	0.07098	0.31096
44		2	3	B	-0.09471	0.09707	-0.09801	0.39771	0.36121	1.47285
45		2	3	B	0.27757	0.27533	0.22262	-0.38631	-0.37864	-0.37813
46		2	3	B	0.59602	0.53915	1.07509	0.61138	0.47756	1.90365
47		2	3	B	-0.92668	-0.92668	-1.41147	0.48482	0.48482	1.68766
48		2	3	B	-0.11299	-0.35019	0.04737	-0.03069	0.05618	-0.35996
49		2	3	B	-0.20196	-0.13418	0.06806	-0.54008	-0.45104	-0.93519
50		2	3	B	-0.57639	-0.53260	-1.54054	0.09443	0.01031	-0.14889
51		2	3	B	-0.11339	0.23321	0.51743	0.18817	-0.05990	0.71063
52		2	3	B	-0.27133	-0.27133	-1.18808	0.22474	0.22474	-0.33884
53		2	3	B	-0.14605	-0.14605	-0.30645	-0.71905	-0.71905	-0.70830
54		2	3	B	0.07240	0.07240	-0.30401	0.81779	0.81779	0.95197
55		2	3	B	-0.24626	-0.22214	0.16285	-0.47439	-0.35624	-0.70561
56		2	3	B	-0.04553	-0.30695	-0.04959	-0.56981	-0.79328	-1.59987
57		2	3	B	-0.44348	-0.69834	-0.58914	-0.03742	-0.54715	-0.06970
58		2	3	B	-0.29917	-0.20427	-1.00400	-0.04427	-0.27127	1.59586

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The Mixed Procedure

Model Information	
Data Set	WORK.PKN
Dependent Variable	LCMAX
Covariance Structures	Factor Analytic, Variance Components
Subject Effects	subj, subj
Group Effect	TRT
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Satterthwaite

Class Level Information	
Class	Levels Values
SEQ	3 1 2 3
subj	58 1 2 3 4 5 6 7 8 9 11 12 13 14 15 16 17 18 19 20 22 23 24 25 26 27 28 29 30 31 33 34 35 36 37 39 40 41 42 43 44 45 46 47 48 49 50 51 53 54 55 56 57 58 59 60 61 62 63
per	3 1 2 3
TRT	2 A B

Dimensions	
Covariance Parameters	5
Columns in X	9
Columns in Z Per Subject	2
Subjects	58
Max Obs Per Subject	3

Number of Observations	
Number of Observations Read	174
Number of Observations Used	174
Number of Observations Not Used	0

Iteration History			
Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	500.49709205	
1	2	468.07675007	0.13170911
2	1	464.24844219	0.00795734
3	1	463.79410672	0.26441008
4	1	463.74446511	0.00000030
5	1	463.74444182	0.00000000

Convergence criteria met.

Estimated G Matrix					
Row	Effect	TRT	subj	Col1	Col2
1	TRT	A	1	0.8009	0.4407
2	TRT	B	1	0.4407	0.5784

Covariance Parameter Estimates				
Cov Parm	Subject	Group	Estimate	
FA(1,1)	subj		0.8949	
FA(2,1)	subj		0.4924	
FA(2,2)	subj		0.5796	
Residual	subj	TRT A	0.1022	
Residual	subj	TRT B	0.4910	

Fit Statistics	
-2 Res Log Likelihood	463.7
AIC (smaller is better)	473.7
AICC (smaller is better)	474.1
BIC (smaller is better)	484.0

Null Model Likelihood Ratio Test		
DF	Chi-Square	Pr > ChiSq

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
4	36.75	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
SEQ	2	55.5	0.05	0.9507
per	2	112	2.76	0.0673
TRT	1	56.2	0.60	0.4417

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
T vs. R	-0.09361	0.1208	56.2	-0.77	0.4417	0.1	-0.2957	0.1085

Least Squares Means

Effect	TRT	Estimate	Standard Error	DF	t Value	Pr > t
TRT	A	7.0246	0.1249	55.4	56.23	<.0001
TRT	B	7.1182	0.1193	55.3	59.66	<.0001

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The Mixed Procedure**Model Information**

Data Set	WORK.PKN
Dependent Variable	LAUCT
Covariance Structures	Factor Analytic, Variance Components
Subject Effects	subj, subj
Group Effect	TRT
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Satterthwaite

Class Level Information			
Class	Levels	Values	
SEQ	3	1	2 3
subj	58	1 2 3 4 5 6 7 8 9 11 12 13 14 15 16 17 18 19 20 22 23 24 25 26 27 28 29 30 31 33 34 35 36 37 39 40 41 42 43 44 45 46 47 48 49 50 51 53 54 55 56 57 58 59 60 61 62 63	
per	3	1	2 3
TRT	2	A	B

Dimensions	
Covariance Parameters	5
Columns in X	9
Columns in Z Per Subject	2
Subjects	58
Max Obs Per Subject	3

Number of Observations	
Number of Observations Read	174
Number of Observations Used	174
Number of Observations Not Used	0

Iteration History			
Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	346.63187857	
1	2	310.46237623	19.15100848
2	1	305.98442281	0.93308387
3	1	305.02737964	0.00215874
4	1	305.02340392	0.00169076
5	1	305.02340192	0.00000002
6	1	305.02340192	0.00000000

Convergence criteria met but final hessian is not positive definite.

Estimated G Matrix					
Row	Effect	TRT	subj	Col1	Col2
1	TRT	A	1	0.2905	0.1718
2	TRT	B	1	0.1718	0.2609

Covariance Parameter Estimates				
Cov Parm	Subject	Group	Estimate	
FA(1,1)	subj		0.5390	
FA(2,1)	subj		0.3188	
FA(2,2)	subj		0.3990	
Residual	subj	TRT A	0.04734	
Residual	subj	TRT B	0.1789	

Fit Statistics		
-2 Res Log Likelihood		305.0
AIC (smaller is better)		315.0
AICC (smaller is better)		315.4
BIC (smaller is better)		325.3

Null Model Likelihood Ratio Test		
DF	Chi-Square	Pr > ChiSq
4	41.61	<.0001

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
SEQ	2	56.2	0.25	0.7772
per	2	111	2.64	0.0761
TRT	1	56.6	1.47	0.2301

Estimates								
Label	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
T vs. R	-0.09355	0.07711	56.6	-1.21	0.2301	0.1	-0.2225	0.03539

Least Squares Means						
Effect	TRT	Estimate	Standard Error	DF	t Value	Pr > t
TRT	A	8.8801	0.07640	55.5	116.23	<.0001
TRT	B	8.9736	0.07780	55.5	115.35	<.0001

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The Mixed Procedure

Model Information	
Data Set	WORK.PKN
Dependent Variable	LAUCINF
Covariance Structures	Factor Analytic, Variance Components
Subject Effects	subj, subj
Group Effect	TRT
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Satterthwaite

Class Level Information	
Class	Levels Values
SEQ	3 1 2 3
subj	58 1 2 3 4 5 6 7 8 9 11 12 13 14 15 16 17 18 19 20 22 23 24 25 26 27 28 29 30 31 33 34 35 36 37 39 40 41 42 43 44 45 46 47 48 49 50 51 53 54 55 56 57 58 59 60 61 62 63
per	3 1 2 3
TRT	2 A B

Dimensions	
Covariance Parameters	5
Columns in X	9
Columns in Z Per Subject	2

Dimensions	
Subjects	58
Max Obs Per Subject	3

Number of Observations	
Number of Observations Read	174
Number of Observations Used	174
Number of Observations Not Used	0

Iteration History				
Iteration	Evaluations	-2 Res	Log Like	Criterion
0	1	345.45939814		
1	2	315.84030203	3.03713346	
2	1	312.08558971	0.49185963	
3	1	311.44377289	4.19544584	
4	1	311.43984636	0.00104275	
5	1	311.43984534	0.00000000	

Convergence criteria met but final hessian is not positive definite.

Estimated G Matrix					
Row	Effect	TRT	subj	Col1	Col2
1	TRT	A	1	0.2915	0.1454
2	TRT	B	1	0.1454	0.2455

Covariance Parameter Estimates			
Cov Parm	Subject	Group	Estimate
FA(1,1)	subj		0.5399
FA(2,1)	subj		0.2694
FA(2,2)	subj		0.4158
Residual	subj	TRT A	0.04947
Residual	subj	TRT B	0.1880

Fit Statistics		
-2 Res Log Likelihood		311.4
AIC (smaller is better)		321.4
AICC (smaller is better)		321.8
BIC (smaller is better)		331.7

Null Model Likelihood Ratio Test		
DF	Chi-Square	Pr > ChiSq
4	34.02	<.0001

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
SEQ	2	56.2	0.67	0.5135
per	2	110	3.92	0.0226
TRT	1	56.6	1.34	0.2527

Estimates								
Label	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
T vs. R	-0.09475	0.08199	56.6	-1.16	0.2527	0.1	-0.2319	0.04236

Least Squares Means						
Effect	TRT	Estimate	Standard Error	DF	t Value	Pr > t
TRT	A	8.9911	0.07675	55.6	117.15	<.0001
TRT	B	9.0859	0.07658	55.6	118.64	<.0001

scaled average BE
intermediate analysis - &ipar glm

The GLM Procedure

Class Level Information

Class	Levels	Values
SEQ	3	1 2 3

Number of Observations Read 58

Number of Observations Used 58

scaled average BE

intermediate analysis - &ipar glm

The GLM Procedure

Dependent Variable: ilat

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	0.97567591	0.48783796	1.39	0.2574
Error	55	19.28616111	0.35065747		
Corrected Total	57	20.26183703			

R-Square	Coeff Var	Root MSE	ilat Mean
0.048153	-634.9460	0.592163	-0.093262

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	2	0.97567591	0.48783796	1.39	0.2574

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	2	0.97567591	0.48783796	1.39	0.2574

Parameter	Estimate	Standard Error	t Value	Pr > t	90% Confidence Limits
average	-0.09219853	0.07785080	-1.18	0.2414	-0.22244556 0.03804849

dev iglmilat1

Obs	Dependent	Source	DF	SS	MS	FValue	ProbF
1	ilat	Model	2	0.97567591	0.48783796	1.39	0.2574
2	ilat	Error	55	19.28616111	0.35065747	—	—
3	ilat	Corrected Total	57	20.26183703		—	—

scaled average BE
intermediate analysis - &dpar glm

The GLM Procedure

Class Level Information

Class	Levels	Values
SEQ	3	1 2 3

Number of Observations Read 58

Number of Observations Used 58

scaled average BE
intermediate analysis - &dpar glm

The GLM Procedure

Dependent Variable: dlat

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	1.24890770	0.62445385	1.72	0.1893
Error	55	20.01834134	0.36396984		
Corrected Total	57	21.26724904			

R-Square	Coeff Var	Root MSE	dlat Mean
0.058724	-8872.355	0.603299	-0.006800

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	2	1.24890770	0.62445385	1.72	0.1893

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	2	1.24890770	0.62445385	1.72	0.1893

output needed for mixed scaled av. BE - using glm

Obs	method_used	unscape_lower	unscape_upper	dfi	s2i param	StdErr	pointest
-----	-------------	---------------	---------------	-----	-----------	--------	----------

Obs	method_used	unscape_lower	unscape_upper	dfi	s2i	param	StdErr	pointest	
1	Scaled/PE	0.80052	1.03603	55	0.35066	LAUCT	0.07785080	0.91192	.002439

final output - ¶meter - using glm

Obs	method_used	unscape_lower	unscape_upper	param	pointest	s2wr	sWR	critbound	outc
1	Scaled/PE	0.80052	1.03603	LAUCT	0.91192	0.18198	0.42660	-0.083179	PAS

scaled average BE
intermediate analysis - &ipar glm

The GLM Procedure

Class Level Information

Class	Levels	Values
SEQ	3	1 2 3

Number of Observations Read 58

Number of Observations Used 58

scaled average BE
intermediate analysis - &ipar glm

The GLM Procedure

Dependent Variable: ilai

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	1.59679802	0.79839901	2.01	0.1437
Error	55	21.84284416	0.39714262		
Corrected Total	57	23.43964217			

R-Square	Coeff Var	Root MSE	ilai Mean
0.068124	-658.7509	0.630193	-0.095665

Source	DF	Type I SS	Mean Square	F Value	Pr > F
--------	----	-----------	-------------	---------	--------

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	2	1.59679802	0.79839901	2.01	0.1437

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	2	1.59679802	0.79839901	2.01	0.1437

Parameter	Estimate	Standard Error	t Value	Pr > t	90% Confidence Limits
average	-0.09366791	0.08285043	-1.13	0.2631	-0.23227949 0.04494368

dev iglmilai1

Obs	Dependent	Source	DF	SS	MS	FValue	ProbF
1	ilai	Model	2	1.59679802	0.79839901	2.01	0.1437
2	ilai	Error	55	21.84284416	0.39714262	—	—
3	ilai	Corrected Total	57	23.43964217	—	—	—

scaled average BE
intermediate analysis - &dpar glm

The GLM Procedure

Class Level Information

Class	Levels	Values
SEQ	3	1 2 3

Number of Observations Read 58

Number of Observations Used 58

scaled average BE
intermediate analysis - &dpar glm

The GLM Procedure

Dependent Variable: dlai

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	1.45051007	0.72525503	1.88	0.1616
Error	55	21.17145846	0.38493561		

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Corrected Total	57	22.62196852			

R-Square	Coeff Var	Root MSE	dlai Mean
0.064120	-1097.271	0.620432	-0.056543

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	2	1.45051007	0.72525503	1.88	0.1616

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	2	1.45051007	0.72525503	1.88	0.1616

output needed for mixed scaled av. BE - using glm

Obs	method_used	unscale_lower	unscale_upper	dfi	s2i	param	StdErr	pointest
1	Scaled/PE	0.79306	1.04327	55	0.39714	LAUCINF	0.08285043	0.91059 .0019

final output - ¶meter - using glm

Obs	method_used	unscale_lower	unscale_upper	param	pointest	s2wr	sWR	critbound	or
1	Scaled/PE	0.79306	1.04327	LAUCINF	0.91059	0.19247	0.43871	-0.086809	P

scaled average BE

intermediate analysis - &ipar glm

The GLM Procedure

Class Level Information

Class	Levels	Values
SEQ	3	1 2 3

Number of Observations Read 58

Number of Observations Used 58

scaled average BE

intermediate analysis - &ipar glm

The GLM Procedure

Dependent Variable: ilc

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	3.38758117	1.69379058	1.98	0.1476
Error	55	47.01347476	0.85479045		
Corrected Total	57	50.40105593			

R-Square	Coeff Var	Root MSE	ilc Mean
0.067213	-1037.794	0.924549	-0.089088

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	2	3.38758117	1.69379058	1.98	0.1476

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	2	3.38758117	1.69379058	1.98	0.1476

Parameter	Estimate	Standard Error	t Value	Pr > t	90% Confidence Limits
average	-0.09100276	0.12154899	-0.75	0.4572	-0.29435835 0.11235282

dev iglmilc1

Obs	Dependent	Source	DF	SS	MS	FValue	ProbF
1	ilc	Model	2	3.38758117	1.69379058	1.98	0.1476
2	ilc	Error	55	47.01347476	0.85479045	—	—
3	ilc	Corrected Total	57	50.40105593	—	—	—

scaled average BE
intermediate analysis - &dpar glm

The GLM Procedure

Class Level Information

Class	Levels	Values
SEQ	3	1 2 3

Number of Observations Read 58

Number of Observations Used 58

scaled average BE

intermediate analysis - &dpar glm

The GLM Procedure

Dependent Variable: dlc

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	5.55862971	2.77931486	3.02	0.0568
Error	55	50.56440289	0.91935278		
Corrected Total	57	56.12303260			

R-Square Coeff Var Root MSE dlc Mean

0.099044 551.0617 0.958829 0.173997

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	2	5.55862971	2.77931486	3.02	0.0568

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	2	5.55862971	2.77931486	3.02	0.0568

output needed for mixed scaled av. BE - using glm

Obs	method_used	unscape_lower	unscape_upper	dfi	s2i	param	StdErr	pointest
1	Scaled/PE	0.74402	1.11456	55	0.85479	LCMAX	0.12154899	0.91302

.006492

final output - ¶meter - using glm

Obs	method_used	unscape_lower	unscape_upper	param	pointest	s2wr	sWR	critbound	out
1	Scaled/PE	0.74402	1.11456	LCMAX	0.91302	0.45968	0.67799	-0.24217	PA

ANDA: 091640-Fed STUDY TYPE: Fed
SUMMARY OF STATISTICAL ANALYSIS - UNSCALED DATA

Geometric Means				90% CI	
Parameter	Test	Reference	T/R Ratio	Lower CI	Upper CI
LAUCT	7187.51	7892.34	0.91	80.05	103.60
LAUCI	8031.67	8829.85	0.91	79.31	104.33
LCMAX	1123.93	1234.23	0.91	74.40	111.46

SUMMARY OF STATISTICAL ANALYSIS - SCALED DATA

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	0.91	80.05	103.60	0.1819849	0.4265969	-0.083179	Scaled/PE	PASS
LAUCI	0.91	79.31	104.33	0.1924678	0.4387115	-0.086809	Scaled/PE	PASS
LCMAX	0.91	74.40	111.46	0.4596764	0.6779944	-0.242166	Scaled/PE	PASS

BIOEQUIVALENCE DEFICIENCIES
(BE part)

ANDA: 091640

APPLICANT: Zydus Pharmaceuticals USA Inc.

DRUG PRODUCT: Mesalamine Delayed-release Tablets, 1200 mg

The Division of Bioequivalence II (DB II) has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

In vivo Bioequivalence (BE) Studies:

1. Per your SOP (b) (4) sample coded as Above the Upper Limit of Quantitation (>ULQ) were diluted appropriately prior to reassay.

The code >ULQ is used where the calculated, un-rounded concentration of a sample falls above the nominal concentration of the ULQ (this does not apply to truncated calibration curves; refer to V.A.1.). Additionally, the >ULQ code is applied to QC and subject samples whose ratios have a greater value than the extrapolated curve's vertex, in the case of a quadratic equation. This code more often applies to subject samples, however, it may also apply to QC samples, e.g., high concentration QC samples assayed as part of sample analysis or method validation that produce concentrations above that of the ULQ calibrant. Subject samples coded >ULQ are generally diluted appropriately prior to re-assay. Refer to SOP (b) (4)

However, we could not locate the dilution factor in your study report or the related SOP (b) (4). Please provide the used dilution factors used for the fasting study MSN-P2-480 and the Fed study MSN-P3-482.

2. It is noted that you reported all repeat assays values as the final concentration for repeat assay under code "SLP", "UIS", "SCT", ">ULQ" and "CR" but reported "Number of recalculated values used after reanalysis" as "NA" for those samples. For your future application, please report the actual number for "Number of recalculated values used after reanalysis" when the final concentration is reported from repeat assays.

In vitro BE dissolution Studies:

3. Day-to-Day variability is observed in your dissolution testing data on both of your Test and Reference product at pH 6.8. We could not locate your method validation report for the in vitro BE dissolution study. Please provide your method validation report, which should include precision and accuracy. In addition, to further investigate the observed high variability, please validate the method's system robustness to cover any possible deviation (e.g. buffer pH, operator, temperature, etc.) and include the data in the validation report. After revalidate your method, please re-conduct the in vitro BE dissolution testing and using

unexpired test (24 units) and **at least two lots (more if needed)** of the reference product (using 12 tablets per lot) for the following conditions:

Apparatus: USP Apparatus 2 (paddle)
Pretreatment Stage 1: 2 hours in 100mM HCl at 100 rpm (750 mL)
Pretreatment Stage 2: 1 hour in pH 6.4 Phosphate buffer at 100 rpm (950 mL)
Evaluation Stage: Each of
(1) pH 6.8 Phosphate buffer at 100 rpm
(b) (4)
Volume: 960 mL
Temperature: 37°C

Sample times: 1, 2, 4, 6 and 8 hours or as needed for profile comparison

4. As stated in our complete response letter dated March 13, 2013, the in vitro BE dissolution testing should be conducted in pretreatment stages (0.1 N HCl and pH 6.4 Phosphate Buffer) and followed by each evaluation stage. However, we only received one set of pretreatment data in your amendment dated October 23, 2013. Please provide your complete study report with data from each pre-treatment stage for the following evaluation stages, pH 6.5, pH 7.2 and pH 7.5. If you did not analyze the drug release for those pretreatment stages or did not conduct pretreatment stage for each evaluation stage (pH 6.5, pH 7.2 and pH 7.5), please re-conduct in vitro BE dissolution testing with pretreatment stage for each evaluation stage (pH 6.5, 7.2 and 7.5) and submit the complete data.
5. You provided mean dissolution profiles for various batches of RLD product in Figure 2 in the cover letter in the amendment dated 10/23/2013. However, we could not locate the raw data for those corresponding dissolution testing. Please provide dissolution testing report on RLD product batches **VC011A**, **WD119A** and **LC105A**. In addition, please provide those RLD products expiration date as well as the testing dates.

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D., R.Ph.
Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCE DEFICIENCY

(Dissolution part)

ANDA: 091640

APPLICANT: Zydus Pharmaceuticals USA Inc.

DRUG PRODUCT: Mesalamine Delayed-release Tablets, 1200 mg

The Division of Bioequivalence II (DBII) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The following deficiency has been identified:

We acknowledge that you conduct your dissolution testing on the new batch test product (Lot No. EMM196, Manufacture date March 2012). However, it is noticed that the volume (b) (4) of dissolution media and the specifications (listed in your Bio-summary table 5: Summary of in vitro dissolution studies) were different from the FDA-recommended below. Please note that you acknowledged the following FDA-recommended method and specifications in your amendment dated September 8, 2010.

Method:

Acid Stage A: 750mL of 100 mM HCl (Acid Stage A)

Buffer Stage B: 950 mL of Phosphate buffer, pH 6.4
(Buffer Stage B: A+ 200 mL 200 mM Na₃PO₄)

Buffer Stage C: 960 mL of Phosphate buffer, pH 7.2
(Buffer Stage C: B + 9 mL 2M NaOH adjusting pH with 2M NaOH or 2M HCl)

Apparatus: USP apparatus 2 (Paddle)

Speed: 100 rpm.

Specifications:

Acid stage A: NMT (b) (4) % in 2 hours

Buffer stage B: NMT (b) (4) % in 1 hour

Buffer stage C: 1 hour: NMT (b) (4) %

2 hours: (b) (4) %

6 hours: NLT (b) (4) %

Please explain the observed discrepancy on dissolution volume and specifications and provide the updated table with correct dissolution volume and specifications.

