CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203568Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	08 January 2013
From	Eric Colman, MD
Subject	Deputy Division Director Summary Review
NDA#	203568
Applicant Name	Genzyme
Date of Submission	29 March 2012
PDUFA Goal Date	29 January 2013
Proprietary Name /Established Name	Mipomersen/Kynamro
Dosage Forms / Strength	200 mg subcutaneous once weekly
Proposed Indication(s)	Treatment of homozygous familial hypercholesterolemia
Recommended Action for NME:	Approve

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Eileen Craig, MD
Statistical Review	Japo Chowdhury, PhD
Pharmacology/Toxicology Review	Ronald Wang, PhD
CMC Review	Joseph Leginus, PhD
Microbiology Review	Robert Mello, PhD
Clinical Pharmacology Review	Ritesh Jain, PhD
OSI	Susan Leibenhaut, MD
OSE/DMEPA	Reasol Agustin, PharmD
OSE/DEPI	Patricia Bright, PhD
OSE/DRISK	Joyce Weaver, PharmD
Division of Therapeutic Proteins	Jinhai Wang, PhD

OND=Office of New Drugs
CMC=Chemistry, Manufacturing, and Controls
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DEPI=Division of Epidemiology
OSI=Office of Scientific Investigations
DRISK=Division of Risk Management

1. Introduction and Background

Mipomersen is a first-in-class antisense oligonucleotide (ASO) inhibitor targeted to human apolipoprotein B-100 (Apo B). Apo B is the principal apolipoprotein of low density lipoprotein (LDL). The majority of circulating cholesterol is found in LDL particles. Apo B is also a component of intermediate density lipoprotein (IDL), very low density lipoprotein (VLDL), and lipoprotein a (Lpa).

Genzyme is seeking approval of mipomersen as an adjunct to maximally-tolerated lipid-lowering therapy and diet to reduce LDL-C, Apo B, total cholesterol, non-high-density lipoprotein cholesterol (non-HDL-C), and Lpa in patients with homozygous familial hypercholesterolemia (HoFH).

HoFH has a prevalence of roughly one in a million and in its most severe form is associated with LDL-C levels of greater than 500 mg/dl and clinically evident cardiovascular disease in the first decade of life. Current therapeutic options include a number of LDL-C lowering drugs, primarily statins, and LDL-C apheresis. For those individuals who do not live within a reasonable distance to an apheresis facility, drugs are the focus of therapy. Given the molecular defect(s) in patients with HoFH, LDL-C lowering drugs, which work by increasing the number of LDL-C receptors on the liver, are modestly effective. There is need for additional pharmaceutical options to treat patients with HoFH.

This memorandum summarizes the review findings from the principal review disciplines. No review discipline is recommending that mipomersen not be approved.

2. CMC/Biopharmaceutics

The CMC reviewer states that there are no pending deficiencies and recommends that the application be approved. I agree that there are no outstanding CMC issues.

3. Nonclinical Pharmacology/Toxicology

Dr. Ron Wang states that there are no pending deficiencies to resolve and recommends that the application be approved. The tumor data from the rat carcinogenicity study will be included in the labeling. As summarized by Dr. Paul Brown in his tertiary review "…….some of the [nonclinical] findings are likely to be of low relevance to humans or offer a risk that may be acceptably balances if adequate clinical benefit has been shown for this particular indication [HoFH]." I agree with this assessment.

4. Clinical Pharmacology

The clinical pharmacology reviewer concludes that the data submitted in support of the application are acceptable. I agree that there are no outstanding clinical pharmacology issues.

As noted in Dr. Craig's review, FDA's interdisciplinary review team's thorough QT study (TQT) review concluded that no significant QTc prolongation effect of mipomersen (200-mg subcutaneous therapeutic dose and 200-mg intravenous supra-therapeutic dose) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean differences between mipomersen and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms. The moxifloxacin profile over time demonstrated that assay sensitivity was established.

The therapeutic protein reviewer concludes that there are no immune-response-induced issues that prevent approval of mipomersen. Potential safety concerns related to antibody response to mipomersen are discussed in part 7 of this memo.

5. Clinical Microbiology

The microbiology reviewer concludes that the data submitted in support of the application are acceptable and support approval. I agree with the reviewer that there are no outstanding clinical microbiology issues.

