CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203568Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 203568	Submission Date(s): 03/29/2012
Brand Name	TBD
Generic Name	Mipomersen Sodium
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OCP Division	Clinical Pharmacology 2
OND division	Metabolism and Endocrinology Products
Sponsor	Genzyme Corporation
Submission Type; Code	NDA 505(b)(1); Standard
Formulation; Strength(s)	Single-use vial containing 1 mL of a 200 mg/mL solution Single-use pre-filled syringe containing 1 mL of a 200 mg/mL solution
Proposed Indication	as an adjunct to maximally tolerated lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol, apolipoprotein B, total cholesterol, non-high density lipoprotein-cholesterol and lipoprotein (a) in patients with homozygous familial hypercholesterolemia

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1 Executive Summary

The sponsor, Genzyme Corporation submitted a 505(b)(1) application, seeking marketing approval for mipomersen sodium. Mipomersen sodium (ISIS 301012) is a 20-base, synthetic, oligonucleotide sodium salt and a first-in-class antisense inhibitor of apolipoprotein B-100 (apo B) synthesis. The sponsor is seeking marketing approval for mipomersen sodium as an adjunct therapy to maximally tolerated lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol, apolipoprotein B, total cholesterol, non-high density lipoprotein-cholesterol and lipoprotein in patients with homozygous familial hypercholesterolemia (HoFH).

HoFH is a rare genetic disorder in which both LDL-receptor alleles are defective. According to the sponsor, the overall prevalence of HoFH in US is about 1 in 1,000,000 persons, which extrapolates to approximately 300 individuals in the US. Untreated HoFH individuals have very high concentrations of LDL-C, in the range of 650 to 1000 mg/dL. Mipomersen received Orphan Drug Designation (No.06-2214) for the treatment of HoFH on May 23, 2006.

Mipomersen sodium is an apo B synthesis inhibitor, which binds to a specific segment of the coding region of the mRNA for apo B, thus inhibiting the synthesis of this target. The efficacy of mipomersen for the proposed indication is evaluated in one pivotal placebo-controlled, double-blind Phase 3 clinical study conducted in patients with HoFH and three supportive Phase 3 studies in patients with severe heterozygous familial hypercholesterolemia (HeFH), patients with HeFH and coronary artery disease (CAD), and patients with high cardiovascular risk hypercholesterolemia.

The proposed formulations are a) single-use vial containing 1 mL of a 200 mg/mL solution b) single-use pre-filled syringe containing 1 mL of a 200 mg/mL solution. The proposed dose of mipomersen is 200 mg once weekly as subcutaneous (SC) injection.
The sponsor used 200 mg once weekly SC dose in all of the Phase 3 clinical trials. The selection of 200 mg once weekly dose for the Phase 3 trials was based on several Phase 2 dose finding trials where increasing doses of up to 400 mg once weekly resulted in increase in change from baseline in LDL-C lowering. However, doses above 200 mg resulted in increase in safety related events such as increased hepatic enzyme elevation and flu like symptoms.

The clinical pharmacology program consists of single- and multiple-dose studies evaluating pharmacokinetic (PK) profiles of mipomersen, a relative bioavailability study, *in-vitro* drug-drug interaction studies, *in-vivo* drug-drug interaction studies with lipid lowering agents (simvastatin and ezetimibe) and warfarin. Exposure-response analysis was performed to evaluate the relationships between exposure of mipomersen to the efficacy and safety data obtained from the Phase 3 trials.

1.1 Recommendation

The Office of Clinical Pharmacology has reviewed the clinical pharmacology data submitted under NDA 203568 (dated 03/29/2012), and finds it acceptable.

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1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology Findings

Pharmacokinetics

The pharmacokinetics (PK) of mipomersen was characterized following single and multiple dose administration in healthy subjects. The PK of mipomersen was also studied in several Phase 2 studies in patients with primary hypercholesterolemia, HoFH and HeFH following multiple dose administration. Mipomersen plasma exposure increased with increasing dose over studied dose range of 30 mg to 400 mg.

Absorption: Plasma bioavailability (relative to IV infusion) of mipomersen following subcutaneous administration ranged from 54% to 78% over a dose range of 50 mg to 200 mg. Peak plasma concentration will typically reach with 3 to 4 hours following SC administration.

Distribution:

Plasma protein binding of mipomersen was high (>90%) at concentrations of 1-8 μg/mL. Mipomersen mainly bound with albumin, α1-acid glycoprotein, and to α2-macroglobulin. Following SC administration mipomersen is rapidly distributed into the tissues with a distribution half life of around 2-5 hours.