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D., R.Ph.

Director

Division of Bioequivalence II

Office of Generic Drugs

Center for Drug Evaluation and Research

4.9 Outcome Page

ANDA: 091640

Enter Review Productivity and Generate Report

Reviewer: Zhao, Joan

Date Completed:

Verifier: ,

Date Verified:

Division: Division of Bioequivalence

Description: Mesalamine Delayed Release Tablets, 1.2 g

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
21919	10/23/2013	Other (REGULAR)	Study Amendment	1	1
21919	10/23/2013	Bioequivalence Study (REGULAR)	Fasting Study	1	1
21919	10/23/2013	Bioequivalence Study (REGULAR)	Fed Study	1	1
21919	10/23/2013	Bioequivalence Study (REGULAR)	Failed Extra Study	2	2
21919	10/23/2013	Dissolution Data (REGULAR)	Dissolution Amendment	1	1
21919	10/23/2013	Bioequivalence Study (REGULAR)	In Vitro BE Dissolution Study (pH 6.5, pH 6.8, pH 7.0, pH 7.2 and pH 7.5)	5	5
21919	10/23/2013	Bioequivalence Study (REGULAR)	T _{max} Analysis	1	1
21919	2/9/2014	Other (REGULAR)	Consult Response Review	1	1
				Total:	13

Division of Bioequivalence 2 Review Complexity Summary

BE Study Fasting	
Clinical (Common to all APIs)	1
Bioanalytical (API 1)	1

Statistical Analysis (API 1)	1
<i>Fasting Study Total</i>	3
BE Study Fed	
Clinical (Common to all APIs)	1
Bioanalytical (API 1)	1
Statistical Analysis (API 1)	1
T _{max} Analysis	1
<i>Fed Study Total</i>	4
Failed BE Study	
Failed Study Rational Summary	2
In vitro BE Study	
pH 6.5, pH 6.8, pH ^{(b) (4)} pH 7.2 and pH 7.5	5
In vitro Dissolution Testing	
New Dissolution testing Data	1
Amendments	
Study Amendment	1
Consult Response Review	
Science Team Consult Review	1
Grand Total	17

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

/s/

ZHUOJUN ZHAO
02/28/2014

MINGLEI CUI
02/28/2014

ETHAN M STIER
03/01/2014

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	091640	
Drug Product Name	Mesalamine Delayed-release Tablets	
Strength(s)	1200 mg	
Applicant Name	Zydus Pharmaceuticals USA Inc.	
Address	210 Carnegie Center, 1 st Floor, Suite 103, Princeton, NJ-08540	
Applicant's Point of Contact	G. Srinivas	
Contact's Telephone Number	609-275-5125	
Contact's Fax Number	609-275-3711	
Original Submission Date(s)	December 12, 2009	
Submission Date(s) of Amendment(s) Under Review	April 13, 2010 (Formulation Data) September 8, 2010 (Dissolution Acknowledgement) February 12, 2011 (Elemental Iron content update)	
First Generic	Yes	
Reviewer	Zhuojun Zhao, Ph.D.	
Study Number (s)	073-08	
Study Type (s)	Clinical Endpoint Study	
Strength (s)	1200 mg	
Clinical Site	NA	
Clinical Site Address	NA	
Analytical Site	NA	
Analytical Site Address	NA	
OVERALL REVIEW RESULT	Inadequate	
Dissolution (USP)	Adequate	
In Vitro Bioequivalence Dissolution Study	Evaluation Stage	Review Result
	pH 6.5	Inadequate
	pH 6.8	Inadequate
	pH 7.2	Inadequate
	pH 7.5	Inadequate

1 EXECUTIVE SUMMARY

This application contains the results of a clinical endpoint comparing the test product, Zydus Pharmaceuticals USA Inc.'s Mesalamine Delayed Release Tablets, 1200 mg to the corresponding reference product, Shire's Lialda® (Mesalamine) Delayed Release Tablets, 1200 mg. The application was received on December 12, 2009. However, in the Agency's response to the Citizen's Petitions (CPs) FDA-2010-P-0111 and FDA-2008-P-0507, dated August 10, 2010, the BE study with clinical endpoints is no longer considered to be sufficiently sensitive to establish BE of this product. The firm should be requested to conduct BE studies with the recommended PK endpoints under both fasting and fed conditions and *in vitro* dissolution study to demonstrate the bioequivalence between its test product and the reference product.

In Zydus' amendment dated September 8, 2010, it acknowledged the FDA-recommended method and specifications. The stability and quality control dissolution testing is acceptable.

No Division of Scientific Investigations (DSI) inspection is pending or necessary.

The application is incomplete.

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3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Mesalamine Delayed Release Tablets, 1200 mg
Reference Product	Lialda® (Mesalamine) Delayed Release Tablets, 1200 mg
RLD Manufacturer	Shire
NDA No.	N022000
RLD Approval Date	January 16, 2007
Indication¹	LIALDA is a locally acting 5-aminosalicylic acid (5-ASA) indicated for the induction of remission in adults with active, mild to moderate ulcerative colitis and for the maintenance of remission of ulcerative colitis.

3.2 PK/PD Information¹

Bioavailability	The total absorption of mesalamine from LIALDA 2.4 g or 4.8 g given once daily for 14 days to healthy volunteers was found to be approximately 21-22% of the administered dose.
Food Effect	Administration of a single dose of LIALDA 4.8 g with a high fat meal resulted in further delay in absorption, and plasma concentrations of mesalamine were detectable 4 hours following dosing. However, a high fat meal increased systemic exposure of mesalamine (mean C _{max} : (91%; mean AUC: (16%) compared to results in the fasted state.
T_{max}	Plasma concentrations of mesalamine were detectable after 2 hours and reached a maximum by 9-12 hours on average for the doses studied.
Metabolism	The only major metabolite of mesalamine (5-aminosalicylic acid) is N-acetyl-5-aminosalicylic acid. Its formation is brought about by N-acetyltransferase (NAT) activity in the liver and intestinal mucosa cells, principally by NAT-1.
Excretion	Elimination of mesalamine is mainly via the renal route following metabolism to N-acetyl-5-aminosalicylic acid (acetylation). However, there is also limited excretion of the parent drug in urine. Of the approximately 21-22% of the dose absorbed, less than 8% of the dose was excreted unchanged in the urine after 24 hours, compared with greater than 13% for N-acetyl-5-aminosalicylic acid.
Half-life	The apparent terminal half-lives for mesalamine and its major metabolite after administration of LIALDA 2.4 g and 4.8 g were, on average, 7-9 hours and 8-12 hours, respectively.
Drug Specific Issues (if any)	

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	3, fasting and fed studies and <i>in vitro</i> comparative dissolution study
---------------------------------------	--

¹ Lialda® Label

1.	Type of study:	Fasting
	Design:	Single-dose, three period, partial replicate (2 R 1T) crossover, <i>in-vivo</i>
	Strength:	1200 mg
	Subjects:	Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study.
	Additional Comments:	Bioequivalence based on (Scaled Average Bioequivalence): (1). Applicants may consider using a reference-scaled average bioequivalence approach for mesalamine. If using this approach, the applicant should provide evidence of high variability in the bioequivalence parameters (i.e., within-subject variability $\geq 30\%$) for the reference product. For general information on this approach refer to the Progesterone Capsule Guidance for additional information regarding highly variable drugs. Other study designs (including a four period fully replicate crossover design) are acceptable if appropriate. (2). For both fasting and fed studies, the following PK parameters are recommended to be evaluated: Log-transformed AUC_{8-48}, AUC_{0-t}, and C_{max}, where AUC_{8-48} is the area under the plasma-concentration vs. time curve from 8 to 48 hours, AUC_{0-t} is the area under the curve from 0 hours to the last measurable time point, and C_{max} is the maximum plasma concentration. Applicants should have extensive sampling points around T_{max} to have accurate estimation of C_{max} and T_{max}, and at least four non-zero measurements of concentration are recommended before T_{max} and between T_{max} and 24 hours. Other partial AUCs may be evaluated as supporting material to evaluate similarity of drug release throughout the GI tract. (3). The study should use the lowest single dose possible to obtain accurate pharmacokinetic parameters for mesalamine. (4). As AUC_{0-t} is recommended in place of $AUC_{0-\infty}$, the last sampling time point should be at least at 72 hours.
2.	Type of study:	Fed
	Design:	Single-dose, three period, partial replicate (2 R 1T) crossover, <i>in-vivo</i>
	Strength:	1200 mg
	Subjects:	Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study.
	Additional Comments:	See additional comments above
3.	Type of study:	<i>In vitro</i> comparative dissolution study
	Strength:	1200 mg
	Apparatus:	USP Apparatus 2 (Paddle)
	Pretreatment Stage 1:	2 hours in 0.1 N HCl at 100 rpm (750 mL)
	Pretreatment Stage 2:	1 hour in pH 6.4 Phosphate buffer at 100 rpm (950 mL)

Evaluation Stage 1:	Each of 960 mL (1) pH 6.5 Phosphate buffer at 50 rpm (2) pH 6.8 Phosphate buffer at 50 rpm (3) pH 7.2 Phosphate buffer at 50 rpm (4) pH 7.5 Phosphate buffer at 50 rpm
Temperature:	37°C
Sample times:	1, 2, 4, 6 and 8 hours or as needed for profile comparison
Additional comments:	The applicant should use at least 12 tablets per test. The f2 metric will be used to compare dissolution profiles

Analytes to measure (in plasma/serum/blood):	Mesalamine in plasma
Bioequivalence based on:	90% CI of mesalamine
Waiver request of in-vivo testing:	N/A
Source of most recent recommendations:	Science Team is in process of preparing the recommendations for Mesalamine (Lialda) and the review for guidance will be loaded to folder of V:\Science Group\Mesalamine_BE. (See section 4.3).
Summary of OGD or DBE History:	for details see Appendix 4.3

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	
Single-dose fed	No	
Steady-state	No	
In vitro dissolution	Yes	1
Waiver requests	N/A	
BCS Waivers	N/A	
Clinical Endpoints	Yes	1
Failed Studies	No	
Amendments	Yes	3

3.5 Pre-Study Bioanalytical Method Validation

N/A

3.6 In Vivo Studies

N/A

3.7 Formulation

Location in appendix	Section 4.1, Page 10
If a tablet, is the RLD scored?	

If a tablet, is the test product biobatch scored	
Is the formulation acceptable?	FORMULATION ACCEPTABLE
If not acceptable, why?	

Product Information Used in the Clinical Endpoint Study

Product	Test	Reference		
Treatment ID	T	R		
Product Name	Mesalamine Delayed-release Tablets	Lialda™ Mesalamine Delayed-release Tablets		
Manufacturer	Cadila Healthcare Limited, India	Shire US Inc.USA		
Batch/Lot No.	EMH345	7L3814	8A4383	8C4562
Manufacture Date	August 2008	N/A		
Expiration Date	N/A	09/2009	01/2011	03/2011
Strength	1.2 g	1.2 g		
Dosage Form	Tablets	Tablets		
Bio-batch Size	(b) (4)	N/A		
Production Batch Size	(b) (4)	N/A		
Potency	103.4%	99.5%	101.7%	99.9 %
Dose Administered	1.2 g	1.2 g		
Route of Administration	Oral	Oral		

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	DARRTS: REV-BIOEQ-02 (Dissolution Review), final date 07/28/2010
Source of Method (USP, FDA or Firm)	FDA
Medium	Acid stage A: 100 mM HCl; Buffer stage B: Phosphate buffer, pH 6.4; Buffer stage C: Phosphate buffer, pH 7.2
Volume (mL)	Acid A: 750 mL Buffer B: 950 mL (A + 200mL 200mM Na ₃ PO ₄)* Buffer C: 960 mL (B+ 9mL 2M NaOH)* *Adjust pH with 2M NaOH or 2M HCl
USP Apparatus type	USP II (Paddle)
Rotation (rpm)	100 rpm
DB-recommended specifications	Acid Stage A: NMT $\frac{(b)(4)}{(4)}\%$, Buffer Stage B: NMT $\frac{(b)(4)}{(4)}\%$, Buffer Stage C: 1 hr: NMT $\frac{(b)(4)}{(4)}\%$, 2 hr: $\frac{(b)(4)}{(4)}\%$, 6h NLT $\frac{(b)(4)}{(4)}\%$
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	Yes

If no, reason why F2 not calculated	
Is method acceptable?	METHOD ACCEPTABLE
If not then why?	

F2 metric, Test (Batch # EMH345) compared to RLD			
RLD Lot #	7L3814	8C4562	8A4383
F2	76.53	90.29	62.05

Comments:

There is no USP method for this product but there is an FDA-recommended method. The firm's dissolution testing procedure in the original application dated December 12, 2009 is slightly different from the FDA-recommended method in the medium volume (See table below).

Dissolution Method		FDA	Zydus
Medium Volume:	Acid A:	750 mL	(b) (4)
	Buffer B:	950 mL	
	Buffer C:	960 mL	

Nevertheless, the firm's dissolution testing data was accepted and the firm was requested to acknowledge the FDA-recommended method and specifications in deficiency letter dated August 3, 2010². In firm's amendment dated September 8, 2010, the firm acknowledged the FDA-recommended method and specifications and submitted documents for the updates. The dissolution testing is deemed acceptable.

The performance of (b) (4) Lialda[®] is an essential attribute of the product. Demonstration of equivalence in multistage dissolution ensures the equivalent integrity of the (b) (4) at acidic pH and at pH 6.4-7.2. The firm voluntarily conducted the comparative dissolution testing in Water and 0.1 N HCl followed by pH 6.8 Phosphate Buffer. The firm should be request to conduct additional in vitro dissolution studies comparing its test product to the RLD Asacol[®] tablets at pH 6.5-7.5 as per the OGD recommendations.

3.9 Deficiency Comments

1. As per Agency's 8/10/10 response to citizen's petitions FDA-2010-P-0111 and FDA-2008-P-0507 (the August 2010 CP Response), the bioequivalence (BE) study with clinical endpoints is no longer considered to be sufficiently sensitive to establish BE of this product. According to the Agency's current recommendation that applicants for generic version of Lialda[®] should demonstrate bioequivalence using data from comparative pharmacokinetic (PK) studies and in vitro dissolution studies, the firm should be requested to conduct PK studies comparing its test product to the reference product, Lialda[®] (mesalamine) DR Tablets, 1200 mg under both fasting and fed conditions. The firm should be informed of our current thinking on the study design in section 3.3.

² DARRTS: REV-BIOEQ-02 (Dissolution Review), final date 07/28/2010.

2. The firm should conduct the comparative dissolution testing on at least 24 units of the test product for its final formulation and two lots of the reference product (12 units per each reference lot). The dissolution testing should be conducted on the test and reference lots used in the PK studies using the following method:

Apparatus:	USP Apparatus 2 (paddle)
Pretreatment Stage 1:	2 hours in 0.1 N HCl at 100 rpm (750 mL)
Pretreatment Stage 2:	1 hours in pH 6.4 Phosphate buffer at 100 rpm (950 mL)
Evaluation Stage:	Each of
	(1) pH 6.5 Phosphate buffer at 100 rpm
	(2) pH 6.8 Phosphate buffer at 100 rpm
	(3) pH 7.2 Phosphate buffer at 100 rpm
	(4) pH 7.5 Phosphate buffer at 100 rpm
Volume:	960 mL
Temperature:	37°C

The DBII will perform an f2 test on firm's submitted dissolution data. If the variability of the dissolution data is high that mean data cannot be used for the f2 test, as per the CDER Guidance for Industry: *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*, we will calculate the f2 metric based on an f2 confidence interval using a 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. The 90% confidence intervals of the f2 values are calculated using the percentile approach as described in the Shah et al. reference. A similar procedure can be followed for comparing reference vs. reference product dissolution profiles.

Only one measurement after 85% dissolution of both the products should be included in the f2 calculation.

3.10 Recommendations

1. As per the 8/10/10 Agency's response to the Citizen Petitions FDA-2010-P-0111 and FDA-2008-P-0507, the BE study with clinical endpoints is no longer considered to be sufficiently sensitive to establish BE of this product. The firm should demonstrate BE using data from comparative PK studies and in vitro dissolution studies comparing its test product to the RLD Asacol[®] tablets.

The firm should be informed the following additional recommendations for the in vivo BE studies with PK endpoints:

- (a). You may consider using a reference-scaled average bioequivalence approach for mesalamine. For general information on this approach, please refer to the Progesterone Capsule Guidance: (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf>). Other study designs (including a four period fully replicate crossover design) are acceptable if appropriate.
- (b). For both fasting and fed studies, the following PK parameters are recommended to be evaluated: Log-transformed AUC_{8-48} , AUC_{0-t} , and C_{max} . Additional exploratory parameters may be included as secondary endpoints.
2. The firm should repeat comparative in vitro BE dissolution testing using the FDA recommended dissolution method on the batches used in the new PK studies.
 3. The firm's in vitro dissolution testing using the FDA-recommended method is acceptable. In Zydus' amendment dated September 8, 2010, the firm acknowledged the FDA-recommended method and specifications.
 4. The application is incomplete due to the deficiencies above.

3.11 Comments for Other OGD Disciplines

Discipline	Comment
	None

4 APPENDIX

4.1 Formulation Data

Ingredient (s)	Mesalamine Delayed-release Tablets, 1.2 g	
	Unit Composition (mg/tablet)	% w/w ^{\$}
(b) (4)		
Mesalamine (b) (4) USP	1200.000	(b) (4)
Colloidal Silicon Dioxide (b) (4) NF	(b) (4)	(b) (4)
Magnesium Stearate (b) (4) NF	(b) (4)	(b) (4)
(b) (4)		
Carboxy methyl cellulose Sodium (b) (4) USP		
Sodium Starch Glycolate (b) (4) NF		
Hypromellose (b) (4) USP		
(b) (4)	(b) (4)	
(b) (4)		
Microcrystalline Cellulose (b) (4) NF		
Colloidal Silicon Dioxide (b) (4) NF		
Magnesium Stearate (b) (4) NF		
(b) (4)		
Methacrylic Acid Copolymer (b) (4) NF		
(b) (4)		
Triethyl Citrate (b) (4) NF		
Talc (b) (4) USP		
(b) (4)		
(b) (4)		
(b) (4)		
Total (Coated Tablets)	1465.000	100.00

^{\$} Calculated based on the coated tablet average weight.

(b) (4)

(b) (4)

Is there an overage of the active pharmaceutical ingredient (API)?	NO
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A

Comments:

1. As per the RLD labeling, the maximum daily dose for Lialda® is 4800 mg/day. The levels of inactive ingredients used in the proposed formulation conform to the reported levels as per FDA's inactive ingredients (IIG) database (see table below).

Ingredient	mg/day	IIG Limit (mg)
Colloidal Silicon Dioxide (b) (4), NF		(b) (4)
Magnesium Stearate, NF		
Carboxy methyl cellulose Sodium (b) (4) USP		
Sodium Starch Glycolate (b) (4) NF		
Hypromellose (b) (4) USP		
Microcrystalline Cellulose (b) (4) NF		
Methacrylic Acid Copolymer (b) (4) NF		
(b) (4)		

Ingredient	mg/day	IIG Limit (mg)
Triethyl Citrate (b) (4) NF		(b) (4)
Talc (b) (4) USP		
(b) (4) Hypromellose (b) (4) USP		
Titanium Dioxide, USP*		
Macrogol /PEG 6000, NF*		
Iron Oxide Red, NF*		
Iron Oxide, Yellow, NF*		

2. (b) (4) (b) (4)

(b) (4) The maximum daily intake of the elemental iron from the test product is now 4.64 mg/day⁹, within the limit for elemental Iron of 5 mg per day (CFR 73.1200(c)).

3. The composition of the product is satisfactory.

⁶ The daily intake of 64 mg Triethyl Citrate is deemed acceptable based on the Pharmacologist's consult for ANDA (b) (4) (DARRTS: CONSULT REV-NONCLINICAL-01, FIANL DATE 08/04/2010).

⁷ DARRTS: REV-QUALITY-03 (General Review), final date 12/03/2010.

⁸ DARRTS: REV-QUALITY-03 (General Review), final date 06/01/2011.

⁹ Reviewer Calculation of maximum daily intake of elemental iron: (b) (4)
(b) (4)=4.64 mg/day.

4.3 Detailed Regulatory History for Lialda[®]¹⁰

Control Number	From
07-0677	(b) (4)
07-0679	
07-0735	
07-1162	
07-1187	
07-1441	
07-1541	
08-0259	
08-0515	
08-0656	
08-0814	
08-1053	
08-1153	
09-0261	
09-0465	
09-0485	
09-0647	
09-0660	
10-0621	

Lialda[®] is similar to two other modified release mesalamine products: Asacol and Pentasa. Thus the framework from the 2010 Citizen Petition response should also apply to Lialda[®]. For all mesalamine products, OGD will ask for PK studies and comparative dissolution studies in multiple pH media to demonstrate bioequivalence (see attachment II, section 4.4.2). The history, rationales, and the development of the BE metrics have been described in a separate document. (V:\Science Group\Mesalamine_BE\mesalamine_oral_BE_summary.doc)

For Asacol and Pentasa, the recognition that clinical endpoint bioequivalence studies may not be sensitive to differences in local delivery (because the clinical studies may be conducted on a plateau of the exposure-response curve for the clinical endpoint) was one factor in the decision to recommend extensive comparative dissolution testing between test and reference products to demonstrate bioequivalence. The clinical studies on Lialda also do not show a significant difference in the clinical endpoints between dose of 2.4g/day and 4.8 g/day.

Both fed and fasted studies are recommended because this is the general OGD policy for modified release dosage forms. Pharmacokinetics of mesalamine from Lialda has been observed to be highly variable and thus a scaled average bioequivalence approach is recommended. Within subject CV% for AUC_{0-t}, AUC_{0-∞} and C_{max} were estimated as 50.1%, 45.5% and 90.7% in study SPD476-106. Part of the high variability in C_{max} arises

¹⁰ V:\Science Group\Mesalamine_BE\mesalamine_Review_022000_Lialda.doc

because most subjects have two widely separated peaks in the plasma concentration profile.