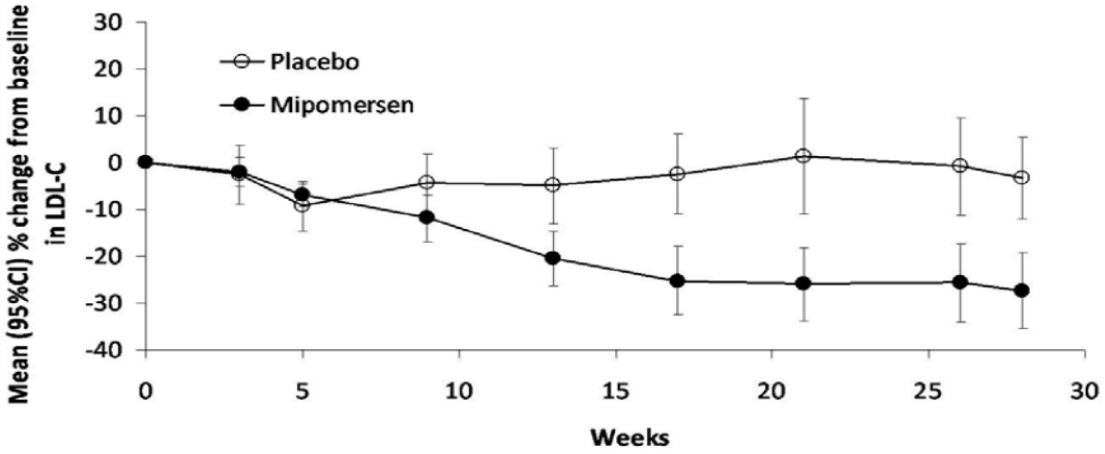
6. Clinical/Statistical-Efficacy

The efficacy of mipomersen in patients with HoFH was examined in one phase 3 clinical trial, ISIS-CS5. Three additional phase 3 clinical trials were conducted in patients without HoFH but at high risk for cardiovascular disease. This section of my memo will focus on the efficacy data from the study of patients with HoFH.

ISIS-CS5 was a randomized, placebo-controlled, double-blind study of 51 patients with HoFH. Thirty-four patients were randomized to 200 mg once-weekly mipomersen and 17 to placebo. The treatment period was 26 weeks. Patients were allowed to be on lipid-lowering therapy as long as the doses were stable ($\geq$ 12 weeks prior to screening). The primary endpoint was the change in LDL-C.

As noted in Dr. Craig's review, the baseline demographic characteristics of the randomized patients were well-matched. The mean age was approximately 32 years, roughly 42% were male, 75% were Caucasian, and the average BMI was 26 kg/m^2. The baseline LDL-C was approximately 420 mg/dl. All but one patient in the mipomersen arm were taking lipid-lowering therapy (mainly statins) at screening. All of the placebo patients and 82% of the mipomersen patients completed the clinical study. Four patients from the mipomersen arm discontinued treatment due to an adverse event.

The mean percent change in LDL-C was -24.7% in the mipomersen group versus -3.3% in the placebo group ($p<0.001$). The below figure taken from the sponsor's submission depicts the group changes in LDL-C over the course of treatment.



In analyses of secondary efficacy endpoints, the mean percent change in Apo B was -27% in the mipomersen group and -2.5% in the placebo group ($p<0.001$). The mean percent change in total cholesterol was -21% in the mipomersen group and -2.0% in the placebo group ($p<0.001$). The mean percent change in non-HDL-C was -25% in the mipomersen group and -3.0% in the placebo group ($p<0.001$).

In analyses of tertiary endpoints, the median percent change in triglyceride (TG) levels was -18% in the mipomersen group and 0.9% in the placebo group ($p<0.001$). The mean percent change in Lpa was -31% in the mipomersen group and -8% in the placebo group ($p<0.001$). The median percent change in VLDL-C was -17% in the mipomersen group and 2% in the placebo group ($p<0.001$). The median percent change in HDL-C was 15% in the mipomersen group and 4% in the placebo group ($p<0.001$).

7. Safety

The safety concerns with mipomersen include hepatic steatosis, transaminitis, injection-site reactions, flu-like symptoms, immune/antibody responses, and proteinuria. As detailed in the table from Dr. Craig's review and in the appendix of this memo, the safety assessment of mipomersen is derived from review of four phase 3 trials. There were a total of 390 subjects randomized into these studies in a 2:1 fashion. The controlled portion of these four studies was 6 months.