The partial AUC_{8-48} is recommended because (1) it reflects the absorption in the colon, which is the site of action¹¹; (2) the variability of $AUC_{T_{max}}$ is too high and it might be over-discriminative (see data analysis description in the Asacol Review, V:\Science Group\Mesalamine_BE\ mesalamine_Review_019651_Asacol.doc). However, since mesalamine oral products are locally acting, it is important to have profile similarity between the reference product and the generic product to ensure they have similar delivery in the gastrointestinal tract. Thus OGD may evaluate other partial AUCs during the review process as supportive information. To aid this evaluation and to ensure the best possible characterization of drug absorption by AUC_{8-48} we recommend dense sampling in the time between T_{max} and 24 hours.

The recommended dose of 1200 mg is one tablet. The results of study SPD476-106 indicate proportionality between 1200 mg and 2400 mg doses. There are no safety concerns with exposure to healthy subjects to a dose of 1200 mg of mesalamine.

Mesalamine has one significant pre-systemic metabolite (5-Ac-ASA) that was measured in most pharmacokinetic studies for the Lialda NDA. For other mesalamine products, OGD has determined that this metabolite does not contribute significantly to safety or efficacy and therefore does not recommend that it be measured in bioequivalence studies.

The performance of the (b) (4) of Lialda is an essential attribute of the product. Demonstration of equivalence in multistage dissolution ensures the equivalent integrity of the enteric coat at acidic pH and at pH 6.4-7.2. Any generic product should have equivalent performance as the RLD. The requirement that ANDA products be equivalent in dissolution to Lialda ensures that dissolution will distinguish the many different products on the market and makes it clear to the ANDA sponsors that they should develop an (b) (4) product with the same extended release performance as the RLD.

¹¹ DARRTS: IND 026093 REV-CLINPHARM-01 (General Review), final date 02/13/2011 and COR-INDAD-02 (Advice/Information Request) final date 02/15/2011 (see attachment III, section 4.4.3).

4.4 Attachment

4.4.1 Attachment I: IIG limit of Eudragit S

From: Chakder, Sushanta K
Sent: Friday, January 13, 2012 5:09 PM
To: Zhao, Joan
Cc: Jiang, Xiaojian
Subject: RE: Question about (b) (4) for ANDA 91640

Hi Joan,

I looked at my review. Yes, based on the available nonclinical data, the amount of (b) (4) in the Zydus formulation is acceptable.

Sushanta

From: Zhao, Joan
Sent: Friday, January 13, 2012 4:53 PM
To: Chakder, Sushanta K
Cc: Jiang, Xiaojian
Subject: Question about (b) (4) for ANDA 91640

Hi Sushanta,

This is bio-reviewer for ANDA 91640.

We read your consult review (CONSULT REV-NONCLINICAL-01(General Consult Review), final date 07/22/2010). It states that (b) (4) in Asacol (800 mg) Tablets (b) (4) than the proposed amount in Zydus's test product (b) (4). However, we noticed that Zydus uses Methacrylic Acid Copolymer (b) (4) while Asacol HD uses (b) (4).

Can amount of (b) (4) in Zydus formulation be deemed acceptable based on its submitted nonclinical data?

Your comment is greatly appreciated!

Thank you and have a great long weekend!

Joan

*Zhuojun Joan Zhao, Ph.D.
Division of Bioequivalence II
Office of Generic Drugs
FDA/CDER/OPS*

4.4.2 Attachment II: OGD OND Harmonization on Recommendation History

On October 28, 2011, a meeting was held among OGD, OCP, ONDQA, and ORP staffs to discuss the differences in Asacol BE recommendations. Three issues were discussed (1) OGD recommends both fasting and fed studies and new drug only recommends fasting study; (2) OGD recommends three-period partially replicate design using scaled average BE analysis while new drug recommends four-period fully replicate design using average BE analysis; (3) differences in partial AUCs recommended.

OGD recommendations are for new ANDAs and OND recommendations are for a post-approval change. OGD generally accepts one study (an in vivo study in healthy subjects, under fasting conditions, with PK endpoints, and comparing reformulated test product with reference product) for post-approval changes. Thus the OGD and OND are consistent in terms of the fasting and fed studies recommended. Although OND recommend average BE analysis, they will accept scaled average BE analysis if the study failed to meet unscaled average BE acceptance limits of 80-125%. OGD agreed to use similar language on the partial AUCs that OND used in their letter to Warner-Chilcott regarding the types of in vivo data needed to support a major post-approval reformulation of Asacol. The recommendations conveyed to Warner-Chilcott are “We recommend the partial AUC₈₋₄₈ hours as opposed to the AUC₁₂₋₄₈ hours. This time period (8-48 hours) is more clinically relevant and is expected to be able to detect significant differences in product performance. Additional exploratory parameters, such as those proposed (0-12 and 12-48 hours, etc.) may be included as secondary endpoints and would be helpful in evaluating partial AUC as a pharmacokinetic parameter for future studies.” (see attachment III for OND letter)

OGD agreed with OND on the partial AUC₈₋₄₈ based on the following reasons: (1) AUC₈₋₄₈ reflects the absorption in the colon, which is the site of action; (2) the variability of AUC_{tmax} is too high and it might be over-discriminative. However, since Asacol and other mesalamine oral products are locally acting, it is important to have profile similarity between the reference product and the generic product to ensure they have similar delivery in the gastrointestinal tract. Thus OGD may evaluate other partial AUCs during the review process as supportive information. To aid this evaluation and to ensure the best possible characterization of drug absorption by AUC₈₋₄₈ we recommend dense sampling in the time between T_{max} and 24 hours.

4.4.3 Attachment III: OND Recommendation For BE Study¹¹



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 026093

ADVICE/INFORMATION REQUEST

Attention: Matthew Lamb, Pharm.D.
Senior Director, Regulatory Affairs
100 Enterprise Drive
Rockaway, NJ 07866

Dear Dr. Lamb:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Asacol (mesalamine) Delayed Release Tablets, 400 mg and Asacol HD (mesalamine) Delayed Release Tablets, 800 mg.

We also refer to your amendment dated December 29, 2010, received January 04, 2011, containing a draft phase 1 protocol to evaluate the relative bioavailability of a dibutyl phthalate-free mesalamine formulation versus the currently marketed Asacol formulation.

We have the following comments and recommendations:

Biopharmaceutics Comments

1. A total of 390 subjects will be enrolled in the study. However, the details of the sample size calculation are not provided. Please provide the details on sample size calculation.

Clinical Pharmacology Comments

2. We recommend the partial AUC₈₋₄₈ hours as opposed to the AUC₁₂₋₄₈ hours. This time period (8-48 hours) is more clinically relevant and is expected to be able to detect significant differences in product performance. Additional exploratory parameters, such as those proposed (0-12 and 12-48 hours, etc.) may be included as secondary endpoints and would be helpful in evaluating partial AUC as a pharmacokinetic parameter for future studies.
3. Regarding the study design, we recommend that the test product be replicated in addition to the reference product. A 3- or 4-period design could be utilized without further increasing the number of subjects in the study. See Guidance for Industry: Statistical Approaches to Establishing Bioequivalence (published January, 2001).

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm>. Your responsibilities include:

Reference ID: 2906117

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 091640

APPLICANT: Zydus Pharmaceuticals USA Inc.

DRUG PRODUCT: Mesalamine Delayed-release Tablets, 1200 mg

The Division of Bioequivalence II (DB II) has completed its review and has no further questions at this time.

1. As per Agency's 8/10/10 response to citizen petitions FDA-2010-P-0111 and FDA-2008-P-0507 (the August 2010 CP Response), the bioequivalence (BE) study with clinical endpoints is no longer considered to be sufficiently sensitive to establish BE of this product. According to the Agency's current recommendation that applicants for generic version of Lialda® should demonstrate bioequivalence using data from comparative pharmacokinetic (PK) studies and in vitro dissolution studies, please conduct PK studies comparing your test product (unexpired) to the reference product, Lialda® (mesalamine) DR Tablets, 1200 mg under both fasting and fed conditions.

You may consider the following additional recommendations for the in vivo BE studies with PK endpoints:

(a) You may consider using a reference-scaled average bioequivalence approach for mesalamine. For general information on this approach, please refer to the Progesterone Capsule Guidance: (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf>). Other study designs (including a four period fully replicate crossover design) are acceptable if appropriate.

(b) For both fasting and fed studies, the following PK parameters are recommended to be evaluated: Log-transformed AUC_{8-48} , AUC_{0-t} , and C_{max} . Additional exploratory parameters may be included as secondary endpoints.

2. Please conduct the comparative dissolution testing on at least 24 units of the test product and two lots of the reference product (12 units per each reference lot). The dissolution testing should be conducted on the test and

reference lots used in the PK studies using the following method:

Apparatus: USP Apparatus 2 (paddle)
Pretreatment Stage 1: 2 hours in 0.1 N HCl at 100 rpm
(750 mL)
Pretreatment Stage 2: 1 hours in pH 6.4 Phosphate
buffer at 100 rpm (950 mL)
Evaluation Stage: Each of
pH 6.5 Phosphate buffer at 100 rpm
pH 6.8 Phosphate buffer at 100 rpm
pH 7.2 Phosphate buffer at 100 rpm
pH 7.5 Phosphate buffer at 100 rpm
Volume: 960 mL
Temperature: 37°C
Sample times: 1, 2, 4, 6 and 8 hours or as needed
for profile comparison

The DBII will perform an f2 test on your submitted dissolution data. If the variability of the dissolution data is high, such that mean data cannot be used for the f2 test, as per the CDER Guidance for Industry: *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*, we will calculate the f2 metric based on an f2 confidence interval using a 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. The 90% confidence intervals of the f2 values are calculated using the percentile approach as described in the Shah et al. reference. A similar procedure can be followed for comparing reference vs. reference product dissolution profiles.

Only one measurement after 85% dissolution of both the products should be included in the f2 calculation.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

4.5 Outcome Page

ANDA: 091640

Enter Review Productivity and Generate Report

Reviewer: Zhao, Joan

Date Completed:

Verifier: ,

Date Verified:

Division: Division of Bioequivalence

Description: Mesalamine Delayed-release Tablets, 1200 mg

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
15845	12/12/2009	Bioequivalence Study	Clinical Endpoint Study	1	1
15845	4/13/2010	Other	Study Amendment	0	0
15845	9/8/2010	Dissolution Data	Dissolution Acknowledgement	0	0
15845	2/12/2011	Other	Study Amendment	1	1
				Bean Total:	2

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

/s/

ZHUOJUN ZHAO
02/15/2012

XIAOJIAN JIANG
02/15/2012

BARBARA M DAVIT
02/23/2012

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	091640
Drug Product Name	Mesalamine Delayed-release Tablets
Strength (s)	1.2 g
Applicant Name	Zydus Pharmaceuticals USA Inc.
Address	210 Carnegie Center, 1 st Floor, Suite 103, Princeton, NJ-08540
Applicant's Point of Contact	G. Srinivas
Contact's Phone Number	609-275-5125
Contact's Fax Number	609-275-3711
Submission Date(s)	December 12, 2009
First Generic	No
Reviewer	Svetlana Cherstniakova, Ph.D.
Study Number (s)	073-08
Study Type (s)	Clinical Endpoint Study
Strength(s)	1.2 g
Clinical Site	NA
Clinical Site Address	NA
Analytical Site	NA
Analytical Address	NA
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 there is an FDA-recommended method. The firm's dissolution testing data with the FDA-recommended method are acceptable. The firm also meets the FDA-recommended specifications. However the firm's proposed specifications are not acceptable. Based on submitted data, the firm should acknowledge the FDA-recommended method and specifications.

The DBE will review the clinical endpoints study 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 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.						

Dissolution Reference

Mesalamine (1.2 gram)

Dosage Form: Tablet (DR)

Medium: Acid stage A: 100 mM HCl; Buffer stage B: Phosphate buffer, pH 6.4; Buffer stage C: Phosphate buffer, pH 7.2

Apparatus: II (Paddle)

Speed/RPMs: 100

Modify Date:

Sampling Times: Acid stage A: 2 hours; Buffer stage B: 1 hour; Buffer stage C: 1, 2, and 6 hours

Volume: Acid A:750 Buffer B:950(A+200mL 200mM Na₃PO₄)* Buffer C: 960 (B+9mL 2M NaOH)* *adjust pH with 2M NaOH or 2M HCl

Notes: Added on 7/16/09 by NT (Source: AR 2009 and CMC review N022000 N 000 21-Dec-2005)

Specification: Acid Stage A: NMT $\frac{(b)(4)}{(4)}\%$, Buffer Stage B: NMT $\frac{(b)(4)}{(4)}\%$, Buffer Stage C: 1 hr: NMT $\frac{(b)(4)}{(4)}\%$, 2 hr: $\frac{(b)(4)}{(4)}\%$, 6h NLT $\frac{(b)(4)}{(4)}\%$

II. COMMENTS:

None

III. DEFICIENCY COMMENTS:

The DBE agrees with the use of the following dissolution method: The dissolution testing should be conducted in 750mL of 100 mM HCl (Acid Stage A), 950 mL of Phosphate buffer, pH 6.4 (Buffer Stage B: A+ 200 mL 200 mM Na₃PO₄) and 960 mL of Phosphate buffer, pH 7.2 (Buffer Stage C: B+ 9 mL 2M NaOH adjusting pH with 2M NaOH or 2M HCl) using apparatus 2 (Paddle) at 100 rpm.

Based on the submitted data, the DBE recommends the following specifications for the test product:

Acid stage A: NMT (b)(4)0% in 2 hours

Buffer stage B: NMT (b)(4)0% in 1 hour

Buffer stage C:

1 hour: NMT (b)(4)0%

2 hours: (b)(4)0%

6 hours: NLT (b)(4)0%

With response to this deficiency, the firm should indicate if it accepts the DBE-recommended specifications.

IV. RECOMMENDATIONS:

The dissolution testing conducted by Zydus Pharmaceuticals USA Inc. on its Mesalamine Delayed-release Tablets, 1.2 g is incomplete due to above deficiency.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 091640

APPLICANT: Zydus Pharmaceuticals USA Inc.

DRUG PRODUCT: Mesalamine Delayed-release Tablets, 1.2 g

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The DBE will review the clinical endpoints study at a later date. The following deficiency has been identified:

Your dissolution testing data are acceptable. However, your proposed specifications are not acceptable. Based on submitted data, please acknowledge your acceptance of the following FDA-recommended dissolution method and specifications:

The dissolution testing should be conducted in 750mL of 100 mM HCl (Acid Stage A), 950 mL of Phosphate buffer, pH 6.4 (Buffer Stage B: A+ 200 mL 200 mM Na₃PO₄) and 960 mL of Phosphate buffer, pH 7.2 (Buffer Stage C: B + 9 mL 2M NaOH adjusting pH with 2M NaOH or 2M HCl) using apparatus 2 (Paddle) at 100 rpm.

Specifications: Acid stage A: NMT (b) (4)% in 2 hours
Buffer stage B: NMT (b) (4)% in 1 hour
Buffer stage C: 1 hour: NMT (b) (4)%
2 hours: (b) (4)%
6 hours: NLT (b) (4)%

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

V. OUTCOME

ANDA: 091640

VI. *Completed Assignment for 91640 ID: 11624*

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
11624	12/12/2009	Dissolution Data	Dissolution Review	1	1
				Bean Total:	1

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

Dissolution Review	1
--------------------	---

Grand Total	1
--------------------	----------

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
-----	-----	-----	-----
ANDA-91640	ORIG-1	ZYDUS PHARMACEUTICA LS USA INC	MESALAMINE

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

/s/

SVETLANA A CHERSTNIAKOVA
07/28/2010

MOHEB H MAKARY
07/28/2010

BARBARA M DAVIT
07/28/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 091640

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

Memorandum

To: ANDA 091640

From: Tiffany Pokora
Project Manager Team Lead, Division of Bioequivalence II
Office of Bioequivalence
Office of Generic Drugs

Date: May 2, 2017

Subject: Product-Specific Guidance (PSG) on Mesalamine

I. Background

In June 2016, the Agency announced the availability of a revised draft PSG entitled “Draft Guidance on Mesalamine.” This draft PSG provides product-specific recommendations for proposed generic drug products referencing Lialda® (Mesalamine) Delayed-Release Tablets, 1200 mg (NDA 22000).

Consistent with 21 CFR 320.24(a), the scientific recommendations reflected in this draft PSG represent FDA’s determination of the most accurate, sensitive, and reproducible approach for conducting bioequivalence (BE) testing.

This memorandum describes whether such scientific recommendations impact the “adequate” BE review of abbreviated new drug application (ANDA) 091640.

II. Discussion

The BE review for this ANDA, completed 10/26/2015¹, is consistent with the scientific recommendations reflected in the Draft Guidance on Mesalamine. Therefore, this guidance has no impact on the current BE review.

¹ GDRP: ANDA-091640-ORIG-1-AMEND-31, Bioequivalence Primary Review, A91640NA090115.doc, Reviewed by Ping Ren on 10/26/2015.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 03/09/2017 04:54:57 PM

To: gsrinivas@zydususa.com

CC: edward.taylor@fda.hhs.gov

BCC:

Subject: TARGET ACTION DATE NOTIFICATION on ANDA 91640

ANDA 091640

NOTIFICATION --
TARGET ACTION DATE

Zydus Pharmaceuticals, (USA) Inc.
73 Route 31 North
Pennington, NJ 08534
Attention: Srinivas Gurram
Vice President & Head of Regulatory Affairs

Dear Sir:

This letter is in reference to your abbreviated new drug application (ANDA) submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Mesalamine Delayed-Release Tablets USP, 1.2 g.

We acknowledge your response to the Complete Response letter dated February 23, 2017.

The Office of Generic Drugs (OGD), Center for Drug Evaluation and Research, Food and Drug Administration (FDA), is notifying you of our new internal, administrative TARGET ACTION DATE for the above indicated ANDA.

The Target Action Date is the date by which FDA will strive to provide a communication on this ANDA. A TAD will be considered met if the applicant receives an Approval, Tentative Approval, Complete Response (CR) or a complete set of Informational Requests (IRs) by

the action date. A complete set of IRs means that each pending discipline communicated its comments to the applicant. In that case, the TAD will be met if the last discipline communicates its IR by the action date.

We note that FDA is not required to inform applicants of Target Action Dates, but is providing Target

Action Dates at this time as a courtesy to help applicants ascertain when communications may occur for their applications as we implement the Generic Drug User Fee Amendments of 2012 (GDUFA). Notification of a Target Action Date does not constitute a commitment or guarantee that we will take action on your application by the Target Action Date. Any amendments submitted after this notification will affect whether FDA will provide a communication on the application by the Target Action Date.

GDUFA establishes goal dates for the review of ANDAs submitted beginning October 1, 2014. Target

Action Dates are not GDUFA goal dates.

The Target Action Date for this ANDA is May 24, 2017.

Please contact your Regulatory Project Manager, Edward Taylor at (240) 402-6094 for an additional status update of your application.

Sincerely,

Edward Taylor
Regulatory Project Manager Team Leader
OFFICE OF GENERIC DRUGS
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

DO NOT RESPOND TO THIS EMAIL ADDRESS – IT IS A SEND-ONLY ACCOUNT. For questions, please contact the Regulatory Project Manager assigned to your application.

BACKLOG & COHORT YEAR 1-2 COMPLETE RESPONSE CHECKLIST**

RPM: EA Taylor	Action Type: cGMP CR
☒ RX or ☐ OTC ANDA #: 091640 Applicant: Zydus Pharmaceuticals (USA) Inc. Cohort Year: BL/FY2010 ANDA Drug Name and Strength: Mesalamine Delayed-Release Tablets USP, 1.2 g	
Basis of Submission (RLD): NDA 022000/Lialda Tablets, 1.2 g/Shire Development LLC MAPP 5240.3 Priority ANDA: ☒ <i>(Is ANDA based on an approved Suitability Petition? ☐ Yes ☒ No)</i>	
Does the ANDA contain REMS? ☐ Yes ☒ No <i>(If YES, CR Letter must go through the Safety Review Team; clearance may take 2-3 weeks)</i>	

<u>Regulatory Project Manager Evaluation:</u>		Date: 11/30/2016
Yes/N/A	No	
☒	☐	Have all submissions been reviewed and relevant disciplines finalized in CDER Informatics Platform? (date or N/A) Date of Product Quality Review <u>7/28/2014 AQ</u> Date of Bioequivalence Review <u>10/26/2015 AQ</u> Date of Labeling Review <u>2/3/2015 AQ</u> If applicable: Date of Last Complete Response <u>12/21/2015</u> Date of Microbiology Review <u>N/A</u> Date of Dissolution Review <u>7/16/2014 AQ</u> Date of Clinical Review <u>N/A</u> Date of REMS Review <u>N/A</u>
☒	☐	Is DMF adequate and/or has the first cycle review been completed (DMF (b) (4)? NAI Adequate 8/18/2016, only LOA after that
☒	☐	Are all consults complete?
☒	☐	Are all issues resolved?
☒	☐	Have all Policy issues (e.g., citizen petitions) been resolved? No alerts per 11/28/2016 DLRS PAL *If Policy issue, check with OGD if necessary (e.g., to see whether CP blocks CR issuance).
☒	☐	Is Overall Manufacturing Inspection Recommendation task acceptable/ withhold ?
☒	☐	Is OSIS complete (if applicable)? Complete per 10/26/2015 BE review
		Notes (if applicable):
<u>Draft Complete Response Letter</u>		
☒	☐	Is CR letter drafted and uploaded to “Final Decision” task?
<u>Review Discipline/Division Endorsements</u>		
N/A	☐	If ANDA has a pending citizen petition, did RPM notify and obtain clearance from Office of Generic Drug Policy at OGDpolicy@fda.hhs.gov? Date _____
N/A	☐	If ANDA contains REMS, did RPM notify and obtain clearance from REMS Coordinator? Date _____
<u>Project Close-Out</u>		
☒	☐	Is CR checklist uploaded into “Quality Check and Close Project” task?