Hepatic Steatosis and Transaminitis

Given its mechanism of action, one would expect mipomersen to cause accumulation of fat (TG) in the liver. Hepatic fat was measured using MRI at baseline and Week 28 or early discontinuation in two of the phase 3 clinical trials. The sponsor defined hepatic steatosis as an increase in fat content of $\geq$ 5%.

The median increase in hepatic fat fraction was 9.6% in the mipomersen group versus 0.02% in the placebo group (below table from Dr. Craig's review). The maximal increase in hepatic fat content was 28% in the placebo group compared with 46% in the mipomersen group.

Approximately 62% of the patients in the mipomersen group compared with 8% of patients in the placebo group had increases ≥ 5% in hepatic fat. About 16% of the mipomersen-treated patients who developed ≥ 5% hepatic fat had at least one ALT value ≥ ULN compared with none of placebo-treated patients who developed ≥ 5% of hepatic fat.

Change in Hepatic Fat Content from Baseline to Week 28/Endpoint

Parameter	Statistic	Placebo (N=93)	Mipomersen (N=188)
Average Fat Fraction (%): Spectral Model	**Baseline**		
	n	75	148
	Mean (SD)	1.66 (6.17)	1.18 (5.99)
	Median (P25, P75)	-0.09 (-2.25, 4.28)	-0.29 (-2.15, 3.51)
	Min, Max	(-10.00, 20.24)	(-10.00, 29.86)
	Nominal Change		
	n	60	102
	Mean (SD)	0.43 (5.55)	12.16 (11.12)
	Median (P25, P75)	0.02 (-1.02, 1.42)	9.61 (2.33, 19.93)
	Min, Max	(-14.93, 28.29)	(-1.21, 46.00)
	95% CI	(-1.00, 1.86)	(9.97, 14.34)
Percent fat content change from baseline ≥5%, n/N (%)		5/60 (8.3)	63/102 (61.8)

A significantly greater proportion of patients treated with mipomersen versus placebo developed elevations in serum transaminases (AST and ALT). As shown in the below table taken from Dr. Craig's review, of the patients enrolled in the pivotal HoFH study, 12% from the mipomersen arm had an ALT ≥ 3xULN versus none from the placebo arm. A similar pattern was noted in the pooled phase 3 clinical trials.

Test	Incidence rate, n (%)	CS5 Placebo (N=17)	CS5 Mipo (N=34)	TOTAL Placebo (N=129)	TOTAL Mipo (N=261)
ALT maximum	> ULN and < 2 x ULN	7 (41.2)	12 (35.3)	42 (32.6)	95 (36.4)
	≥ 2 x ULN and < 3 x ULN	2 (11.8)	12 (35.3)	6 (4.7)	61 (23.4)
	≥ 3 x ULN and < 5 x ULN	0	1 (2.9)	1 (0.8)	31 (11.9)
	≥ 5 x ULN and < 10 x ULN	0	3 (8.8)	0 (0.0)	9 (3.4)
	≥ 10 x ULN and < 20 x ULN	0	0	0 (0.0)	3 (1.1)
	≥ 20 x ULN	0	0	0	0
	Total ≥ 3x ULN	**0**	**4 (12%)**	**1 (1%)**	**43 (16%)**
ALT	≥ 3 x ULN, two consecutive results (at least 7 days apart), n (%)	0	1 (2.9)	0 (0.0)	22 (8.4)
AST maximum	> ULN and < 2 x ULN	8 (47.1)	11 (32.4)	49 (38.0)	124 (47.5)
	≥ 2 x ULN and < 3 x ULN	1 (5.9)	3 (8.8)	4 (3.1)	27 (10.3)
	≥ 3 x ULN and < 5 x ULN	1 (5.9)	1 (2.9)	1 (0.8)	19 (7.3)

Test	Incidence rate, n (%)	CS5 Placebo (N=17)	CS5 Mipo (N=34)	TOTAL Placebo (N=129)	TOTAL Mipo (N=261)
	≥ 5 x ULN and < 8 x ULN	0	1 (2.9)	0 (0.0)	4 (1.5)
	≥ 8 x ULN	0	0	0 (0.0)	3 (1.1)
AST	≥ 3 x ULN, two consecutive results (at least 7 days apart), n (%)	0	1 (2.9)	0 (0.0)	11 (4.2)

Data from the phase 3 clinical trials that incorporated MRI assessment of hepatic fat indicate that there is a modest correlation (r=0.4) between changes in hepatic fat and serum ALT.

There were no cases of Hy's Law (concomitant increases in transaminases and bilirubin).