****Entire Complete Response Checklist to be completed by the RPM**

Complete Response Letter Checklists
ANDA 091640

Complete Response Letter (**not cGMP**)

Yes	No	If any statement is checked NO, STOP and DO NOT issue letter
☒	☐	All relevant discipline reviews are complete and finalized in GDRP
☒	☐	DMF first cycle review(s) complete (b) (4)
☒	☐	DMF Deficiency letter(s) issued to DMF holder(s) prior to ANDA CR issuance <u>OR</u> DMF is adequate AQ 9/14/2015
N/A	☐	Status of the DMF(s) cited in the Product Quality and Microbiology (if applicable) sections is/are current →if needed, update DMF deficiencies to reflect current status per DMF Status and ANDA CR Chart
☒	☐	All amendments have been addressed (reviewed or deferred per IQP 4025.02)
☒	☐	There are no pending consults
N/A	☐	Received clearance from REMS Coordinator (if applicable)
☒	☐	ANDA is not on hold for "other" reasons (e.g. safety, tamper resistance, abuse deterrent) No alerts per 12/14/2015 DLRS list
☒	☐	Chemistry (Product Quality) deficiencies have been accurately added to CR letter <u>OR</u> Chemistry is adequate AQ 7/28/2014
☒	☐	Bioequivalence deficiencies have been accurately added to the CR letter <u>OR</u> Bioequivalence is adequate AQ 10/26/2015
☒	☐	Dissolution deficiencies have been accurately added to the CR letter <u>OR</u> Dissolution is adequate AQ 7/16/2014
N/A	☐	Microbiology deficiencies have been accurately added to the CR letter <u>OR</u> Microbiology is adequate (if applicable)
N/A	☐	Clinical deficiencies have been accurately added to the CR letter <u>OR</u> Clinical is adequate (if applicable)
☒	☐	Labeling deficiencies have been accurately added to the CR letter <u>OR</u> Labeling is adequate AQ 2/3/2015
☒	☐	EES is acceptable or withheld (if withheld EES provided approval of selected CR template language) <u>OR</u> RPM followed proper procedure to send with pending inspections see email pasted below
☒	☐	OSI is not pending /is not required <u>OR</u> RPM followed proper procedure followed to send with pending inspections Complete per 5/3/2015 BE review

ANDA 091640

cGMP Complete Response Letter

Yes	No	If any statement is checked NO, STOP and DO NOT issue letter
☒	☐	All relevant discipline reviews are ADEQUATE and finalized DARRTS (including REMS)
☒	☐	There are no open amendments
☒	☐	There are no pending consults
☒	☐	OSI is adequate/is not pending
☒	☐	Received written confirmation from EES staff authorizing issuance of the cGMP CR letter referencing the withheld facility and approving the selected template language – see email pasted below

From: [Dobbin, Ebern](#)
To: [Taylor, Edward](#)
Subject: RE: Comment on Overall Manufacturing Inspection Recommendation on ANDA-091640-ORIG-1-AMEND-31 (ref# 5729039)
Date: Tuesday, December 15, 2015 9:44:09 AM
Attachments: [image001.png](#)

The name of the facility that has the Withhold is CADILA Healthcare Limited and the FEI# is: 3002984011

From: Taylor, Edward
Sent: Tuesday, December 15, 2015 9:14 AM
To: Dobbin, Ebern
Subject: RE: Comment on Overall Manufacturing Inspection Recommendation on ANDA-091640-ORIG-1-AMEND-31 (ref# 5729039)

Hi Ebern,
Could you please list the name(s) and FEI #(s) of the Facility(ies) to name in option B of our CR.

Thank you,

Edward (Andrew) Taylor

From: Dobbin, Ebern
Sent: Tuesday, December 15, 2015 8:41 AM
To: Taylor, Edward
Cc: OPF Facilities Questions
Subject: RE: Comment on Overall Manufacturing Inspection Recommendation on ANDA-091640-ORIG-1-AMEND-31 (ref# 5729039)

Good morning Edward,
I took a look at ANDA 091640 as per your request. Since one of the facilities received a Withhold and is either pending regulatory action or the action has been taken, it would be appropriate to use Option B for your CR. Option B is appropriate when a facility is found unacceptable as in this case.

From: Edward Taylor [<mailto:edward.taylor@fda.hhs.gov>]
Sent: Monday, December 14, 2015 4:29 PM
To: Dobbin, Ebern
Subject: RE: Comment on Overall Manufacturing Inspection Recommendation on ANDA-091640-ORIG-1-AMEND-31 (ref# 5729039)

 [Overall Manufacturing Inspection Recommendation](#)
[ANDA-091640-ORIG-1-AMEND-31](#)

REF# 5729039



 [Edward Taylor](#), Hi Ebern,

I am having difficulty getting a response from the OPF Facilities questions box on this one. Could you please send a reply email confirming the WH recommendation and the facility name/FEI number to use in option B of our CR. The confirmation is the only thing holding up issuing a cGMP CR. Our leadership requests this confirmation prior to taking action on the application.

Thank you for your help,
Edward (Andrew) Taylor

 You and Edward Taylor
December 14, 2015 at 4:28 PM - [See it in Workfront](#)

[Comment](#)

[Change Notification settings](#)



APPEARS THIS WAY ON ORIGINAL

From: [Dobbin, Ebern](#)
To: [Taylor, Edward](#)
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Subject: RE: Comment on Overall Manufacturing Inspection Recommendation on ANDA-091640-ORIG-1-AMEND-31 (ref# 5729039)

 [Overall Manufacturing Inspection Recommendation](#)
[ANDA-091640-ORIG-1-AMEND-31](#)

REF# 5729039



[Edward Taylor](#), Hi Ebern,

I am having difficulty getting a response from the OPF Facilities questions box on this one. Could you please send a reply email confirming the WH recommendation and the facility name/FEI number to use in option B of our CR. The confirmation is the only thing holding up issuing a cGMP CR. Our leadership requests this confirmation prior to taking action on the application.

Thank you for your help,
Edward (Andrew) Taylor

 You and Edward Taylor
December 14, 2015 at 4:28 PM - [See it in Workfront](#)

[Comment](#)

[Change Notification settings](#)



APPEARS THIS WAY ON ORIGINAL



ANDA 091640

**MEETING REQUEST GRANTED
WRITTEN RESPONSES ONLY**

Zydus Pharmaceuticals (USA), Inc.
73 Route 31 North
Pennington, NJ 08534
Attention: G. Srinivas
Head, Regulatory Affairs

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated December 12, 2009, received December 16, 2009, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Mesalamine Delayed-release Tablets USP, 1.2 g.

We also refer to your June 5, 2015, correspondence requesting a Post Complete Response Teleconference Meeting to discuss deficiencies noted in the Complete Response Letter dated May 28, 2015.

Further reference is made to our Meeting Granted letter dated June 12, 2015, wherein we stated that written responses to your questions would be provided in lieu of a teleconference.

The enclosed document constitutes our written responses to the questions contained in your Post Complete Response Teleconference Meeting Request dated June 5, 2015.

If you have any questions, call Edward Taylor, Regulatory Project Manager at (240) 402-6094.

Sincerely,

Edward Taylor
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure:
Written Responses



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: Post Complete Response Teleconference Meeting
Meeting Category: End of Review

Application Number: 091640
Product Name: Mesalamine Delayed-release Tablets USP, 1.2 g
Applicant Name: Zydus Pharmaceuticals (USA), Inc.

A. BACKGROUND

On June 5, 2015, Zydus Pharmaceuticals (USA), Inc. requested a Post Complete Response Teleconference Meeting to discuss deficiencies noted in the Complete Response Letter dated May 28, 2015, for ANDA 091640, Mesalamine Delayed-release Tablets USP, 1.2 g. The Office of Generic Drugs provides the following responses to Zydus Pharmaceuticals (USA), Inc.'s questions as per the June 12, 2015, Meeting Request Granted – Written Responses Only correspondence.

B. QUESTIONS AND RESPONSES

BIOEQUIVALENCE

Question 1:

Based on past Complete Response Letter dated September 09, 2014, agency had acknowledged the day to day analytical variability expected in pH 6.8 buffer and recommended to perform testing of test and reference product on same day, we would like to understand agency's rational for comparing the dissolution data generated on two different days for F2 calculation (i.e. Data from 1 month and 31 month)?

Question 2:

If agency accepts our scientific rational explained above in background section, we request agency to waive-off the additional data requested in the Complete Response Letter dated May 28, 2015.

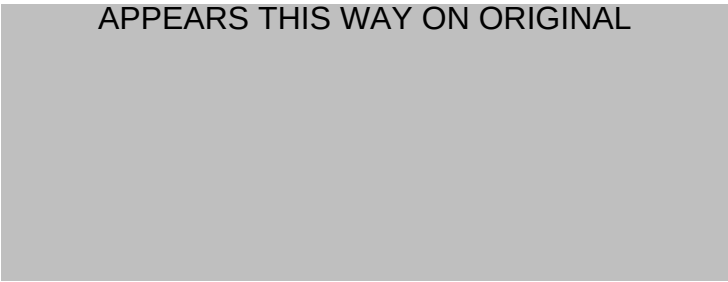
FDA Response to Question 1 and 2:

The Division of Bioequivalence II (DBII) has re-evaluated the data for the in vitro BE dissolution studies, as well as your rationale for the high variability of dissolution data at pH 6.8.

Written Response

The DBII concludes that the in vitro BE dissolution testing at pH 6.8 is now acceptable. Therefore, DB II agrees with your request to waive the additional data requested in the complete response letter dated May 28, 2015.

APPEARS THIS WAY ON ORIGINAL



POST CR MEETING REQUEST WRITTEN RESPONSES - BIOEQUIVALENCE

Meeting Type: Post Complete Response Teleconference Meeting Request
Meeting Category: End of Review
Application Number: ANDA#091640
Product Name: Mesalamine Delayed-release Tablets, 1.2 g
Sponsor/Applicant Name: Zydus Pharmaceuticals (USA) Inc.

1.0 BACKGROUND

On June 05, 2015, Zydus requested a Post Complete Response Teleconference Meeting to discuss deficiencies noted in the Complete Response Letter dated May 29, 2015, for ANDA 091640, Mesalamine Delayed-release Tablets, 1.2 g. The Office of Generic Drugs provides the following responses to Zydus' questions as per the Meeting Request Granted – Written Response correspondence.

2. QUESTIONS AND RESPONSES

2.1. BIOEQUIVALENCE

The Division of Bioequivalence (DB) deficiency (05/29/2015)

Although your test product at 31 month (expired) met the shelf life specification, we noticed that the dissolution data of the fresh test product (1 month) in your submission dated October 23, 2013 is significantly different from that of 31 month old product (submitted in amendment 12/8/2014) under pH 6.8. Using bootstrapping method, the F2 value between the data of your 1 month and 31 month test product at pH 6.8 is only 25.66. Therefore, your dissolution testing data at pH 6.8, (b) (4) in the current amendment (12/8/2014) is not acceptable. Please provide your explanation for the observed faster release of the aged product when compared to the fresh product. The firm should be requested to re-conduct the study at (b) (4) pHs, 6.8, (b) (4) using fresh lots of test and RLD products.

Firm's Questions:

Background:

Cadila healthcare Limited conducted method validation for dissolution method with pH 6.8 phosphate buffer based on the deficiency cited in complete response letter dated March 26, 2014 to address day to day variability. Based on the intermediate precision and trend of dissolution data on robustness experiments it was concluded that day to day variability of both test and reference product at pH 6.8 is due to formulation characteristics resulting from pH dependent polymer (b) (4). It was also supported with the consistent in-vitro dissolution data on higher pH (i.e. pH 7.2- OGD method).

Written Response

In the subsequent complete response letter issued by the agency dated September 09, 2014, based on the submitted data the agency acknowledged the firm's investigations on day to day variability at pH 6.8 and suggested to re-perform in-vitro dissolution comparison on test product and reference product on same day. Based on agency's recommendation we have generated data on the same day for 24 units of test product of age 31 month complying to our shelf-life specification and two different lots of reference product with 12 units each at pH 6.8, (b) (4). Based on this reanalysis F2 was calculated by bootstrapping method as per the guidance.

In (b) (4) pH buffers, satisfactory F2 above 50 was established based on same day analysis. On the basis of firm's investigations and re-analysis data on same day we are concluding that F2 value calculated by agency comparing the dissolution data of 1 month sample and 31 month sample of test product as cited in the recent complete response letter dated May 29, 2015 may not be appropriate since these two dissolution data were generated on two different days. We believe that lower F2 value between 1 month and 31 month analysis is the result of inherent analytical variability due to day to day variability in pH 6.8. It is also evident from the fact that the drug release data in official OGD method (Firm's Quality control method) on aged sample (31 month) did not show any significant change and the data is well within the shelf-life specification.

Question 1

Based on past complete response letter dated September 09, 2014, agency had acknowledged the day to day analytical variability expected in pH 6.8 buffer and recommended to perform testing of test and reference product on same day, we would like to understand agency's rational for comparing the dissolution data generated on two different days for F2 calculation (i.e. Data from 1 month and 31 month)?

Question 2

If agency accepts our scientific rational explained above in background section, we request agency to waive-off the additional data requested in the complete response letter dated May 29, 2015.

FDA Response to Question 1 and 2:

The Division of Bioequivalence II (DBII) has re-evaluated the data for the in vitro BE dissolution studies, as well as your rationale for the high variability of dissolution data at pH 6.8. The DBII concludes that the in vitro BE dissolution testing at pH 6.8 is now acceptable. Therefore, DB II agrees with your request to waive the additional data requested in the complete response letter dated May 29, 2015.



ANDA 091640

**MEETING REQUEST GRANTED
WRITTEN RESPONSES ONLY**

Zydus Pharmaceuticals (USA), Inc.
73 Route 31 North
Pennington, NJ 08534
Attention: G. Srinivas
Head, Regulatory Affairs

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated December 12, 2009, received December 16, 2009, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Mesalamine Delayed-release Tablets USP, 1.2 g.

We also refer to your June 5, 2015, correspondence requesting a Post Complete Response Teleconference Meeting to discuss deficiencies noted in the Complete Response Letter dated May 28, 2015.

We have determined that written responses to your questions would be the most appropriate means for responding to the meeting request. Therefore, a teleconference will not be scheduled. Our goal date for providing our written responses is August 19, 2015.

If you have any questions, call Edward Taylor, Regulatory Project Manager at (240) 402-6094.

Sincerely,

Edward A.
Taylor -S

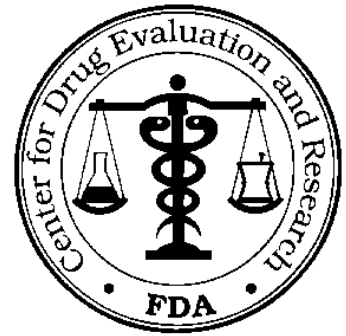
Digitally signed by Edward A.
Taylor -S
DN: cn=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=20014
99339, cn=Edward A. Taylor -S
Date: 2015.06.12 09:00:30 -04'00'

Edward Taylor
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research

EASILY CORRECTABLE DEFICIENCY FAX

ANDA 091640

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855



APPLICANT: Zydus Pharmaceuticals, Inc.

TEL: 609-275-5125

ATTN: G. Srinivas

FAX: 609-275-3711

FROM: Frank J. Nice

FDA CONTACT PHONE: 240-276-8555

:

This facsimile is in reference to your abbreviated new drug application (ANDA) dated December 12, 2009, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Mesalamine Delayed-release Tablets USP, 1200 mg.

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 with an “*EASILY CORRECTABLE DEFICIENCY AMENDMENT*” within ten (10) working days.

If you do not submit a complete response within ten (10) working 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. In addition, please notify the Project Manager listed below.

A partial response to this fax will not be processed as an amendment and will not start a review. Please submit official archival copies of your response to the ANDA. Please notify the above Project Manager when your amendment has been submitted.

If you have questions regarding these deficiencies please contact the Project Manager, at 240-276-8555.

SPECIAL INSTRUCTIONS:

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We have completed our review of this ANDA, as amended October 23, 2013, and have the following comments:

PRODUCT QUALITY

A. The following deficiencies listed below may be delivered via the easily correctable deficiency method (10 day firm response expected) if the situation allows ☒ YES ☐ NO

- 1) Proposed “Any unknown impurity” limit for your Drug substance is much wider than the DMF holder's Drug substance specification. Please consult your DMF vendor, if needed, and proposed a tighter limit for “Any unknown impurity”. Please provide updated Drug substance specification.

Sincerely yours,

{See appended electronic signature page}

Glen J. Smith
Director, Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

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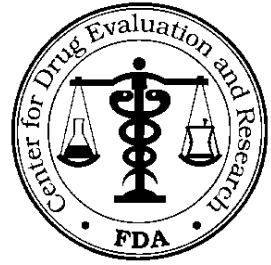
/s/

RADHIKA RAJAGOPALAN
02/04/2014

QUALITY DEFICIENCY - MINOR

ANDA 091640

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855



TO: Zydus Pharmaceuticals USA Inc.

TEL: (609) 730-1900

ATTN: G. Srinivas

FAX: (609) 730-1999

FROM: Frank J. Nice

FDA CONTACT PHONE: (240) 276-8555

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 12, 2009, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Mesalamine Delayed Release Tablets USP, 1200 mg.

Reference is also made to your amendments dated June 20 and July 17, 2012.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ____ 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/>

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/s/

RADHIKA RAJAGOPALAN

08/21/2012

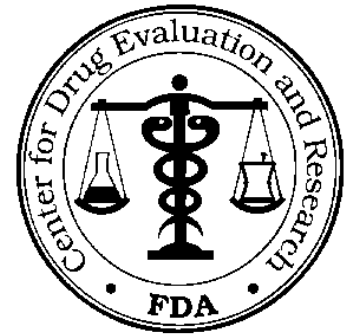
For Glen Smith,

**** Please email me at chan.park@fda.hhs.gov to confirm that you have received this labeling comment.**

Telephone Fax

ANDA 091640

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8951



TO: Zydus Pharmaceuticals (USA), Inc.

TEL: 609-730-1900

ATTN: G. Shrinivas

FAX: 609-730-1999

FROM: Chan Park

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 Mesalamine D-R Tablets.

Pages (including cover): 4

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.

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

ANDA Number: 091640

Applicant's Name: Zydus Pharmaceuticals (USA) Inc.

Submission Date: May 19, 2011, September 29, 2011 and June 27, 2012 (Amendments)

Established Name: Mesalamine Delayed-release Tablets USP, 1.2 g

Labeling Deficiencies:

1. GENERAL COMMENT

We acknowledge that you revised the NDC numbers on the labeling to reflect the revised imprinting of your drug product from (b) (4) to "711". Please submit the CMC information associated with the revised imprint of your drug product and/or comment.

2. CONTAINER – 34s and 120s

(b) (4)

3.

4.

5. INSERT

a. GENERAL

We note that you replaced "LIALDA" with (b) (4) or "mesalamine delayed-release tablets" (b) (4)

(b) (4)

b. HIGHLIGHTS OF PRESCRIBING INFORMATION - DOSAGE AND ADMINISTRATION:

Revise to read "For induction of remission of active, mild to moderate ulcerative colitis, two to four 1.2 g tablets taken once daily with food (1, 2)".

c. FULL PRESCRIPTION INFORMATION - 11 DESCRIPTION:

- i. We note that you revised this section from your original proposal regarding the mechanism on the delayed-release of your drug product. Please justify/explain this revision.
- ii. According to your labeling amendment dated May 11, 2011, it appears that your drug product does not meet the dissolution specification appearing in the USP monograph for your drug product. Please include the following statement at the end of this section until it meets the USP dissolution specification:

Revise the labeling as described above and submit final printed labeling electronically. Please provide the labeling in the Structured Product Labeling (SPL) as well as pdf. format.

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, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug's 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

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/s/

CHAN H PARK
07/16/2012

BIOEQUIVALENCE AMENDMENT

ANDA 091640

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810



APPLICANT: Zydus Pharmaceuticals USA Inc.

TEL: (609) 730-1900

ATTN: G. Srinivas

FAX: (609) 730-1999

FROM: Chitra Mahadevan

FDA CONTACT PHONE: (240) 276-8817

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on December 12, 2009, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Mesalamine Delayed Release Tablets USP, 1200 mg.

Reference is also made to your amendment dated April 13, 2010, September 8, 2010 and February 12, 2011.

The Division of Bioequivalence II has completed its review of the submissions referenced above and has identified deficiencies which are presented on the attached ____ page. 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.** Your cover letter should clearly indicate:

Bioequivalence Response to Information Request

If applicable, please 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 an archival (blue) jacket and unless submitted electronically through the gateway, 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 II, 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:

Effective 01-Aug-2010, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents is:

**Office of Generic Drugs
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855-2810**

ANDAs 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/>

Please submit your response in electronic format. This will improve document availability to review staff.

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BIOEQUIVALENCE COMMENTS

ANDA: 091640

APPLICANT: Zydus Pharmaceuticals USA Inc.

DRUG PRODUCT: Mesalamine Delayed-release Tablets, 1200 mg

The Division of Bioequivalence II (DB II) has completed its review and has no further questions at this time.

1. As per Agency's 8/10/10 response to Citizen Petitions FDA-2010-P-0111 and FDA-2008-P-0507 (the August 2010 CP Response), the bioequivalence (BE) study with clinical endpoints is no longer considered to be sufficiently sensitive to establish BE of this product. According to the Agency's current recommendation that applicants for a generic version of Lialda[®] should demonstrate bioequivalence using data from comparative pharmacokinetic (PK) studies and in vitro dissolution studies, please conduct PK studies comparing your test product (unexpired) to the reference product, Lialda[®] (mesalamine) DR Tablets, 1200 mg under both fasting and fed conditions.

You may consider the following additional recommendations for the in vivo BE studies with PK endpoints:

- a. You may consider using a reference-scaled average bioequivalence approach for mesalamine. For general information on this approach, please refer to the Progesterone Capsule Guidance: (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf>). Other study designs (including a four period fully replicate crossover design) are acceptable if appropriate.
 - b. For both fasting and fed studies, the following PK parameters are recommended to be evaluated: log-transformed AUC_{8-48} , AUC_{0-t} , and C_{max} . Additional exploratory parameters may be included as secondary endpoints.
2. Please conduct comparative dissolution testing on at least 24 units of the test product and two lots of the reference product (12 units per each reference lot). The dissolution testing should be conducted on the test and reference lots used in the PK studies using the following method:

Apparatus: USP Apparatus 2 (paddle)
Pretreatment Stage 1: 2 hours in 0.1 N HCl at 100 rpm
(750 mL)
Pretreatment Stage 2: 1 hours in pH 6.4 Phosphate buffer
at 100 rpm (950 mL)
Evaluation Stage: Each of
pH 6.5 Phosphate buffer at 100 rpm
pH 6.8 Phosphate buffer at 100 rpm
pH 7.2 Phosphate buffer at 100 rpm
pH 7.5 Phosphate buffer at 100 rpm
Volume: 960 mL
Temperature: 37°C
Sample times: 1, 2, 4, 6 and 8 hours or as needed
for profile comparison

The DBI I will perform an f2 test on your submitted dissolution data. If the variability of the dissolution data is high, such that mean data cannot be used for the f2 test, as per the CDER Guidance for Industry: *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*, we will calculate the f2 metric based on an f2 confidence interval using a 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 the f2 calculation. The 90% confidence intervals of the f2 values are calculated using the percentile approach as described in the Shah et al. reference. A similar procedure can be followed for comparing reference vs. reference product dissolution profiles.

Only one measurement after 85% dissolution of both the products should be included in the f2 calculation.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

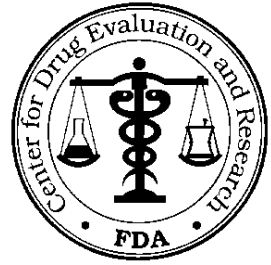
CHITRA MAHADEVAN
03/09/2012

BARBARA M DAVIT
03/13/2012

QUALITY DEFICIENCY - MINOR

ANDA 091640

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855



APPLICANT: Zydus Pharmaceuticals USA Inc.

TEL: (609) 730-1900

ATTN: G Srinivas

FAX: (609) 730-1999

FROM: Frank J. Nice

FDA CONTACT PHONE: (240) 276-8555

Dear Sir or Madam:

This facsimile is in reference to your abbreviated new drug application dated December 12, 2009, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Mesalamine Delayed Release Tablets USP, 1200 mg.

Reference is also made to your amendments dated February 11 and February 12, 2011.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ____ 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***

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/s/

RADHIKA RAJAGOPALAN

06/01/2011

For Glen Smith,

Labeling Comments

ANDA 091640

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2773
240-276-8995



TO: Zydus Pharmaceuticals (USA) Inc.

TEL: 609-730-1900

ATTN: G. Srinivas

FAX: 609-730-1999

FROM: Sarah Park

Dear Sir or 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 for Mesalamine Delayed-release Tablets USP, 1.2 g.

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

1. Labeling comments are attached.

2. Please note the following:

Effective 01-Aug-2010, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents has become:

**Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20855**

ANDAs 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/>

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

ANDA Number: 091640

Date of Submission: December 12, 2009 (Original)

Applicant's Name: Zydus Pharmaceuticals (USA) Inc.

Established Name: Mesalamine Delayed-release Tablets USP, 1.2 g

Labeling Deficiencies:

1. GENERAL COMMENT

This drug product is subject of a USP monograph. Please revise your labels and labeling accordingly.

2. INSERT

Please revise your insert labeling to be in accordance with the labeling for Lialda Delayed-Release Tablets, 1.2 g, NDA 022000/S-003, approved September 22, 2010.

Revise your labels and labeling, as instructed above, and submit final printed 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, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug's 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

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/s/

SOOJUNG S PARK
05/02/2011
For Wm Peter Rickman

BIOEQUIVALENCY INFORMATION REQUEST

ANDA 091640

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)



APPLICANT: Zydus Pharmaceuticals USA Inc.
ATTN: G. Srinivas
Senior Director - Regulatory Affairs

TEL: (609) 730-1900

FAX: (609) 730-1999

FROM: Nitin K. Patel

PROJECT MANAGER: (240) 276-8887
(240) 276-8966 (fax)

Dear Sir:

This facsimile is a request for information from the Clinical Review Team, regarding your ANDA 091640 for Mesalamine Delayed Release Tablets, 1200 mg, dated December 12, 2009.

The information request is presented on the attached 3 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

Your cover letter should clearly indicate that the response is a "Clinical Bioequivalency Amendment". 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/>*

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MEMORANDUM

To: ANDA 091640

Drug: Mesalamine Delayed Release Tablets, 1200 mg

Sponsor: Zydus Pharmaceuticals USA Inc.
G. Srinivas, Senior Director - Regulatory Affairs
Fax: (609) 730-1999
PH: (609) 730-1900

From: Carol Y. Kim, Pharm.D.
Clinical Reviewer
Office of Generic Drugs

Dena R. Hixon, MD
Associate Director for Medical Affairs
Office of Generic Drugs

Date: April 15, 2011

Re: Request for Information

The data for study #073-08 submitted on March 22, 2011 in response to OGD's letter faxed on January 31, 2011, are not sufficient for the review. The following information is needed in order to complete the review of this study:

1. You stated that the summary dataset was provided in a single PDF file instead of a SAS .xpt file because we requested too many variables. For our statistical analysis, we need the primary data in SAS .xpt file. Please provide the primary summary dataset, including those variables you previously provided in "summary data (pdf)", in two separate SAS .xpt files as shown below:

First SAS .xpt file variables

For each subject, provide the following:

1. center/site, pt number (e.g., subject ID)
2. drug treatment (e.g., A, B, C)
3. race
4. sex
5. age
6. reason for discontinuation ("not applicable" is unclear. Please specify in detail.)
7. safety population (yes/no)
8. ITT population (yes/no)
9. PP population (yes/no)
10. reason for exclusion from the safety population
11. reason for exclusion from the ITT population
12. reason for exclusion from the PP population

13. designation of remission (yes/no); remission is defined as modified UC-DAI score of ≤ 1 with a score of 0 for rectal bleeding and stool frequency and at least a 1 point reduction from baseline in sigmoidoscopy score at week 8.
14. designation of improvement (yes/no); improvement is defined as a decrease of ≥ 3 points from baseline in the total modified UC-DAI score at week 8.
15. designation of failure (yes/no)
16. visit 5 (week 8) within +/-4 days visit window (yes/no)
17. treatment compliance rate (the proportion of prescribed doses that the patient actually took)
18. baseline total UC DAI score
19. baseline PGA score
20. baseline mucosal appearance score
21. baseline rectal bleeding score
22. baseline stool/bowel frequency score
23. total UC DAI score at week 8
24. PGA score at week 8
25. mucosal appearance score at week 8
26. rectal bleeding score at week 8
27. stool frequency score at week 8

Second SAS .xpt file variables

For each subject, provide the following:

1. center/site, pt number (e.g., subject ID)
2. drug treatment (e.g., A, B, C)
3. safety population (yes/no)
4. ITT population (yes/no)
5. PP population (yes/no)
6. stool frequency while in remission, or “normal stool frequency before Ulcerative Colitis diagnosis or relapse”, specified as the normal number of stools per day
7. amount of rectal bleeding 3 days prior to treatment (day -3)
8. amount of rectal bleeding 2 days prior to treatment (day -2)
9. amount of rectal bleeding 1 day prior to treatment (day -1)
10. amount of rectal bleeding during the fifth day of week 8 (day 53)
11. amount of rectal bleeding during the sixth day of week 8 (day 54)
12. amount of rectal bleeding during the last day of week 8 (day 55)
13. total number of stools (bowel movements) 3 days prior to treatment (day -3)
14. total number of stools (bowel movements) 2 days prior to treatment (day -2)
15. total number of stools (bowel movements) 1 day prior to treatment (day -1)
16. total number of stools (bowel movements) during the fifth day of week 8 (day 53)
17. total number of stools (bowel movements) during the sixth day of week 8 (day 54)
18. total number of stools (bowel movements) during the last day of week 8 (day 55)
19. stool frequency score 3 days prior to treatment (day -3)
20. stool frequency score 2 days prior to treatment (day -2)
21. stool frequency score 1 day prior to treatment (day -1)
22. stool frequency score during the fifth day of week 8 (day 53)
23. stool frequency score during the sixth day of week 8 (day 54)

24. stool frequency score during the last day of week 8 (day 55)

Provide a detailed explanation for each variable or code used in the primary summary dataset (e.g., define.pdf).

3. You stated that the number of stools per day while in remission was not included in the response because it was not part of the CRF, clinical database, and not defined in the study protocol. How was stool frequency score determined if you did not collect the number of stools per day while in remission (normal/day) for each patient? According to CRF for patient (b) (6) "normal stool frequency before Ulcerative Colitis diagnosis or relapse" is assessed on visit 1 screening (week -2). Please provide this information in the SAS .xpt file as requested above. In addition, please explain how the average stool frequency score was determined. For example, for this patient, a stool frequency score at week -1 was observed as 0, 1, and 1 (mean=0.67). For average stool frequency score, it was reported in CRF as "1". Please provide a detailed explanation and criteria for calculating average stool frequency score and rectal bleeding score when the average or mean was not a whole number.

4. You also stated that the treatment compliance, number of missed doses, was not included in the response because it was not part of the CRF, clinical database, and not defined in the study protocol. How was treatment compliance assessed to verify that patient took the study drugs as scheduled?

5. Some of variables or codes used in your dataset were not fully defined. For datasets "summary-dataset-clinre07308", "itt-clinre07308.xpt", and "pp-clinre07308.xpt", each variable was not defined. For example, it is unclear what "STL_DT", "Elig" or "Diff" means. For each dataset, provide a complete description of each code or variable.

6. Please specify the patient population (e.g., safety, ITT population, or PP population) for the frequency tables you have previously provided for distribution of patients for each DAI index assessment category (e.g., PGA, mucosal appearance, rectal bleeding, and stool/bowel frequency) including severity at baseline and at week 8. A separate frequency table should be provided for each safety, ITT and PP population for each treatment group.

7. (b) (4)

8. Your inclusion criterion specified enrollment of patients who are newly diagnosed or relapsing (relapsed $\leq$ 6 weeks prior to randomization) mild-to-moderate active UC. However, we noted that majority of patients were on 5-ASA related drug products for treatment of UC during the screening period until the baseline visit. Please provide complete explanation and justification.

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/s/

NITIN K PATEL
04/15/2011

DENA R HIXON
04/15/2011

BIOEQUIVALENCY INFORMATION REQUEST

ANDA 091640

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)



APPLICANT: Zydus Pharmaceuticals USA Inc.
ATTN: G. Srinivas
Senior Director - Regulatory Affairs

TEL: (609) 730-1900

FAX: (609) 730-1999

FROM: Nitin K. Patel

PROJECT MANAGER: (240) 276-8887
(240) 276-8966 (fax)

Dear Sir:

This facsimile is a request for information from the Clinical Review Team, regarding your ANDA 091640 for Mesalamine Delayed Release Tablets, 1200 mg, dated December 12, 2009.

The information request is presented on the attached 3 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

Your cover letter should clearly indicate that the response is a "Clinical Bioequivalency Amendment". 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/>*

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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.

MEMORANDUM

To: ANDA 091640

Drug: Mesalamine Delayed Release Tablets, 1200 mg

Sponsor: Zydus Pharmaceuticals USA Inc.
G. Srinivas, Senior Director - Regulatory Affairs
Fax: (609) 730-1999
PH: (609) 730-1900

From: Carol Y. Kim, Pharm.D.
Clinical Reviewer
Office of Generic Drugs

Dena R. Hixon, MD
Associate Director for Medical Affairs
Office of Generic Drugs

Date: January 24, 2011

Re: Request for Information

The following additional information is being requested by the Clinical Review Team:

1. For each clinical study site, provide the following information:
 - Number of patients enrolled.
 - Number of patients included in the Per Protocol Population.
2. A frequency table comparing number of patients designated as in remission (UC-DAI score of 0 or 1, where the rectal bleeding and stool frequency components must be zero and having a reduction in sigmoidoscopy score of 1 point or more from baseline), improved (includes remission), or failure at week 8 for each treatment group in the ITT and PP populations.
3. A frequency table comparing total DAI score at baseline and at Week 8 for each treatment group in the ITT and PP populations.
4. A frequency table showing distribution of patients for each DAI index assessment category (e.g., PGA, mucosal appearance, rectal bleeding, and stool/bowel frequency score) including severity at baseline and at week 8. Please include assessment from the last day prior to treatment visit for baseline score and the last visit day of week 8 for Week 8 score. An example for PGA is shown below.

PGA at baseline	Test N=X	Reference N=X	PGA at Week 8	Test N=X	Reference N=X
0			0		
1			1		
2			2		
3			3		

5. Study data should be submitted in electronic format.
 - a. A list of file names included in the CD or diskette(s), with a simple description of the content of each file, should be included. Such a list should include an explanation of the variables included in each of the data sets.
 - b. A “pdf” document with a detailed description of the codes that are used for each variable in each of the SAS datasets (for example, Y=yes, N=no for analysis population).
 - c. SAS transport files, covering all variables collected in the Case Report Forms (CRFs) per patient, should include .xpt as the file extension and should not be compressed. A simple SAS program to open the data transport files and SAS files should be included.
 - d. Primary data sets should consist of two data sets: No Last Observation Carried Forward (NO-LOCF-pure data set) and Last Observation Carried Forward (LOCF-modified data set).
 - e. A separate dataset for variables such as demographics, UC-DAI scores, rectal bleeding, stool frequency, mucosal appearance, PGA, vital signs, adverse events, disposition (including reason for discontinuation of treatment), concomitant medications, medical history, compliance and comments, etc.
 - f. The methods used to derive the variables should be included and explained.
 - g. A summary dataset (SAS .xpt file) should contain a separate line listing of all primary efficacy variables for each patient (if data exist).
6. A summary dataset in a single file including the following line listings for each patient:
 - center/site, patient number
 - drug/treatment
 - race, sex , age
 - reason for discontinuation
 - baseline total UC-DAI score
 - total UC-DAI score at Week 8
 - baseline PGA score
 - PGA score at Week 8
 - baseline mucosal appearance score
 - mucosal appearance score at Week 8
 - baseline rectal bleeding score
 - rectal bleeding score at Week 8
 - baseline bowel/stool frequency score
 - stool/bowel frequency score at Week 8
 - number of stools per day while in remission

- presence/quantity of rectal bleeding during last three days of screening visit prior to receiving treatment (e.g., day -3, -2, and -1)
- presence/quantity of rectal bleeding during the last three days of Week 8 (e.g., day 53, 54, and 55)
- total number of actual bowel/stool passage during last three days of screening visit prior to receiving treatment (e.g., day -3, -2, and -1)
- total number of actual bowel/stool passage during last three days of Week 8 (e.g., day 53, 54, and 55)
- bowel frequency score during last three days of screening visit prior to receiving treatment (e.g., day-3, -2, and -1)
- bowel frequency score during the last three days of Week 8 (e.g., day 53, 54, and 55)
- extent of UC involvement (cm)
- designation of success (responder)/failure*
- designation of improved (includes remission)
- designation of remission only
- clinical relapse (yes/no)
- safety population (yes/no), reason for exclusion
- ITT population** (yes/no), reason for exclusion
- PP population** (yes/no), reason for exclusion
- treatment compliance, number of missed doses

*Success/failure (responder/non-responder) should be designated based on available data at week 8. Only patients who are considered treatment failures due to lack of treatment response or relapse should be designated as treatment failures.

**Patients who did not meet inclusion/exclusion criteria should be excluded from both ITT and PP populations.

Primary data sets should consist of two data sets: No Last Observation Carried Forward (No-LOCF-pure data set) and Last Observation Carried Forward (LOCF– modified data set).

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/s/

NITIN K PATEL
01/24/2011

CAROL Y KIM
01/24/2011

DENA R HIXON
01/28/2011

From: [Shimer, Martin](#)
To: ["G Srinivas";](#)
Subject: RE: Mesalamine Dr Tablets 1.2g ANDA # 91640 - Zydus Pharmaceuticals USA Inc.
Date: Thursday, May 27, 2010 1:07:48 PM

Mr. Srinivas,

(b) (4) the US Postal service for the purpose of providing notice to the NDA holder and any patent assignees associated with PIV certifications contained within ANDA 91640.

Regards,

Martin Shimer

From: G Srinivas [mailto:gsrinivas@zydususa.com]
Sent: Thursday, May 27, 2010 11:37 AM
To: Shimer, Martin
Subject: Mesalamine Dr Tablets 1.2g ANDA # 91640 - Zydus Pharmaceuticals USA Inc.

Good Morning Dr. Martin

First of all thank you for the acceptance letter on the subject ANDA.

With reference to subject ANDA we would like to request your permission to send a Paragraph IV notice letter to the NDA holder and/or patent assignee, who are located in Ireland and other domestic recipients, (b) (4)

As always greatly appreciate your advice on this matter.

Best Regards

G. Srinivas

Drug Regulatory Affaris
Zydus Pharmaceuticals USA Inc.
Tel: 609-275-5125 Ext: 103



Preserve the Nature. Please don't print this e-mail unless you really need to print it.

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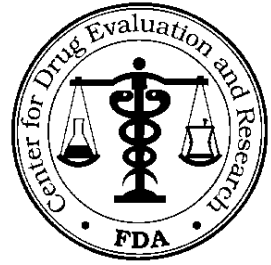
/s/

MARTIN H Shimer
01/18/2011

QUALITY DEFICIENCY - MINOR

ANDA 091640

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855



APPLICANT: Zydus Pharmaceuticals USA Inc.

TEL: (609) 730-1900

ATTN: G Srinivas

FAX: (609) 730-1999

FROM: Frank J. Nice

FDA CONTACT PHONE: (240) 276-8555

Dear Sir or Madam:

This facsimile is in reference to your abbreviated new drug application dated December 12, 2009, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Mesalamine Delayed Release Tablets, 1200 mg.

Reference is also made to your amendments dated February 11 and May 20, 2010.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 5 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/>

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Reference ID: 2872076

4 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

RADHIKA RAJAGOPALAN

12/03/2010

For Florence Fang,

BIOEQUIVALENCE AMENDMENT

ANDA 091640

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: Zydus Pharmaceuticals USA Inc.

TEL: (609) 275-5125

ATTN: G Srinivas

FAX: (609) 275-3711

FROM: Chitra Mahadevan

FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on December 12, 2009, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Mesalamine Delayed Release Tablets, 1.2 g.

The Division of Bioequivalence has completed its review of the submission referenced above and has identified deficiencies which are presented on the attached 1 page. 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.** Your cover letter should clearly indicate:

Bioequivalence Dissolution Acknowledgement

If applicable, please 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 an archival (blue) jacket and unless submitted electronically through the gateway, 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:

Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:

**Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20857**

After the effective date, **01-Aug-2010**, ANDAs will only be accepted at the new mailing address listed above. **DO NOT** submit your **ANDA Regulatory documents to this address prior to 01-Aug-2010**. 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/>

Please submit your response in electronic format. This will improve document availability to review staff.

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BIOEQUIVALENCE DEFICIENCIES

ANDA: 091640

APPLICANT: Zydus Pharmaceuticals USA Inc.

DRUG PRODUCT: Mesalamine Delayed-release Tablets, 1.2 g

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The DBE will review the clinical endpoints study at a later date. The following deficiency has been identified:

Your dissolution testing data are acceptable. However, your proposed specifications are not acceptable. Based on submitted data, please acknowledge your acceptance of the following FDA-recommended dissolution method and specifications:

The dissolution testing should be conducted in 750 mL of 100 mM HCl (Acid Stage A), 950 mL of Phosphate buffer, pH 6.4 (Buffer Stage B: A + 200 mL 200 mM Na₃PO₄) and 960 mL of Phosphate buffer, pH 7.2 (Buffer Stage C: B + 9 mL 2M NaOH adjusting pH with 2M NaOH or 2M HCl) using apparatus 2 (Paddle) at 100 rpm.

Specifications: Acid stage A:	NMT (b) (4) % in 2 hours
Buffer stage B:	NMT (b) (4) % in 1 hour
Buffer stage C:	1 hour: NMT (b) (4) %
	2 hours: (b) (4) %
	6 hours: NLT (b) (4) %

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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ANDA-91640	ORIG-1	ZYDUS PHARMACEUTICA LS USA INC	MESALAMINE

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/s/

BARBARA M DAVIT
08/03/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 10, 2010

TO: Shannon Hill, OGD/DLPS/RSB

FROM: Sushanta K. Chakder, Ph.D.
Supervisory Pharmacologist
Division of Gastroenterology Products, HFD-180

Through: Donna Griebel, M.D.
Director
Division of Gastroenterology Products (HFD-180)

SUBJECT: Consult Request from the OGD for assessment of safety of the proposed level of Methacrylic Acid Copolymer (b) (4) levels in Mesalamine Delayed Release Tablets (Zydus Pharma USA Inc.) (Consult No. 2010-0427).

Attached, please find the review of the consult request (#2010-0427) for safety assessment of the proposed level of Methacrylic Acid Copolymer (b) (4) levels in Mesalamine Delayed Release Tablets.

Sushanta K. Chakder, Ph.D.
Pharmacologist, DGP

Date

CC:
DGP
DGP/RPM/BStrongin
OGD/TLiu
DGP/DGriebel
DGP/SChakder

Pharmacologist's Consult Review on the Safety Assessment of the Proposed Methacrylic Acid Copolymer (b) (4) Levels in Mesalamine Delayed Release Tablets.
(ANDA 091640 Dated 05/26/2010; Consult No: 2010-0427)

Background: Zydus Pharmaceuticals USA Inc. submitted an ANDA application for Mesalamine Delayed Release Tablets (1.2 g). Each Mesalamine Delayed Release Tablet contains (b) (4) of methacrylic acid co-polymer (b) (4). The proposed amount of (b) (4) than the amount listed in the existing approved Drug Products Database (IGG). The Office of Generic Drugs has sent a consult to the DGP for nonclinical safety assessment of the proposed level of Methacrylic Acid Copolymer (b) (4) levels in mesalamine delayed release tablets.

AVAILABLE NONCLINICAL DATA:

The sponsor submitted a summary of available nonclinical data on (b) (4) and (b) (4). The two polymers differ in their content of free carboxyl groups. The ratio of free carboxyl groups to ester groups is approximately 1:1 for (b) (4) and approximately 1:2 for (b) (4).

Absorption and Excretion of Radiolabeled (b) (4)

There is very limited absorption of (b) (4) following oral administration. In rats, following oral administration of ¹⁴C-labelled (b) (4) (dry substance corresponding to 11.6 µCi/animal), the blood level of the radioactivity was in the 'range of detection limit' (detection limit, about 0.004% of the applied radioactivity).

General Toxicology:

Acute Toxicity:

Rat: Following oral administration of a single dose of (b) (4) to male and female rats at doses up to 15,900 mg/kg dry polymer substance, no mortalities were observed. No abnormal clinical signs were observed during a four-week observation period. Necropsy examinations after the four-week observation period did not reveal any abnormalities. Thus, the LD₅₀ was >15,900 mg/kg in rats.

Dog: There were no mortalities in dogs following oral administration of (b) (4) at oral doses up to 10 g/kg (10,000 mg/kg).