Injection-Site Reactions

Injection-site reactions were the most commonly-reported adverse events in the mipomersen development program: 84% of mipomersen-treated patients compared with 33% of placebo-treated patients. The specific adverse events considered within the injection-site reaction category included injection-site erythema, pain, hematoma, pruritus, swelling, and discoloration. Approximately 5% of mipomersen-treated subjects discontinued study drug due to an ISR compared with none of the placebo-treated subjects.

Flu-Like Symptoms

Flu-like symptoms included influenza-like illness, pyrexia, chills, myalgia, arthralgia, malaise, and fatigue starting within 2 days after an injection of mipomersen or placebo. In the phase 3 clinical trials, flu-like symptoms were reported by 30% of patients treated with mipomersen and by 16% of patients treated with placebo. Three percent of mipomersen-treated patients and 0.8% of placebo-treated patients discontinued treatment during the phase 3 clinical trials due to a flu-like symptom(s). The majority of these patients in both treatment groups experienced flu-like symptoms within the first four weeks of the studies. Dr. Craig notes in her review that there do not appear to be significant correlations between changes in plasma levels of cytokines or chemokines and the development of flu-like symptoms.

Antibody Response

As noted by Dr. Wang, mipomersen is highly immunogenic in humans. In the phase 3 clinical trials and an open-label extension, the percentage of subjects treated with mipomersen who developed anti-drug antibody (ADA) increased from 4% at Week 13 to 20% at Week 28 to 33% at Week 50. None of the subjects treated with placebo developed ADA. Some mipomersen-treated subjects developed ADA after 50 weeks of exposure. Mipomersen-treated subjects who were ADA positive had more FLS (71%) compared with subjects who were not ADA positive (53%). Dr. Craig points out in her review that a 46-year-old male treated with mipomersen developed a hypersensitivity reaction with angioedema after having been on the drug for five years. This subject tested positive for ADA once, with negative ADA results during the 10 months preceding the development of angioedema. The causal relationship

between the angioedema and mipomersen ADA is doubtful. There was no attenuation of LDL-C lowering in subjects who were ADA positive versus negative. One question that will be addressed in a post-marketing requirement, is whether subjects treated with mipomersen develop antibodies to double stranded DNA (dsDNA), increasing the odds for autoimmune disease.

Proteinuria

In the phase 3 clinical trials, 0.8% of subjects on placebo compared with 2.3% of subjects on mipomersen had proteinuria reported as an adverse event. Blood creatinine increased was reported for 1.6% and 1.1% of placebo and mipomersen subjects, respectively. Approximately 3% of placebo subjects versus 9.0% of mipomersen subjects had $\geq$ 1+ urine protein. There were no obvious differences in the changes from baseline to endpoint in eGFR noted between the placebo and mipomersen subjects. The clinical significance of the proteinuria observed in some subjects treated with mipomersen is unknown.

Cardiovascular Events Reported as Adverse Events

Approximately 9% of mipomersen subjects versus 6% of placebo subjects developed a cardiac or vascular adverse event. Angina and hypertension were the most commonly-reported of these events: 3.8% of mipomersen versus 1.6% of placebo and 6.5% of mipomersen versus 3.1% of placebo, respectively. In a retrospective analysis, 3.4% of mipomersen subjects compared with 3.1% of placebo subjects developed a "major adverse cardiovascular event" during the phase 3 clinical trials. Given the small number of events and the lack of adjudication, I do not believe that any conclusions can be drawn regarding the cardiovascular adverse event data.

Neoplasms

Malignant fibrous histiocytomas were observed in male and female rats treated chronically with mipomersen. In female, but not male, rats, there was an increase in malignant fibrosarcomas in mipomersen-treated animals. Dr. Craig writes in her review that 1.2% of mipomersen-treated subjects versus 0.5% of placebo-treated subjects were recorded as having developed a malignant neoplasm. There were no meaningful imbalances between treatment groups in organ-specific malignancies. The clinical development program for mipomersen is inadequate to assess the potential carcinogenic potential of the drug. I do not believe that the "imbalance" in reports of malignancies in mipomersen subjects compared with placebo subjects is clinically meaningful. Much longer treatment in a much larger number of subjects would be required to adequately evaluate mipomersen and cancer incidence.