Repeat-Dose Toxicity:

Six-Month Oral Toxicity Study in Rats:

In a 6-month oral toxicity study in rats, groups of male and female animals (15 males and 15 females in each group) were administered (b) (4) at dose levels of 0, 10, 30, 100, 200, 600 and 1500 mg/kg/day by oral gavage. Identically dosed control and the high dose group animals underwent a 4-week treatment-free recovery period. No treatment-related mortalities were observed in any group. 'A tendency towards the activation of the thyroid epithelium' was observed at 200 mg/kg and higher doses, and was decreased to 'borderline' in the high dose group after the 4-week recovery period. At the 1500 mg/kg dose, a fatty degeneration of peripheral liver cells was observed, but was not present after the recovery period. Macroscopic and histopathological examinations did not show any other abnormalities in any group. The NOAEL was identified as the 100 mg/kg/day.

Six-Week Oral Toxicity Study in Rabbits:

In a 6-week oral toxicity study in rabbits (6 males and 6 females/group), (b) (4) was administered by oral gavage at 0, 100, 600 and 1500 mg/kg/day doses. There were no mortalities at any doses. There were no treatment-related effects on clinical signs, body weights, food consumption, hematology, or organ weights. Histopathology examinations showed dose-related activation of the thyroid epithelium in the mid- and high- dose groups. The NOAEL in rabbits was 100 mg/kg/day.

In a six-week oral toxicity study in mice, thyroid gland was also the target organ of toxicity and the NOAEL was 100 mg/kg/day.

Genetic Toxicology: (b) (4) and (b) (4) did not show any mutagenic properties in the bacterial reverse mutation (Ames test) assay.

Teratogenicity: (b) (4) and (b) (4) did not show any teratogenic potential in rats at an oral dose of 500 mg/kg/day.

SUMMARY AND EVALUATION:

The Office of Generic Drugs (OGD) has sent a consult to the DGP for nonclinical safety assessment of the proposed of Methacrylic Acid Copolymer (b) (4) levels in Mesalamine Delayed Release Tablets (1.2 g). Each Mesalamine Delayed Release Tablet contains (b) (4) of methacrylic acid co-polymer (b) (4). The proposed amount of (b) (4) than the amount in the existing approved Drug Products Database (IGG). Anticipated maximum daily intake of (b) (4) from Mesalamine Delayed Release Tablets is (b) (4).

The sponsor submitted a summary of available toxicology data on (b) (4) and (b) (4) to assess the safety of the proposed (b) (4) levels in the mesalamine tablet formulation. The two polymers differ in their content of free carboxyl groups.

There is very limited absorption of (b) (4) following oral administration to rats. In acute toxicity studies in rats and dogs, no mortalities were observed at oral (b) (4) doses up to 15,900 and 10,000 mg/kg, respectively. In a 6-month oral toxicity study of (b) (4) in rats, thyroid was the target organ of toxicity, and the NOAEL was identified as the 100 mg/kg/day. The NOAEL of 100 mg/kg provides about 43 times safety margin for the anticipated daily intake of 2.3 mg/kg from the maximum daily recommended dose of mesalamine (4.8 g/day). The 100 mg/kg/day dose was also identified as the NOAEL for (b) (4) in a 6-week oral toxicity study in rabbits, and a 6-week oral toxicity study in mice.

(b) (4) showed no genotoxic potential in the Ames test, and was not teratogenic in rats.

Although, not listed in the existing approved Drug Products Database, (b) (4); anticipated maximum daily intake, 211.4 mg) (b) (4) than the proposed amount in Mesalamine Delayed Release Tablets (b) (4)

Thus, from a nonclinical standpoint, there are no safety concerns for the sponsor's proposed amount of (b) (4) in Mesalamine Delayed Release Tablets, and the proposed amount of (b) (4) per tablet (b) (4) is acceptable.

Sushanta K. Chakder, Ph.D.
Supervisory Pharmacologist, DGP

Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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ANDA-91640	ORIG-1	ZYDUS PHARMACEUTICA LS USA INC	MESALAMINE

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/s/

SUSHANTA K CHAKDER
07/22/2010

DONNA J GRIEBEL
07/22/2010



ANDA 091640

Zydus Pharmaceuticals USA Inc.
Attention: G. Srinivas
210 Carnegie Center, 1st Floor, Suite 103
Princeton, NJ 08540

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.

Reference is also made to the telephone conversation dated February 4, 2010 and email correspondence May 19, 2010 and your correspondence dated February 11, 2010 and May 20, 2010.

NAME OF DRUG: Mesalamine Delayed-release Tablets, 1.2 g

DATE OF APPLICATION: December 12, 2009

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 16, 2009

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:

Theresa Liu
Project Manager
240-276-8555

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
-----	-----	-----	-----
ANDA-91640	ORIG-1	ZYDUS PHARMACEUTICA LS USA INC	MESALAMINE

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

/s/

MARTIN H Shimer
05/27/2010
Signing for Wm Peter Rickman

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 #: 91-640

FIRM NAME: ZYDUS PHARMACEUTICALS USA INC.

PIV: YES

Electronic or Paper Submission: ECTD FORMAT (ELECTRONIC DATA)

RELATED APPLICATION(S): NA

First Generic Product Received? YES

DRUG NAME: MESALAMINE

DOSAGE FORM: DELAYED RELEASE TABLETS, 1.2 G

Review Team: (Bolded/Italicized & Checked indicate Assignment or DARRTS designation)

Quality Team: DC2 Team 7 ☒ Activity	Bio Team 7: Jiang Xiaojian ☒ Activity
ANDA/Quality RPM: Theresa Liu ☒ FYI	Bio PM: Chitra Mahadevan ☐ FYI
Quality Team Leader: Acting Radhika Rajagopalan No assignment needed in DARRTS	Clinical Endpoint Team Assignment: (No) ☐ Activity
Labeling Reviewer: Sarah Soojung Park ☒ Activity	Micro Review (No) ☐ Activity

***Document Room Note: for New Strength amendments and supplements, if specific reviewer(s) have already been assigned for the original, please assign to those reviewer(s) instead of the default random team(s). ***

Letter Date: DECEMBER 12, 2009	Received Date: DECEMBER 16, 2009
Comments: EC- 1 YES On Cards: YES Therapeutic Code: 8015651 ULCERATIVE COLITIS	
Archival copy: ECTD FORMAT ELECTRICION COLITIS Sections I Review copy: 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 Shannon Hill Date May 20, 2010	Recommendation: ☒ FILE ☐ REFUSE to RECEIVE
Supervisory Concurrence/Date: _____ Date: _____	

1. Edit Application Property Type in DARRTS where applicable for
 - a. First Generic Received
☒ Yes ☐ No
 - b. Market Availability
☒ Rx ☐ OTC
 - c. Pepfar
☐ Yes ☒ No
 - d. Product Type
☐ Small Molecule Drug (usually for most ANDAs except protein drug products)
 - e. USP Drug Product (at time of filing review)
☐ Yes ☒ No
2. Edit Submission Patent Records
☒ Yes
3. Edit Contacts Database with Bioequivalence Recordation where applicable
☒ Yes
4. Requested EER
☒ Yes

ADDITIONAL COMMENTS REGARDING THE ANDA:

1. Ask firm to resubmit FDA form 3674 selecting the correct option; **received 2/11/10**
2. Ask firm to resubmit Type II DMF giving authorization for FDA to review; **received email 2/16/10**
3. Ask firm to submit Summary Tables 4,2,3,7, & 8 in section 2.7; **received 2/11/10**
4. Ask firm to resubmit a clearer copy of the supplier COA for sodium starch, hypromellose, & isopropyl alcohol; **received 2/11/10**
5. Ask firm to submit Tables 9-16 in Module 5; **received 2/11/10**
6. Level for excipient, (b) (4) PharmTox Summary provided in 3.2.P.1; will send out consult;
7. Spoke with G. Srinivas on 2/4/10 @ 9:25 am.
8. Waiting for Bio results; DOES NOT MEET bio requirements; **received 3/1/10**
9. Waiting for Clinical Endpoint Review; MEETS clinical requirements; **received 5/11/2010**
10. Summary of Clinical Safety and Efficacy in 2.7
11. Emailed G. Srinivas for complete PharmTox Results on 5/19/2010; **received 5/20/2010**
12. No Individual Product Bio Recommendations found for this product; no bio controlled documents found; Therefore Acknowledging this ANDA based on Clinical Review results dated 2/4/2010; Pending Citizens Petition (FDA-2008-P-05007-0001)

**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: DECEMBER 12, 2009	☒
1.2.1	Form FDA 3674 (PDF) YES	☒
*	Table of Contents (paper submission only) N/A	☒
1.3.2	Field Copy Certification (original signature) N/A (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 SEE SECTION 1.3.4 Disclosure Statement (Form FDA 3455, submit copy to Regulatory Branch Chief) N/A	☒																								
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) 6773720 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☐ PII ☐ PIII ☐ PIV ☒ (Statement of Notification) ☒ 3. Expiration of Patent(s): 6-08-2020 a. Pediatric exclusivity submitted? b. Expiration of Pediatric Exclusivity? 4. Exclusivity Statement: YES; WILL NOT MARKET UNTIL EXPIRATION Patent and Exclusivity Search Results from query on Appl No 022000 Product 001 in the OB_Rx list. <table border="1" data-bbox="354 829 1224 951"> <thead> <tr> <th>Appl No</th><th>Prod No</th><th>Patent No</th><th>Patent Expiration</th><th>Drug Substance Claim</th><th>Drug Product Claim</th><th>Patent Use Code</th><th>Delist Requested</th></tr> </thead> <tbody> <tr> <td>N022000</td><td>001</td><td>6773720</td><td>Jun 8, 2020</td><td></td><td>Y</td><td></td><td></td></tr> </tbody> </table> <table border="1" data-bbox="354 976 907 1087"> <thead> <tr> <th>Appl No</th><th>Prod No</th><th>Exclusivity Code</th><th>Exclusivity Expiration</th></tr> </thead> <tbody> <tr> <td>N022000</td><td>001</td><td>NP</td><td>Jan 16, 2010</td></tr> </tbody> </table> NP NEW PRODUCT	Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested	N022000	001	6773720	Jun 8, 2020		Y			Appl No	Prod No	Exclusivity Code	Exclusivity Expiration	N022000	001	NP	Jan 16, 2010	☒
Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested																			
N022000	001	6773720	Jun 8, 2020		Y																					
Appl No	Prod No	Exclusivity Code	Exclusivity Expiration																							
N022000	001	NP	Jan 16, 2010																							

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 YES; (b) (4) Type II DMF No. N/A b. Type III DMF authorization letter(s) for container closure YES; (b) (4) (b) (4) 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) N/A (b) (4)	☒
1.12.11	Basis for Submission NDA# : 22-000 Ref Listed Drug: LIALDA Firm: SHIRE US INC. USA 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 SAME 3. Inactive ingredients JUSTIFIED 4. Route of administration SAME 5. Dosage Form SAME 6. Strength SAME	☒

1.12.14	Environmental Impact Analysis Statement YES SEE SECTION 1.12.14	☒
1.12.15	Request for Waiver Request for Waiver of In-Vivo BA/BE Study(ies): N/A SEE SECTION 1.12.15	☒
1.14.1	Draft Labeling (Mult Copies N/A for E-Submissions) 1.14.1.1 4 copies of draft (each strength and container) YES 1.14.1.2 1 side by side labeling comparison of containers and carton with all differences annotated and explained YES 1.14.1.3 1 package insert (content of labeling) submitted electronically YES ***Was a proprietary name request submitted? N/A (If yes, send email to Labeling Reviewer indicating such.) HOW SUPPLIED Mesalamine Delayed-release Tablets, 1.2 g are pale red-brown, oval-shaped, biconvex, film-coated tablets, debossed on one side with the (b) (4) and plain on other side and are supplied as follows: NDC 68382-362-64 in bottles of 34 tablets NDC 68382-362-19 in bottles of 120 tablets (b) (4)	☒
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 YES 1.14.3.3 1 RLD label and 1 RLD container label YES	☒

MODULE 2
SUMMARIES

ACCEPTABLE

2.3	Quality Overall Summary (QOS) E-Submission: PDF YES Word Processed e.g., MS Word YES 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) YES 2.3.S Drug Substance (Active Pharmaceutical Ingredient) YES 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 YES 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	☒
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2.7	Clinical Summary (Bioequivalence) Model Bioequivalence Data Summary Tables E-Submission: PDF YES Word Processed e.g., MS Word YES 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods 2.7.1.1 Background and Overview Table 1. Submission Summary YES Table 4. Bioanalytical Method Validation N/A; data provided in clinical endpoint study Table 6. Formulation Data YES 2.7.1.2 Summary of Results of Individual Studies Table 5. Summary of In Vitro Dissolution YES 2.7.1.3 Comparison and Analyses of Results Across Studies Table 2. Summary of Bioavailability (BA) Studies REFER TO TABLE 14.1.10 IN MODULE 5.3.1.2 Table 3. Statistical Summary of the Comparative BA Data REFER TO TABLE 14.2.5 IN MODULE 5.3.1.2 2.7.1.4 Appendix N/A 2.7.4.1.3 Demographic and Other Characteristics of Study Population Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study SEE MODULE 5.3.1.2 2.7.4.2.1.1 Common Adverse Events Table 8. Incidence of Adverse Events in Individual Studies SEE MODULE 5.3.1.2	
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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) YES 2. Function or Responsibility YES 3. Type II DMF number for API YES 4. CFN or FEI numbers YES Zydus Pharmaceuticals USA Inc. has identified M/s (b) (4) (b) (4) as the source of Active Pharmaceutical Ingredient (API) – Mesalamine, USP. <table border="1" data-bbox="415 701 1252 1457"> <thead> <tr> <th data-bbox="415 701 1118 753">Active Ingredient(s)</th> <th data-bbox="1118 701 1252 753">DMF No.</th> </tr> </thead> <tbody> <tr> <td colspan="2" data-bbox="415 753 1252 1457" style="text-align: center;">(b) (4)</td> </tr> </tbody> </table>	Active Ingredient(s)	DMF No.	(b) (4)		☒
Active Ingredient(s)	DMF No.					
(b) (4)						
3.2.S.3	Characterization	☒				

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) YES 3.2.S.4.2 Analytical Procedures YES 3.2.S.4.3 Validation of Analytical Procedures 1. Spectra and chromatograms for reference standards and test samples YES 2. Samples-Statement of Availability and Identification of: a. Drug Substance YES b. Same lot number(s) This is to state that sample of drug substance Mesalamine, USP will be provided to agency based upon request. <table border="1" data-bbox="418 514 1271 695"> <thead> <tr> <th><i>Drug Substance</i></th><th><i>Drug Substance Manufacturer's lot no.</i></th><th><i>Drug Product Manufacturer's SAP Batch No.</i></th><th><i>Pack</i></th><th><i>Quantity</i></th></tr> </thead> <tbody> <tr> <td>Mesalamine, USP</td><td>08P0416</td><td>0301000935</td><td>HDPE Bottle</td><td>3 x 20 g</td></tr> </tbody> </table> 3.2.S.4.4 Batch Analysis 1. COA(s) specifications and test results from drug substance mfgr(s) YES 2. Applicant certificate of analysis YES 3.2.S.4.5 Justification of Specification	<i>Drug Substance</i>	<i>Drug Substance Manufacturer's lot no.</i>	<i>Drug Product Manufacturer's SAP Batch No.</i>	<i>Pack</i>	<i>Quantity</i>	Mesalamine, USP	08P0416	0301000935	HDPE Bottle	3 x 20 g	☒
<i>Drug Substance</i>	<i>Drug Substance Manufacturer's lot no.</i>	<i>Drug Product Manufacturer's SAP Batch No.</i>	<i>Pack</i>	<i>Quantity</i>								
Mesalamine, USP	08P0416	0301000935	HDPE Bottle	3 x 20 g								
3.2.S.5	Reference Standards or Materials YES	☒										
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 YES 2. Inactive ingredients and amounts are appropriate per IIG YES	☒
3.2.P.2	Pharmaceutical Development Pharmaceutical Development Report YES	☒
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 SEE SECTION 3.2.P.3.1 3. Function or Responsibility YES 4. CFN or FEI numbers YES; 3002984011 Cadila Healthcare Limited (b) (4) (b) (4) Ahmedabad (b) (4) (b) (4) India (b) (4) 3.2.P.3.2 Batch Formula YES 3.2.P.3.3 Description of Manufacturing Process and Process Controls 1. Description of the Manufacturing Process YES 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified YES 3. If sterile product: Aseptic fill / Terminal sterilization N/A 4. Reprocessing Statement YES 3.2.P.3.4 Controls of Critical Steps and Intermediates 3.2.P.3.5 Process Validation and/or Evaluation 1. Microbiological sterilization validation N/A 2. Filter validation (if aseptic fill) N/A PROPOSED COMMERCIAL BATCH SIZE: (b) (4)	☒
3.2.P.4	Controls of Excipients (Inactive Ingredients) Source of inactive ingredients identified YES 3.2.P.4.1 Specifications 1. Testing specifications (including identification and characterization) YES 2. Suppliers' COA (specifications and test results) YES 3.2.P.4.2 Analytical Procedures 3.2.P.4.3 Validation of Analytical Procedures 3.2.P.4.4 Justification of Specifications Applicant COA YES	☒

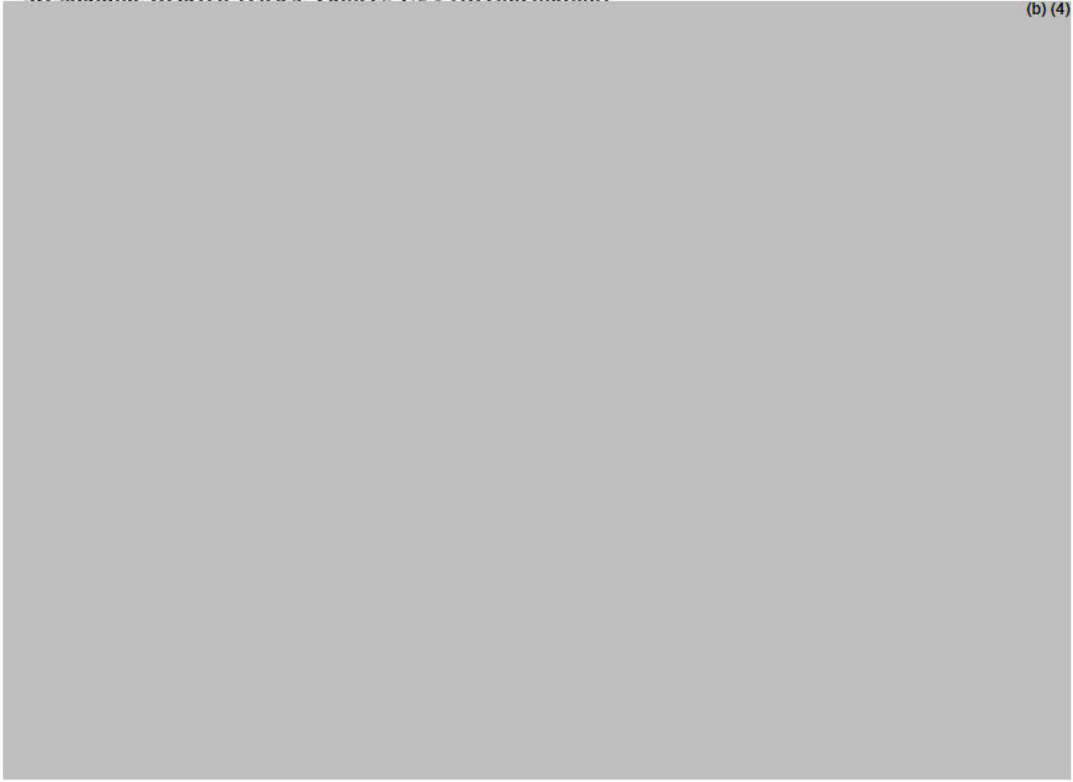
MODULE 3**3.2.P DRUG PRODUCT**

ACCEPTABLE

3.2.P.5	Controls of Drug Product 3.2.P.5.1 Specification(s) YES 3.2.P.5.2 Analytical Procedures YES 3.2.P.5.3 Validation of Analytical Procedures Samples - Statement of Availability and Identification of: 1. Finished Dosage Form YES 2. Same lot numbers This is to state that the samples of drug product (Mesalamine Delayed-release Tablets, 1.2 g) will be provided to the Agency based upon request. <table border="1" data-bbox="344 562 1198 751"><thead><tr><th><i>Name of the Drug Product</i></th><th><i>Batch No. of the Drug Product</i></th><th><i>Quantity</i></th></tr></thead><tbody><tr><td>Mesalamine Delayed-release Tablets, 1.2 g</td><td>EMH 345</td><td>3 x 100 Tablets</td></tr></tbody></table> 3.2.P.5.4 Batch Analysis Certificate of Analysis for Finished Dosage Form YES 3.2.P.5.5 Characterization of Impurities 3.2.P.5.6 Justification of Specifications	<i>Name of the Drug Product</i>	<i>Batch No. of the Drug Product</i>	<i>Quantity</i>	Mesalamine Delayed-release Tablets, 1.2 g	EMH 345	3 x 100 Tablets	☒
<i>Name of the Drug Product</i>	<i>Batch No. of the Drug Product</i>	<i>Quantity</i>						
Mesalamine Delayed-release Tablets, 1.2 g	EMH 345	3 x 100 Tablets						
3.2.P.7	Container Closure System 1. Summary of Container/Closure System (if new resin, provide data) YES 2. Components Specification and Test Data YES 3. Packaging Configuration and Sizes YES 4. Container/Closure Testing YES 5. Source of supply and suppliers address YES	☒						
3.2.P.8	3.2.P.8.1 Stability (Finished Dosage Form) 1. Stability Protocol submitted YES 2. Expiration Dating Period 24 MONTHS 3.2.P.8.2 Post-approval Stability and Conclusion Post Approval Stability Protocol and Commitments YES 3.2.P.8.3 Stability Data 1. 3 month accelerated stability data YES 2. Batch numbers on stability records the same as the test batch EMH345	☒						

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 YES Mesalamine Delayed-release Tablets, 1.2 g (Reconciliation)  3.2.R.1.P.2 Information on Components YES 3.2.R.2.P Comparability Protocols N/A 3.2.R.3.P Methods Validation Package YES 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 NO	☒
5.3.1 (complete study data)	Bioavailability/Bioequivalence 1. Formulation data same? a. Comparison of all Strengths (check proportionality of multiple strengths) one strength 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): ANDA: EMH345 RLD: 7L3814,8A4383, & 8C4562 3. Study Type: (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) NO; SEE BE SUMMARY FINDINGS 2. Summary Bioequivalence tables: Table 10. Study Information YES Table 12. Dropout Information SEE APPENDIX 16.2.1.2 IN MODULE 5.3.1.2 Table 13. Protocol Deviations SEE APPENDIX 16.2.2 IN MODULE 5.3.1.2 5.3.1.3 In Vitro-In-Vivo Correlation Study Reports 1. Summary Bioequivalence tables: Table 11. Product Information YES Table 16. Composition of Meal Used in Fed Bioequivalence Study N/A 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies 1. Summary Bioequivalence table: Table 9. Reanalysis of Study Samples N/A Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses N/A Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples N/A 5.3.7 Case Report Forms and Individual Patient Listing YES	☒
5.4	Literature References	☒
	Possible Study Types:	
Study Type	IN-VIVO BE STUDY(IES) with PK ENDPOINTS (i.e., fasting/fed/sprinkle) NA 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) NO 2. EDR Email: Data Files Submitted: NA 3. In-Vitro Dissolution: NA	☒
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) 1. Study(ies) meets BE criteria (90% CI of 80-125) YES PLEASE DOUBLE CHECK 2. EDR Email: Data Files Submitted: YES SENT TO EDR 3. In-Vitro Dissolution: YES	☐
Study Type	NASALLY ADMINISTERED DRUG PRODUCTS 1. <u>Solutions</u> (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) 2. <u>Suspensions</u> (Q1/Q2 sameness): a. <u>In-Vivo PK Study</u> 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. <u>In-Vivo BE Study with Clinical End Points</u> 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. <u>In-Vitro Studies</u> (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. <u>In-Vivo PK Study</u> 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. <u>Adhesion Study</u> 3. <u>Skin Irritation/Sensitization Study</u>	☐

Updated 10/19/2009

Patent and Exclusivity Search Results - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Back Search Favorites

Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexcdnew.cfm?Appl_No=022000&Product_No=001&table1=OB_Rx Go Links

U.S. Department of Health & Human Services www.hhs.gov

FDA U.S. Food and Drug Administration A-Z Index Search

Home | Food | Drugs | Medical Devices | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Radiation-Emitting Products | Tobacco Products

FDA Home

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Patent and Exclusivity Search Results from query on Appl No 022000 Product 001 in the OB_Rx list.

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N022000	001	6773720	Jun 8, 2020		Y		

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
N022000	001	NP	Jan 16, 2010

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.

Done Local intranet

(b) (4)

Table 6 Formulation Data

Ingredient (s)	Mesalamine Delayed-release Tablets, 1.2 g	
	Unit Composition (mg/tablet)	% w/w [§]
(b) (4)		
Mesalamine (b) (4)USP	1200.000	(b) (4)
Colloidal Silicon Dioxide (b) (4)NF	(b) (4)	(b) (4)
Magnesium Stearate (b) (4)NF	(b) (4)	(b) (4)
Carboxy methyl cellulose Sodium (b) (4)USP	(b) (4)	(b) (4)
Sodium Starch Glycolate (b) (4)NF	(b) (4)	(b) (4)
Hypromellose (b) (4)USP	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Microcrystalline Cellulose (b) (4)NF	(b) (4)	(b) (4)
Colloidal Silicon Dioxide (b) (4)NF	(b) (4)	(b) (4)
Magnesium Stearate (b) (4)NF	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Methacrylic Acid Copolymer (b) (4)	(b) (4)	(b) (4)
(b) (4)NF	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Triethyl Citrate (b) (4)NF	(b) (4)	(b) (4)
Talc (b) (4)USP	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Total (Coated Tablets)	1465.000	100.00

[§] Calculated based on the coated tablet average weight.

(b) (4)

<i>Inactive ingredient(s)</i>	<i>Listing In the Inactive Ingredients Database</i>	<i>Levels recommended in Inactive Ingredients Database(mg) (solid orals)</i>	<i>Mesalamine Delayed-release Tablets , 1.2 g</i>
Colloidal Silicon Dioxide (b) (4) NF	Yes	(b) (4)	(b) (4)
Magnesium Stearate, NF	Yes		
Carboxy methyl cellulose Sodium (b) (4) USP	Yes		
Sodium Starch Glycolate (b) (4) NF	Yes		
Hypromellose (b) (4) USP	Yes		
Microcrystalline Cellulose (b) (4) NF	Yes		
Methacrylic Acid Copolymer (b) (4) NF	No		
(b) (4)	Yes		
Triethyl Citrate (b) (4) NF	Yes		
Talc (b) (4) USP	Yes		
(b) (4) Hypromellose (b) (4) USP	Yes		
Titanium Dioxide, USP*	Yes		
Macrogol /PEG 6000, NF*	Yes		
Iron Oxide Red, NF*	Yes		
Iron Oxide, Yellow, NF*	Yes		
(b) (4)			

As cited in the above table, all the inactive ingredients used in the manufacturing of the subject product (b) (4)

(b) (4) Methacrylic Acid Copolymer (b) (4)

\$ The **toxicology data** studied by the manufacturer, (b) (4) to support the used quantity and (b) (4) **justification** for safety assessment has been submitted in Module 3.2.P.1. We have included the detailed iron content calculation and justification in **Module 3.2.P.1**.

JUSTIFICATION OF INACTIVE INGREDIENTS:

(b) (4)

(b) (4)

(b) (4)

Establishment Evaluation System

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ORACLE

Application Drawer

Application Establishments Status Milestones Comments Contacts Product

Application: 91640/000 Sponsor: ZYDUS PHARMS USA INC

Drug Name: 180790

CFN / FEI	Establishments Name	Profile Code	Last Milestone Name	Last Milestone Date	Last Compliance Status	Last Compliance Date	OAI Alert
	CADILA HEALTHCARE	TCT	SUBMITTED TO OC	20-MAY-2010	FN	20-MAY-2010	(b) (4)

Overall Compliance:
Date Recommendation

Save Close

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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ANDA-91640	ORIG-1	ZYDUS PHARMACEUTICA LS USA INC	MESALAMINE

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/s/

SHANNON L HILL
05/26/2010

MARTIN H Shimer
05/27/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION Consult No: 2010-0427	
TO (Division/Office) DGP - HFD-180 Thru: Bronwyn E. Collier, ODEIII HFD-103			FROM: Shannon Hill, OGD/DLPS/RSB	
DATE: 5/26/2010	IND NO.	ANDA NO. 091640	TYPE OF DOCUMENT Original	DATE OF DOCUMENT 12/12/2009,
NAME OF DRUG 180790		PRIORITY CONSIDERATION 60 days	CLASSIFICATION OF DRUG Treatment of Ulcerative Colitis	DESIRED COMPLETION DATE 7/25/2010
NAME OF FIRM ZYDUS PHARMS USA INC				
REASON FOR REQUEST				
I. GENERAL				
☐ NEW PROTOCOL ☐ PRE NDA MEETING ☐ RESPONSE TO DEFICPENCY LETTER ☐ PROGRESS REPORT ☐ END OF PHASE II MEETING ☐ FINAL PRINTED LABELING ☐ NEW CORRESPONDENCE ☐ RESUBMISSION ☐ LABELING REVISION ☐ DRUG ADVERTISING ☐ SAFETY/EFFICACY ☐ ORIGINAL NEW CORRESPONDENCE ☐ ADVERSE REACTION REPORT ☐ PAPER NDA ☐ FORMULATIVE REVIEW ☐ MANUFACTURING CHANGE/ADDITION ☐ CONTROL SUPPLEMENT ☒ OTHER ('specify below') ☐ MEETING PLANNED BY _____				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER			☐ CHEMISTRY ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER	
III. BIOPHARMACEUTICS				
☐ DISSOLUTION ☐ PROTOCOL-- BIOPHARMACEUTICS ☐ IN--VIVO WAIVER REQUEST			☐ DEFICIENCY LETTER RESPONSE ☐ BIOAVAILABILITY STUDIES ☐ PHASE IV STUDIES	
IV. DRUG EXPERIENCE				
☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES ☐ CASE REPORTS OF SPECIFIC REACTIONS(List below) ☐ COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP			☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY ☐ SUMMARY OF ADVERSE EXPERIENCE POISON RISK ANALYSIS	
V. SCIENTIFIC INVESTIGATIONS				
☐ CLINICAL			☐ PRECLINICAL	
COMMENTS OGD is requesting a Pharm/Tox Review. (b) (4) Please cc Theresa Liu, HFD-01/ (theresa.liu@fda.hhs.gov) on the review when it is being checked into DFS. Thank you.				
SIGNATURE OF REQUESTER			METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND	
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER	

FORM FDA 3291 (7/83)

cc: ANDA
Drug File Folder

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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ANDA-91640	ORIG-1	ZYDUS PHARMACEUTICA LS USA INC	MESALAMINE

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/s/

SHANNON L HILL
05/26/2010

THERESA C LIU
05/26/2010

**CLINICAL REVIEW TEAM CHECKLIST FOR GENERIC ANDA
FOR APPLICATION COMPLETENESS**

ANDA# 091640_____ **FIRM NAME** Zydus Pharmaceuticals USA Inc. (subsidiary of Cadilla
Healthcare Limited, India)_____

DRUG NAME Mesalamine Delayed-release Tablet, 1.2 g_____

DOSAGE FORM Tablet_____

REFERENCE LISTED DRUG (RLD) Lialda® (mesalamine delayed-release) tablet, 1.2 g, NDA
022000_____

Requested by: Nitin Patel_____ Date: 2/4/10_____
Clinical Review Team

	Summary of Findings by Clinical Review Team
X	Study meets statutory requirements
	Study does NOT meet statutory requirements
	Waiver meets statutory requirements
	Waiver does NOT meet statutory requirements
	Reason:

RECOMMENDATION: X COMPLETE INCOMPLETE

Reviewed by:

Reviewer
Carol Y. Kim, Pharm.D.
Clinical Reviewer

Date: _____

Dena R. Hixon, M.D.
Associate Director for Medical Affairs

Date: _____

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	X				Protocol #073-08 Electronic Submission
Summary of Study	X				
Clinical Site (s)	X				
Study Investigator (s)	X				
List of subjects included in PP/ (M)ITT populations per treatments		X			Not provided
List of subjects excluded/ from PP/ (M)ITT per treatments		X			Not provided
Reasons for discontinuation from the study if discontinued	X				
Adverse Events	X				
Concomitant Medications	X				
Individual subject's scores/data per visit	X				
Pre-screening of Patients	X				
IRB Approval	X				
Consent Forms	X				
Randomization Schedule	X				
Protocol Deviations	X				
Case Report Forms	X				
PD Data Disk (or Elec Subm)		X			No SAS dataset was submitted.
Study Results	X				
Clinical Raw Data/ Medical Records	X				

Financial Disclosure	X				
Composition	X				
BioStudy Lot Numbers	X				
Date of Manufacture	X				
Exp. Date of RLD	X				
Statistical Reports	X				
Defined BE endpoints	X				
Summary results provided by the firm indicate studies pass BE criteria	X				See below for comments
Summary results provided by the firm indicate superiority of the active treatments over the vehicle/placebo	X				See below for comments
Waiver requests for other strengths / supporting data		X			N/A

Comments not to be conveyed to the sponsor:

Summary of the sponsor's study

Three hundred fifty nine (359) patients with mild to moderately active ulcerative colitis with a score of 4-10 on the Ulcerative Colitis Disease Activity Index (UC-DAI) were enrolled and treated with the study drugs, taken with a meal once daily for 8 weeks. In the test arm, patients took 2 tablets (1.2 g) of the test product and 2 tablets of a placebo matched with the reference product. In the reference arm, patients took 2 tablets (1.2 g) of the reference product and 2 tablets of a placebo matched with the test product. In the placebo arm, patients took 2 tablets of the placebo matched with the test product and 2 tablets of the placebo matched with the reference product.

Reviewer's Comment: *On April 12, 2010, the OGD requested the formulation for placebo tablets used in the sponsor's study. According to the placebo formulation submitted on April 13, 2010 by the sponsor, the formulation of the placebo tablet matching the test product is identical to the placebo matching the reference product.*

The primary endpoint of the study was the **remission rate**, defined as “a UC-DAI score of 0 or 1, where the rectal bleeding and stool frequency components must be zero, with a reduction in sigmoidoscopy score of 1 point or more from baseline” at week 8. An additional exploratory analysis was provided by the sponsor for “**clinical remission**” defined by the sponsor as “absence of rectal bleeding and stool frequency symptoms” at week 8.

The sponsor performed a statistical analysis that is quite different from the statistical method usually

recommended by the OGD. According to the sponsor, the 95% lower bound for Odds ratio analysis for the difference in proportion of patients in remission for the test vs. reference was -0.11 in the PP population. The remission rate was 10.8% for the test product and 14.1% for the reference product in the PP population at week 8, according to the sponsor's analysis. In the ITT population, the remission rate was 12.6% for the test product, 12.4% for the reference product, and 4.3% for the placebo at week 8, demonstrating superiority of the active treatment groups over the placebo. The sponsor's analysis is summarized below.

Primary endpoint: (remission defined as a UC-DAI score of ≤ 1 with a score of 0 for rectal bleeding and stool frequency and at least a 1 point reduction from baseline in sigmoidoscopy score at week 8)

14.2.6 Proportion of patients in remission at Visit 5 (PP population)

	Odds ratio	95% CI for Odds Ratio	p-value	95% Lower Bound
Comparison of Lialda® Mesalamine Delayed-Release Tablets (1.2 g), Shire US Inc. versus Placebo	6.17	1.35 - 28.3	0.01	0.05
Comparison of Mesalamine Delayed-Release Tablets (1.2 g), Cadila Healthcare Limited versus Lialda® Mesalamine Delayed-Release Tablets (1.2 g), Shire US Inc.	0.74	0.30 - 1.83	0.51	-0.11
Comparison of Mesalamine Delayed-Release Tablets (1.2 g), Cadila Healthcare Limited versus Placebo	4.56	0.95 - 21.8	0.04	0.02

14.2.5 Proportion of patients in remission at Visit 5 (ITT population)

	Odds ratio	95% CI for Odds Ratio	p-value	95% Lower Bound
Comparison of Lialda® Mesalamine Delayed-Release Tablets (1.2 g), Shire US Inc. versus Placebo	3.11	1.09 - 8.87	0.03	0.02
Comparison of Mesalamine Delayed-Release Tablets (1.2 g), Cadila Healthcare Limited versus Lialda® Mesalamine Delayed-Release Tablets (1.2 g), Shire US Inc.	1.02	0.47 - 2.19	0.96	-0.07
Comparison of Mesalamine Delayed-Release Tablets (1.2 g), Cadila Healthcare Limited versus Placebo	3.17	1.11 - 9.04	0.02	0.02

Secondary endpoint: (remission defined as a score of 0 for stool frequency and rectal bleeding at week 8)

14.2.4 Summary of Efficacy Response data (PP population)

	Treatment Group		
	Reference	Test	Placebo
Clinical Improvement N (%)	55 (59.78)	33 (39.76)	36 (46.75)
Clinical Remission N (%)	27 (29.35)	21 (25.30)	16 (20.78)
Time to Withdrawal (Days)	NA	NA	NA
Treatment Failures N (%)	13 (14.13)	17 (20.48)	14 (18.18)

14.2.3 Summary of Efficacy Response data (ITT population)

	Treatment Group		
	Reference	Test	Placebo
Clinical Improvement N (%)	61 (50.41)	44 (36.97)	45 (39.13)
Clinical Remission N (%)	31 (25.62)	30 (25.21)	23 (20.00)
Time to Withdrawal (Days)*	29.500	18.000	25.000
Treatment Failures N (%)	33 (27.27)	37 (31.09)	39 (33.91)

* Median is presented

According to the NDA review of the RLD (Lialda) using the same primary endpoint of remission, higher remission rates were observed in the NDA studies than those observed with the RLD in this ANDA study. For the ITT population, the remission rate of the reference product was 12.4% in this study vs. 34.1% or 40.5% in the NDA clinical studies. See below for the excerpt from the NDA review.

In both pivotal studies (Study 301 and Study 302) the primary efficacy endpoint was the proportion of subjects who were in remission at Week 8. Remission was defined as ulcerative colitis disease activity index (UC-DAI) score of ≤ 1 , with scores of 0 for rectal bleeding and stool frequency, and a sigmoidoscopy score reduction of 1 point or more from baseline.

The efficacy results are summarized in the table below.

Proportion of Subjects in Remission at Week 8			
	Mesavance		Placebo n (%)
	2.4g/day n (%)	4.8g/day n (%)	
Study-301	n=88	n=89	n=85
Subjects in Remission	30 (34.1)	26 (29.2)	11 (12.9)
p-value	0.001	0.009	
Study-302	n=84	n=85	n=86
Subjects in Remission	34 (40.5)	35 (41.2)	19 (22.1)
p-value	0.010	0.007	
Pooled Studies	n=172	n=174	n=171
Subjects in Remission	64 (37.2)	61 (35.1)	30 (17.5)
p-value	<0.001	<0.001	

According to the DBE II filing review dated 2/26/10, the sponsor was requested to conduct two pharmacokinetic studies, one study under fasting and one study under fed conditions, and submit additional dissolution data at pH 6.8.

The sponsor's formulation is shown below.

Ingredient (s)	Mesalamine Delayed-release Tablets, 1.2 g	
	Unit Composition (mg/tablet)	% w/w [#]
(b) (4)		
Mesalamine (b) (4) USP	1200.000	(b) (4)
Colloidal Silicon Dioxide (b) (4) NF	(b) (4)	
Magnesium Stearate (b) (4) NF		
Granulation		
Carboxy methyl cellulose Sodium (b) (4) USP		
Sodium Starch Glycolate (b) (4) NF		
Hypromellose (b) (4) USP		
(b) (4)		
(b) (4)		
Microcrystalline Cellulose (b) (4) NF		
Colloidal Silicon Dioxide (b) (4) NF		
Magnesium Stearate (b) (4) NF		
(b) (4)		
Methacrylic Acid Copolymer (b) (4) NF		
(b) (4)		
(b) (4)		
Triethyl Citrate (b) (4) NF		
Talc (b) (4) USP		
(b) (4)		
(b) (4)		
(b) (4)		
Total (Coated Tablets)	1465.000	100.00
[#] Calculated based on the coated tablet average weight.		
(b) (4)		

The sponsor provided qualitative differences between the RLD and their formulation as shown below.

Reference Listed Lialda (Mesalamine) Delayed-release 1.2 g	Mesalamine Delayed-release Tablets
Carboxymethylcellulose sodium	Carboxymethylcellulose sodium
Carnauba wax	Microcrystalline cellulose
Stearic acid	Hypromellose (b) (4)
Silica (colloidal hydrated)	Colloidal silicon dioxide
Sodium starch glycolate (type A)	Sodium starch glycolate
Talc	Talc
Magnesium stearate	Magnesium stearate
Methacrylic acid copolymer types A and B	Methacrylic acid copolymer
Triethyl citrate	Triethyl citrate
Titanium dioxide	Iron oxide yellow*
Red ferric oxide	Iron oxide red*
Polyethylene glycol 6000	Polyethylene glycol*
	Talc*
	Titanium dioxide*
	(b) (4)

(b) (4)

On April 12, 2010, the sponsor provided formulation data for the placebo tablets used in their study as shown below.

(b) (4)



This study satisfies the BE recommendations previously provided for generic mesalamine DRT products. However, a citizen petition is currently under review, and the current recommendation is for a pharmacokinetic study and rigorous comparative dissolution data for establishing bioequivalence of a mesalamine DRT. The results of the clinical endpoint study may not be sensitive enough for detecting differences between test and reference products.

The following additional information may be requested when the OGD decides that a clinical endpoint study should be reviewed:

- 1. For each clinical study site, provide the following information:**
 - Number of patients enrolled.
 - Number of patients included in the Per Protocol Population.
- 2. A frequency table comparing number of patients designated as in remission (UC-DAI score of 0 or 1, where the rectal bleeding and stool frequency components must be zero and having a reduction in sigmoidoscopy score of 1 point or more from baseline), improved (includes remission), or failure at week 8 for each treatment group in the ITT and PP populations.**
- 3. A frequency table comparing total DAI score at baseline and at Week 8 for each treatment group in the ITT and PP populations.**
- 4. A frequency table showing distribution of patients for each DAI index assessment category (e.g., PGA, mucosal appearance, rectal bleeding, and stool/bowel frequency score) including severity at baseline and at week 8. Please include assessment from the last day prior to treatment visit for baseline score and the last visit day of week 8 for Week 8 score. An example for PGA is shown below.**

PGA at baseline	Test N=X	Reference N=X	PGA at Week 8	Test N=X	Reference N=X
0			0		
1			1		
2			2		
3			3		

5. Study data should be submitted in electronic format.
 - a. A list of file names included in the CD or diskette(s), with a simple description of the content of each file, should be included. Such a list should include an explanation of the variables included in each of the data sets.
 - b. A “pdf” document with a detailed description of the codes that are used for each variable in each of the SAS datasets (for example, Y=yes, N=no for analysis population).
 - c. SAS transport files, covering all variables collected in the Case Report Forms (CRFs) per patient, should include .xpt as the file extension and should not be compressed. A simple SAS program to open the data transport files and SAS files should be included.
 - d. Primary data sets should consist of two data sets: No Last Observation Carried Forward (NO-LOCF-pure data set) and Last Observation Carried Forward (LOCF-modified data set).
 - e. A separate dataset for variables such as demographics, UC-DAI scores, rectal bleeding, stool frequency, mucosal appearance, PGA, vital signs, adverse events, disposition (including reason for discontinuation of treatment), concomitant medications, medical history, compliance and comments, etc.
 - f. The methods used to derive the variables should be included and explained.
 - g. A summary dataset (SAS .xpt file) should contain a separate line listing of all primary efficacy variables for each patient (if data exist).