Deaths

Four deaths were reported in the development program for mipomersen; three of these subjects were on mipomersen and one on placebo. The three deaths in the mipomersen groups were recorded as acute hepatic failure and two as acute myocardial infarction. The placebo death

was also an acute myocardial infarction. As Dr. Craig discusses in her review, there were confounding factors involved in the subject who died of hepatic failure. This individual was hospitalized for an acute myocardial infarction and had acetaminophen in his system when he died. Moreover, the hepatic failure occurred four months after he completed treatment with mipomersen. The case has been reviewed by two FDA hepatologists. They concluded that the hepatic failure was most likely secondary to a myocardial infarction (i.e., vascular collapse).

Non-Fatal Serious Adverse Events

Eight percent of mipomersen subjects compared with 5.4% of placebo subjects reported at least one non-fatal serious adverse event during the phase 3 clinical trials. The majority of the events were coded as cardiac disorders (as described above). One subject, a 63-year-old female treated with mipomersen developed transaminitis which was recorded as a serious adverse event. The narrative for this case is provided in Dr. Craig's review. It supports a probable causal relationship with mipomersen.

Adverse Events Leading to Discontinuation

In the phase 3 clinical trials, 18% of mipomersen-treated subjects and 2.3% of placebo-treated subjects discontinued study drug due to an adverse event. Injection-site reactions, flu-like symptoms, and transaminitis were the most common reasons for discontinuation in the mipomersen subjects.

Common Adverse Reactions

The most commonly reported adverse reactions (incidence > 10% and greater than placebo) were injection-site reaction, flu-like symptoms, nausea, headache, and elevations in serum transaminases.

8. Advisory Committee Meeting

The Division's advisory committee met on 18 October 2012 to discuss the efficacy and safety of mipomersen when used as a therapeutic option for patients with HoFH. When asked if the efficacy and safety data for mipomersen supported marketing for the treatment of HoFH, the committee voted 9 "yes" and 6 "no". Among the committee members who voted against approval, the modest mean lowering of LDL-C was insufficient to offset the potential safety concerns, in particular, liver toxicity.

9. Pediatrics

Because the treatment of HoFH is an orphan indication, the company was not required to address the study of mipomersen in the pediatric population. If the company conducts a dedicated clinical trial in pediatric subjects with HoFH, the data from such a trial would be included in the product's labeling. Because HoFH is most often diagnosed during childhood, the sponsor will be encouraged to conduct a dedicated trial in the pediatric population.

10. Other Relevant Regulatory Issues

The Office of Surveillance and Epidemiology and the Office of Prescription Drug Promotion evaluated the proposed tradename, Kynamro. They found the name acceptable. I agree with this assessment.

Dr. Craig notes in her review that the sponsor was unable to obtain the financial information for five principal investigators and 31 sub-investigators involved in study 3500108. Of the investigators involved in the phase 3 clinical trials that provided financial information, the sponsor has certified that none entered into a financial agreement with the company.

Routine inspection of clinical sites by the Office of Scientific Investigation did not uncover any significant deficiencies or irregularities in reporting of clinical data.

It has been determined that in order for the potential benefits of mipomersen to outweigh the potential risk of liver injury a Risk Evaluation and Mitigation Strategy (REMS) will be required for approval. The components of the REMS include 1) elements to assure safe use, 2) an implementation system, and 3) a timetable for submission of assessments. The elements to assure safe use include A) health care professionals who prescribe mipomersen are specially certified, B) pharmacies that dispense mipomersen are specially certified, and C) mipomersen will be dispensed to patients with evidence or other documentation of safe-use conditions. The goals of the REMS are 1) to educate prescribers about the potential risk of hepatotoxicity associated with the use of mipomersen, 2) to educate prescribers of the need to monitor patients during treatment per the product labeling, and 3) to restrict access to mipomersen to patients with a phenotype consistent with HoFH.

The sponsor will be required to conduct four postmarketing studies: 1) development and validation of a sensitive assay to assess for the presence of antibodies to double-stranded DNA to allow for testing of patients treated with mipomersen, 2) a study to assess for the presence of antibodies that bind to double-stranded DNA among patients treated with mipomersen, 3) a long-term prospective observational study of patients with HoFH treated with mipomersen to evaluate known and potential serious risks related to mipomersen, including hepatotoxicity, malignancy, and autoimmune disorders, and 4) an assessment and analysis of spontaneous reports of serious hepatic abnormalities, malignancy, and immune-mediated reactions in patients treated with mipomersen.