6. A summary dataset in a single file including the following line listings for each patient:
 - center/site, patient number
 - drug/treatment
 - race, sex , age
 - reason for discontinuation
 - baseline total UC-DAI score
 - total UC-DAI score at Week 8
 - baseline PGA score
 - PGA score at Week 8
 - baseline mucosal appearance score
 - mucosal appearance score at Week 8
 - baseline rectal bleeding score
 - rectal bleeding score at Week 8
 - baseline bowel/stool frequency score
 - stool/bowel frequency score at Week 8
 - number of stools per day while in remission
 - presence/quantity of rectal bleeding during last three days of screening visit prior to receiving treatment (e.g., day -3, -2, and -1)
 - presence/quantity of rectal bleeding during the last three days of Week 8 (e.g., day 53, 54, and 55)

- total number of actual bowel/stool passage during last three days of screening visit prior to receiving treatment (e.g., day -3, -2, and -1)
- total number of actual bowel/stool passage during last three days of Week 8 (e.g., day 53, 54, and 55)
- bowel frequency score during last three days of screening visit prior to receiving treatment (e.g., day-3, -2, and -1)
- bowel frequency score during the last three days of Week 8 (e.g., day 53, 54, and 55)
- extent of UC involvement (cm)
- designation of success (responder)/failure*
- designation of improved (includes remission)
- designation of remission only
- clinical relapse (yes/no)
- safety population (yes/no), reason for exclusion
- ITT population** (yes/no), reason for exclusion
- PP population** (yes/no), reason for exclusion
- treatment compliance, number of missed doses

*Success/failure (responder/non-responder) should be designated based on available data at week 8. Only patients who are considered treatment failures due to lack of treatment response or relapse should be designated as treatment failures.

**Patients who did not meet inclusion/exclusion criteria should be excluded from both ITT and PP populations.

Primary data sets should consist of two data sets: No Last Observation Carried Forward (No-LOCF-pure data set) and Last Observation Carried Forward (LOCF– modified data set).

Comments to be conveyed to the sponsor

The data provided in your application are sufficient to receive your ANDA.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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ANDA-91640	ORIG-1	ZYDUS PHARMACEUTICA LS USA INC	MESALAMINE

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/s/

CAROL Y KIM
05/11/2010

DENA R HIXON
05/11/2010
I concur.

**BIOEQUIVALENCE CHECKLIST for First Generic ANDA
FOR APPLICATION COMPLETENESS**

ANDA# 091640 **FIRM NAME** Zydus Pharmaceuticals USA Inc.

DRUG NAME Mesalamine

DOSAGE FORM Delayed Release Tablets

Strength 1200 mg

SUBJ: Request for examination of: Bioequivalence Study

Requested by: _____ Date: January 25, 2010
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Division of Bioequivalence
☐	Study meets statutory requirements
☒	Study does NOT meet statutory requirements
	Reason: The submitted studies do not fulfill the current BE requirements with respect to Pharmacokinetic (PK) studies since the firm did not submit the requested fasting and fed BE studies. Please note that the OGD Clinical Division will conduct a separate filing review of the submitted BE study with clinical endpoint. The acceptability of that study is deferred to the OGD Clinical Division.
☐	Waiver meets statutory requirements
☐	Waiver does NOT meet statutory requirements
	Reason:

RECOMMENDATION: ☐ COMPLETE ☒ INCOMPLETE

Reviewed by:

Zhuojun Zhao
Reviewer

Date: _____

Xiaojian Jiang
Team Leader

Date: _____

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	☐	☐			The firm did not submit any BE study with PK endpoint. The sponsor conducted a bioequivalence study with a clinical endpoint in patients with mild to moderate active Ulcerative Colitis (UC) to demonstrate bioequivalence between the test and the reference products. The OGD Clinical Division will conduct the filing review of this study (see Attachment II).
Assay Methodology	☐	☐			
Procedure SOP	☐	☐			
Methods Validation	☐	☐			
Study Results Ln/Lin	☐	☐			
Adverse Events	☐	☐			
IRB Approval	☐	☐			
Dissolution Data	☒	☐			5.3.1.3 (the firm submitted the quality control and stability dissolution testing using the FDA-recommended method but did not submitted additional in vitro comparative dissolution testing supporting bioequivalence)
Pre-screening of Patients	☐	☐			
Chromatograms	☐	☐			
Consent Forms	☐	☐			
Composition	☐	☐			
Summary of Study	☐	☐			
Individual Data & Graphs, Linear & Ln	☐	☐			
PK/PD Data Disk Submitted)	☐	☐			
Randomization Schedule	☐	☐			

Protocol Deviations	☐	☐			
Clinical Site	☐	☐			
Analytical Site	☐	☐			
Study Investigators	☐	☐			
Medical Records	☐	☐			
Clinical Raw Data	☐	☐			
Test Article Inventory	☐	☐			
BIO Batch Size	☐	☐			
Assay of Active Content Drug	☐	☐			
Content Uniformity	☐	☐			
Date of Manufacture	☐	☐			
Exp. Date of RLD	☐	☐			
BioStudy Lot Numbers	☐	☐			
Statistics	☐	☐			
Summary results provided by the firm indicate studies pass BE criteria	☐	☐			
Waiver requests for other strengths / supporting data	☐	☐			N/A

GENERAL COMMENTS:

1. The reference listed drug product (RLD) is Lialda® delayed release (DR) tablet for oral administration containing 1200 mg mesalamine, an aminosalicylate anti-inflammatory agent for gastrointestinal use (NDA 22000, approved on Jan 16, 2007).

2. The current BE recommendations for demonstration of bioequivalence of mesalamine are as follows¹:

¹The current BE recommendation is not yet finalized. Per discussion with the DBE II management dated Feb. 5, 2010, the pharmacokinetic studies and dissolution recommends are considered final but the details of the clinical endpoint study is pending the decision of the OGD Clinical Division (see Attachment I for e-mail communication and V:\FIRMSAM\LUPIN\ CONTROLS\071162C0807Addendum2.doc for the DBE review of control document#71162)

Active ingredient: Mesalamine

Form/Route: Delayed Release Tablet/Oral

Recommended studies 4 studies

1. Type of study: In vivo bioequivalence study with clinical endpoints
Design: Parallel three arm (test, reference, and placebo) bioequivalence study
Strength: 1200 mg
Subjects: Patients with ulcerative colitis, males and females
Additional comments: OGD Clinical Team will add recommendation for appropriate patient population, treatment regimen, and endpoints (Indication from label is for induction of remission in patients with active, mild to moderate ulcerative colitis).

Analytes to measure (in appropriate biological fluid): N/A

Bioequivalence based on (90% CI): Difference in treatment success within +/- 20%.
Test and reference should be significantly better than placebo.

-
2. Type of study: Fasting
Design: Single-dose, three period, partial replicate (2 R 1T) crossover, *in-vivo*
Strength: 1200 mg
Subjects: Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study.
 3. Type of study: Fed
Design: Single-dose, three period, partial replicate (2 R 1T) crossover, *in-vivo*
Strength: 1200 mg
Subjects: Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study.

Analytes to measure (in appropriate biological fluid): Mesalamine in plasma

Bioequivalence based on (Scaled Average Bioequivalence): Applicants may consider using a reference-scaled average bioequivalence approach for mesalamine. If using this approach, the applicant should provide evidence of high variability in the bioequivalence parameters AUC and/or C_{max} (i.e., within-subject variability $\geq 30\%$). For general information on this approach, please refer to Haidar et al., Bioequivalence Approaches for Highly Variable Drugs and Drug Products, Pharm. Res. 25:237-241(2008).

4. Type of study: In vitro comparative dissolution study
Strength: 1200 mg
Apparatus: USP Apparatus 2 (paddle)
Pretreatment Stage 1: 2 hours in 0.1 N HCl at 100 rpm
Pretreatment Stage 2: 1 hours in pH 6.4 Phosphate buffer at 100 rpm

(b) (4)

Temperature: 37°C
Sample times: as needed for profile comparison
Additional comments: The applicant should use at least 12 tablets per test.

Waiver request of in-vivo testing: Not applicable

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.

Mesalamine (1.2 gram)	Tablet (Delayed Release)	II (Paddle)	100	Acid stage (A): 100 mM HCl Buffer stage (B): Phosphate Buffer, pH 6.4 Buffer stage (C): Phosphate Buffer, pH 7.2	Acid stage (A): 750 mL; Buffer stage (B): 950 mL; Buffer stage (C): 960 mL	Acid stage (A): 2 hours; Buffer stage (B): 1 hour; Buffer stage (C): 1, 2, 4, 6 and 8 hours	06/10/2009
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3. The sponsor conducted a bioequivalence study with a clinical endpoint in patients with mild to moderate active Ulcerative Colitis (UC) to demonstrate bioequivalence between the test and the reference products. Patients with mild to moderate (score of 4-10 on a modified UC-disease activity index UC-DAI) active UC were enrolled. The sponsor's randomized multi-center, parallel group, placebo-controlled study was designed to include the following three study treatments in 1:1:1 ratio: 1) test product , 2) active comparator arm (RLD), 3) Placebo. The OGD Clinical Division will conduct a separate filing review of this study (see Attachment II).

4. In the current application, the firm conducted the comparative dissolution testing for its test and RLD products using the current FDA-recommended method (<http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm>, updated on 06/10/09). The dissolution method is as follows:

Medium:	Acid Stage (A) 100 mM HCl Buffer Stage (B) Phosphate Buffer, pH 6.4 Buffer Stage (C) Phosphate Buffer, pH 7.2
Volume:	750 ml/ 950 ml/ 960 ml
USP Apparatus:	II (Paddle)
Speed:	100 rpm
Sampling Time:	Acid Stage (A), 2 hours Buffer Stage (B), 1 hour Buffer Stage (C), 1, 2, 4, 6 and 8 hours.

This dissolution testing is the quality control and stability testing for this product. However, for this locally acting drug product, additional in vitro comparative dissolution study in pH 6.8 should be also submitted and the profile comparison between the test and reference products should be performed.

COMMENTS ON ZYDUS'S SUBMITTED STUDY:

Zydus conducted a randomized multi-center, parallel group, placebo-controlled clinical endpoint bioequivalence study comparing its mesalamine DR tablets with Lialda® (mesalamine) DR tablets 120 mg. The firm did not submit any PK studies (i.e. BE studies under fasting and fed conditions), as well as the in vitro comparative dissolution study. Therefore, the submitted studies do not fulfill the current BE requirements recommended in the control document # 71162 with respect to the PK aspect of the BE recommendation and the application is considered **refused to file**. The firm should be requested to conduct additional Fasting, Fed BE studies and in vitro comparative dissolution study comparing its test product with Lialda® DR tablets. The OGD Clinical Division will conduct a separate filing review of the submitted BE study with clinical endpoint. The acceptability of that study is deferred to the OGD Clinical Division.

RECOMMENDATIONS TO THE FIRM:

The application is refused for filing with respect to PK studies. Please note that the OGD Clinical Division will conduct a separate filing review of the submitted BE study with clinical endpoint. The acceptability of that study is deferred to the OGD Clinical Division.

1) The OGD currently recommends the following studies for demonstration of bioequivalence of mesalamine delayed release tablets:

Recommended studies 4 studies

1. Type of study: In vivo bioequivalence study with clinical endpoints
Design: Parallel three arm (test, reference, and placebo) bioequivalence study
Strength: 1200 mg
Subjects: Patients with ulcerative colitis, males and females

Analytes to measure (in appropriate biological fluid): N/A

Bioequivalence based on (90% CI): Difference in treatment success within +/- 20%.
Test and reference should be significantly better than placebo.

-
2. Type of study: **Fasting**
Design: Single-dose, three period, partial replicate (2 R 1T) crossover, *in-vivo*
Strength: 1200 mg
Subjects: Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study.
 3. Type of study: **Fed**
Design: Single-dose, three period, partial replicate (2 R 1T) crossover, *in-vivo*
Strength: 1200 mg
Subjects: Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study.

Analytes to measure (in appropriate biological fluid): Mesalamine in plasma

Bioequivalence based on (Scaled Average Bioequivalence): Applicants may consider

using a reference-scaled average bioequivalence approach for mesalamine. If using this approach, the applicant should provide evidence of high variability in the bioequivalence parameters AUC and/or Cmax (i.e., within-subject variability $\geq 30\%$). For general information on this approach, please refer to Haidar et al., Bioequivalence Approaches for Highly Variable Drugs and Drug Products, Pharm. Res. 25:237-241(2008).

4. Type of study: **In vitro comparative dissolution study**
Strength: 1200 mg
Apparatus: USP Apparatus 2 (paddle)
Pretreatment Stage 1: 2 hours in 0.1 N HCl at 100 rpm
Pretreatment Stage 2: 1 hours in pH 6.4 Phosphate buffer at 100 rpm

(b) (4)

Temperature: 37°C
Sample times: as needed for profile comparison
Additional comments: The applicant should use at least 12 tablets per test.
-

Waiver request of in-vivo testing: Not applicable

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.

2) Therefore, the DBE recommends that the firm conduct additional single dose, three period, partial replicate (2R1T) crossover BE study with PK endpoint under both the Fasting and Fed conditions comparing the test product to the RLD, Lialda® DR tablets. In addition, the firm should conduct In vitro comparative dissolution study using the following conditions on 12 units each of the test and reference products and the profile comparison between the test and reference products should be performed:

Apparatus: USP Apparatus 2 (paddle)
Pretreatment Stage 1: 2 hours in 0.1 N HCl at 100 rpm
Pretreatment Stage 2: 1 hours in pH 6.4 Phosphate buffer at 100 rpm

(b) (4)

Temperature: 37°C
Sample times: as needed for profile comparison
Additional comments: The applicant should use at least 12 tablets per test.

ATTACHMENT I (Not to be released under FOI):

From: Lionberger, Robert
Sent: Thursday, February 18, 2010 10:23 AM
To: Jiang, Xiaojian
Cc: Zhao, Joan
Subject: RE: Mesalamine Control

Xiaojian,

1)

Yes, the current discussion is for Asacol. Once that issue is resolved then we would need to see if the conclusion could be applied to Lialda.

For Lialda, because there is no IVIVC you cannot use dissolution to replace the PK study (which is what we did for Asacol).

I think that if we accept dissolution plus PK study for Asacol, then it is very possible we could do the same thing for Lialda, but with additional dissolution test conditions

2) For Lialda, under the current clinical study recommendation we do want them to submit the data at 6.8 as well as at 7.2

The reason for this is that we want to encourage the generic sponsor to use polymers with a similar pH dependent release as the RLD and we need information about the RLD performance in the 6.8 media (there was none in the NDA. The NDA just had 6.4 and 7.2)

In the BE recommendation review, we leave open the possibility of not applying an equivalence test to the 6.8 data and just basing the BE conclusion on the 7.2 buffer stage. But you need to see the 6.8 data to be sure this is appropriate.

Rob

From: Jiang, Xiaojian
Sent: Thursday, February 18, 2010 9:57 AM
To: Lionberger, Robert
Cc: Zhao, Joan
Subject: FW: Mesalamine Control

Dear Rob:

Thank you so much for your help on our first generic checklist review.

I have two questions and want to confirm with you with regard to the BE recommendation for Lialda:

1) The discussion we have with New Drug Division is for Asacol, right? As noted in your review that since the dissolution testing is not reliable for Lialda, both clinical endpoint and PK studies are requested. My understanding is that for Lialda, we might not have choice for either clinical endpoint or PK studies, whereas for Asacol, the dissolution testing is so intensive, we might be able to replace insensitive clinical study with PK study. Am I correct?

2) In the draft Lialda guidance, we ask one in vitro comparative dissolution testing in pH 6.8, in addition to the regulatory method (the RLD method), which is in pH 7.2. From your review, my impression is that we are not going to ask in vitro dissolution testing but only the regulatory method. Can you confirm with me that the additional in vitro dissolution testing in pH 6.8 is needed?

This firm conducted only clinical endpoint study and dissolution testing using the RLD method. We will have to ask them to conduct PK studies and additional dissolution testing in pH 6.8.

Greatly appreciate your help!

Best regards,
Xiaojian

From: Lionberger, Robert
Sent: Thursday, February 04, 2010 4:53 PM

To: Zhao, Joan
Subject: RE: Mesalamine Control

Joan

That is the latest version. There is some ongoing discussion with the new drug division about whether PK studies and dissolution studies would be acceptable for modified release mesalamine products, but there has been no change to the recommendations yet. I think that this discussion is the reason the this BE recommendation has not yet been published.

Rob

From: Zhao, Joan
Sent: Thursday, February 04, 2010 4:46 PM
To: Lionberger, Robert
Subject: Mesalamine Control

Hi Bob,

I'm working on a checklist of 1200 mg Mesalamine ER Tablets (RLD Lialda®). I got your following control from Minglei. Have you done any update based on this version? If so, could you kindly send me a copy?

Thank you!

<< File: Review 22000BEdatabase-mesalamine040809 final (2).doc >>

Zhuojun Joan Zhao, Ph.D.
Division of Bioequivalence II
Office of Generic Drugs
FDA/CDER/OPS
Office (240)-276-8770
Fax (240)-276-8766
[*Joan.zhao@fda.hhs.gov*](mailto:Joan.zhao@fda.hhs.gov)

From: Davit, Barbara M
Sent: Thursday, April 09, 2009 4:54 PM
To: Cui, Minglei; Jiang, Xiaojian; Munshi, Utpal
Cc: Zhang, Yi; Sigler, Aaron
Subject: FW: Mesalamine (Lialda) BE Review

Hello:

Here is the final mesalamine review, this is for a generic to Lialda. I told the Science Team that I will sign off on this review.

Utpal: Leah Williamson needs this to finish her addendum to the review on the 1200-mg strength of Lialda. You and/or Leah can both stop by my office and I can fill you in about what is going on -- Yi was taking care of this.

Minglei: You can add this to your report. We do not have the clinical endpoint yet, Dena will take care of that. As far as I am concerned, our part is finished.

Barbara

intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Barbara.Davit@fda.hhs.gov.

From: Lionberger, Robert
Sent: Wednesday, April 08, 2009 9:44 AM
To: Davit, Barbara M; Haidar, Sam H
Cc: Nguyen, Doan
Subject: RE: Mesalamine (Lialda) BE Review

Here is the BE recommendation for Lialda

If this is acceptable, then it would need to go to the clinical team to add whatever details about the clinical endpoint BE study are needed.

<< File: Review 22000BEDatabase-mesalamine040809 final (2).doc >>
Rob

ATTACHMENT II (Not to be released under FOI):

From: Mahadevan, Chitra
Sent: Wednesday, February 17, 2010 4:13 PM
To: Zhao, Joan; Jiang, Xiaojian
Subject: FW: ANDA 091640 - First Generic Checklist

Hi Joan and Xiaojian,

I have been informed that the Clinical PM, Nitin Patel, has assigned this to the Clinical Team for review. Please see the emails below for further information.

Thanks,
Chitra

From: Patel, Nitin K. (CDER/OGD)
Sent: Wednesday, February 17, 2010 4:09 PM
To: Mahadevan, Chitra
Cc: Patel, Nitin K. (CDER/OGD)
Subject: FW: ANDA 091640 - First Generic Checklist

Hi Chitra,

I have assigned this to the Clinical Team for review. DBE will also need to review the dissolution data (see email traffic below).
Thanks,

Nitin

From: Hixon, Dena R
Sent: Friday, February 05, 2010 3:15 PM
To: Kim, Carol Y; Patel, Nitin K. (CDER/OGD)
Subject: RE: ANDA 091640 - First Generic Checklist

This is the product that we need to further discuss with the GI division to make a final decision about recommending clinical endpoint studies or PK. Definitely, dissolution is a requirement. We will need to follow-up on this one.

From: Kim, Carol Y
Sent: Thursday, February 04, 2010 4:02 PM
To: Patel, Nitin K. (CDER/OGD)
Cc: Hixon, Dena R; Kim, Carol Y
Subject: RE: ANDA 091640 - First Generic Checklist

Nitin,

I checked my files for 2009 and 2010 and I didn't receive this request.
At this point, the dissolution data would be more important to establish bioequivalence of this product more than the clinical endpoint study for this drug product.
I will check to see how the clinical endpoint was conducted but it is my understanding that the dissolution data must be acceptable too.
Thanks

Dena,

Do you want me to do the full filing review of this submission?

Thanks
Carol

From: Patel, Nitin K. (CDER/OGD)
Sent: Thursday, February 04, 2010 3:31 PM
To: Kim, Carol Y
Cc: Patel, Nitin K. (CDER/OGD)
Subject: FW: ANDA 091640 - First Generic Checklist

Hi Carol,

I am not sure if you have received word about this ANDA (dated 12/12/2009) from Reg Support?
Do you need to do a filing review?
I checked quickly in EDR and it looks like the firm has conducted a clinical endpoint study.
Thanks,

Nitin

From: Mahadevan, Chitra
Sent: Thursday, February 04, 2010 3:15 PM
To: Patel, Nitin K. (CDER/OGD)
Subject: ANDA 091640 - First Generic Checklist

Hi Nitin,

I assigned a First Generic Checklist for ANDA 091640, Mesalamine DR Tablets, to one of my bio reviewers. She informed me that a clinical endpoint study has been recommended for this drug and that the clinical team will also have to review this application?

I'm not sure how the process works, whether you need to assign it, etc. Please advise at your convenience.

Thanks!

Chitra Mahadevan, Pharm.D.
LT, US Public Health Service
Project Manager, Branch 7
Division of Bioequivalence II
Office of Generic Drugs
CDER/FDA

Outcome Page

ANDA: 091640

Reviewer: Zhao, Joan

Date Completed:

Verifier: ,

Date Verified:

Division: Division of Bioequivalence

Description: Mesalamine Delayed Release Tablet, 1200 mg

Productivity:

ID	Letter Date	Productivity Category	Sub Category	Productivity	Subtotal
10372	12/12/2009	Paragraph 4	Paragraph 4 Checklist	1	1
				Bean Total:	1

DBE2 Productivity points:

Checklist	
First Generic Checklist	1
Total	1

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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ANDA-91640	ORIG-1	ZYDUS PHARMACEUTICA LS USA INC	MESALAMINE

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

/s/

Zhuojun Z ZHAO
02/26/2010

XIAOJIAN JIANG
02/26/2010

BARBARA M DAVIT
02/26/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : January 23, 2010

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 91-640 for Mesalamine Delayed-release Tablets, 1.2 g to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to 21 USC 355(j)(5)(B)(iv).

Zydus Pharmaceuticals USA Inc. has submitted ANDA 91-640 for Mesalamine Delayed-release Tablets, 1.2 g. 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. Also it is a first generic. In order to accept an ANDA that contains a first generic, 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 Zydus Pharmaceuticals USA Inc. on December 12, 2009 for its Mesalamine 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".

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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ANDA-91640	ORIG-1	ZYDUS PHARMACEUTICA LS USA INC	MESALAMINE

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

/s/

EDA E HOWARD
01/25/2010