11. Decision/Risk-Benefit Assessment

HoFH is a rare but serious disorder associated with premature cardiovascular morbidity and mortality. There are very few treatment options for HoFH. Mipomersen lowered LDL-C by an average of approximately 21% relative to placebo. While ample data support the use of LDL-C as a surrogate for cardiovascular disease with statins, there will always be some uncertainty about whether the LDL-C lowering with a novel lipid-altering drug, including mipomersen,

equates with reduced cardiovascular morbidity and mortality. However, conducting a cardiovascular outcomes trial of mipomersen in patients with HoFH is not feasible given the prevalence of this lipid disorder. Moreover, the current safety database does not support the use of mipomersen in lower-risk subjects generally studied in large cardiovascular outcomes trials of lipid-altering drugs.

The chief safety concern with mipomersen is potential liver injury secondary to chronic fat accumulation. Larger and longer-term exposure to mipomersen are necessary to adequately define this potential risk. Other safety issues include injection-site reactions, flu-like symptoms, and proteinuria.

I believe the mipomersen efficacy and safety data, albeit limited, support its approval as an adjunct to lipid-lowering medication and diet to reduce LDL-C, Apo B, total cholesterol, and non-HDL-C in patients with HoFH. A REMS, which includes specially certified prescribers and pharmacies and documentation of safe use conditions, will enhance the safe and effective use of mipomersen in the target population.

If the post-marketing experience in patients with HoFH and the investigational use in moderate-risk patients (e.g., "severe heterozygous familial hypercholesterolemia") indicate that mipomersen is well tolerated, consideration should be given to requiring a cardiovascular outcomes trial to document that the drug reduces the risk for cardiovascular events.

Appendix

Mipomersen Phase 3 Clinical Trials

Requirement	ISIS301012-CS5 (Pivotal)	MIPO3500108 (Supportive)	ISIS301012-CS7 (Supportive)	ISIS301012-CS12 (Supportive)
Diagnosis	HoFH (See Table 5 for definition)	Severe hypercholesterolemia (See Table 5 for definition)	HeFH (See Table 5 for definition)	High-risk according to NCEP ATP III guidelines (See Table 5 for definition)
Screening Lipid Levels	Fasting LDL-C ≥130 mg/dL and TG <350 mg/dL	Fasting LDL-C ≥300 mg/dL, or fasting LDL-C ≥200 mg/dL in the presence of CAD, and TG <350 mg/dL	Fasting LDL-C ≥100 mg/dL and TG <200 mg/dL	Fasting LDL-C ≥100 mg/dL and TG <200 mg/dL
Comorbidities	[none required]	CAD required if fasting LDL-C ≥200 mg/dL but <300 mg/dL (See Table 5 for definition)	CAD (See Table 5 for definition)	CHD or CHD risk equivalents as defined by NCEP ATP III guidelines (See Table 5 for definition)
Lipid-lowering Regimen	Stable low-fat diet and stable lipid-lowering regimen prior to screening	Stable low-fat diet and stable, maximally tolerated lipid-lowering regimen, including statin therapy	Stable low-fat diet and stable lipid-lowering regimen, including maximally tolerated statin therapy	Stable low-fat diet and stable lipid- lowering regimen, including maximally tolerated statin therapy
Other Medications	Not required, but if on allowed lipid-lowering therapies (i.e., statins, cholesterol absorption inhibitors, bile acid sequestrants, niacin), dose and regimen had to be stable for at least 12 weeks prior to screening and expected to remain stable throughout trial	Required: Additional lipid-lowering therapy (e.g., bile acid sequestrants, niacin/nicotinic acid, fibrates) for at least 8 weeks prior to screening	Not required, but if on a stable dose of another class of lipid-lowering therapy (e.g., cholesterol absorption inhibitors, bile-acid sequestrants, niacin, and fibrates), must have been for at least 12 weeks prior to screening and expected to remain stable throughout trial	Additional therapies not required, but if on a dose of another class of lipid-lowering therapy (e.g., cholesterol absorption inhibitors, bile-acid sequestrants, fibrates, niacin, fish oil), dose must have been stable for at least 8 weeks prior to screening, and expected to remain on it through Week 28
Demographic and Other Baseline Characteristics	Male or female ≥12 years old, Tanner stage >2; body weight ≥40 kg	Male or female ≥18 years old	Male or female ≥18 years old	Male or female ≥18 years old
Apheresis	No apheresis within 8 weeks of screening	No apheresis within 12 weeks of screening	No apheresis within 8 weeks of screening	None

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/s/

ERIC C COLMAN
01/29/2013