Metabolism:

In-vitro studies in human liver microsomes showed that mipomersen is not metabolized by CYP450 enzymes. Mipomersen is believed to be metabolized in tissues by endonucleases to form shorter oligonucleotides that are then substrates for additional metabolism by exonucleases.

Elimination:

Following SC administration mipomersen has a prolonged terminal half-life of 22-51 days. Elimination of mipomersen occurs primarily through metabolism in tissues and excretion in urine. In healthy human subjects less than 2% of the administered dose was recovered in urine following 24 hr urine collection.

Dose/Exposure-Response relationships:

The sponsor used 200 mg once weekly SC dose in all of the Phase 3 trials. The selection of 200 mg once weekly dose for the Phase 3 trials was based on several Phase 2 trials where increasing doses of up to 400 mg once weekly resulted in increase in change from baseline in LDL-C lowering. However, doses above 200 mg resulted in increase in safety related events such as increased hepatic enzyme elevation and flu like symptoms.

During the review cycle it was found that the antidrug antibody can interfere with the bioanalytical method which was used to analyze the mipomersen concentration in the plasma. Given this limitation and the fact that approximately 33% subjects developed antidrug antibody during the course of treatment in the Phase 3 trial conducted in HoFH

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patients, the exposure response analysis for efficacy was conducted just for exploratory purposes. The sponsor studied only 200 mg once weekly dose in the Phase 3 trial in HoFH patients. Exposure response analysis for efficacy in patients with HoFH showed that % change from baseline in LDL-C decreases with increasing steady state plasma trough concentration (Figure 6). Efficacy relationship with safety showed that higher efficacy in terms of reduction in % change from baseline in LDL-C results in increase in liver fat accumulation. The results are consistent with mechanism of action of the drug where apo-B inhibition is expected to result in liver fat accumulation.

Intrinsic factors:

Age, gender, race, and weight: Sponsor's claim of no dose adjustment based on age, gender, race and weight results from population pharmacokinetics (PopPK) analysis. PopPK analysis includes study results from short term Phase 1, Phase 2 trials and long term Phase 3 and extension trials. During the review cycle it was found that the antidrug antibody can interfere with the bioanalytical method which was used to analyze the mipomersen concentration in the plasma. According to the sponsor's analysis, 37.5 % of the Phase 3 patients are antidrug antibody positive and 72% patients are antidrug antibody positive in the extension trials. Given this affect of antidrug antibody on the bioanalytical method, the exposure data from these clinical trials are not reliable and hence labeling claims regarding age, race, gender and weight that are based on population PK analysis are not acceptable.

Renal impairment: No formal PK studies have been conducted in patients with renal impairment. Analysis of trough concentration data from Phase 3 clinical trials around week 13 showed that mild and moderate renal impairment had no impact on the pharmacokinetics of mipomersen.

Hepatic impairment:

The effects of hepatic impairment on mipomersen PK have not been studied. *In-vitro* studies in human liver microsomes showed that mipomersen is not metabolized by CYP450 enzymes. Mipomersen is believed to be metabolized in tissues by endo- and exonucleases to form shorter oligonucleotides. Thus, from a clinical pharmacology perspective, the applicant's recommendation of no dose adjustment for individuals with hepatic impairment is reasonable. However, based on the mechanism of action of this drug, where the liver is the primary site of action, and the available safety and efficacy data from the Phase 3 trials, the sponsor recommends contraindication of mipomersen in individuals with significant hepatic dysfunction, which may include persistent elevations of serum transaminases.

Extrinsic factors:

Drug-Drug Interaction (DDI)

In vitro studies:

In vitro studies have demonstrated that mipomersen is not a substrate for CYP450 metabolism. Mipomersen concentrations up to 800 µg/mL did not inhibit CYP1A2,

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CYP2C9, CYP2C19, CYP2D6, and CYP3A4 *in-vitro*. Mipomersen did not induce CYP1A2, CYP2B6, and CYP3A4 enzymes in plated cultures of cryopreserved human hepatocytes at the concentrations tested (1.0 to 500µg/mL). Mipomersen was not a substrate or inhibitor P-glycoprotein.

In-vivo studies: Figure 1 summarizes the impact of other drugs on the pharmacokinetics of mipomersen. Figure 2 summarizes the effect of mipomersen on the pharmacokinetics of co-administered drugs. In summary, there was no impact of simvastatin, ezetimibe and warfarin on the pharmacokinetics of mipomersen. Although, based on their metabolic routes no DDI is expected between mipomersen and simvastatin and ezetimibe. Co-administration of mipomersen with simvastatin and ezetimibe showed reduction in C_{max} and increased AUC values for both simvastatin and ezetimibe. These changes were considered to be clinically relevant and thus no dose adjustment is needed.

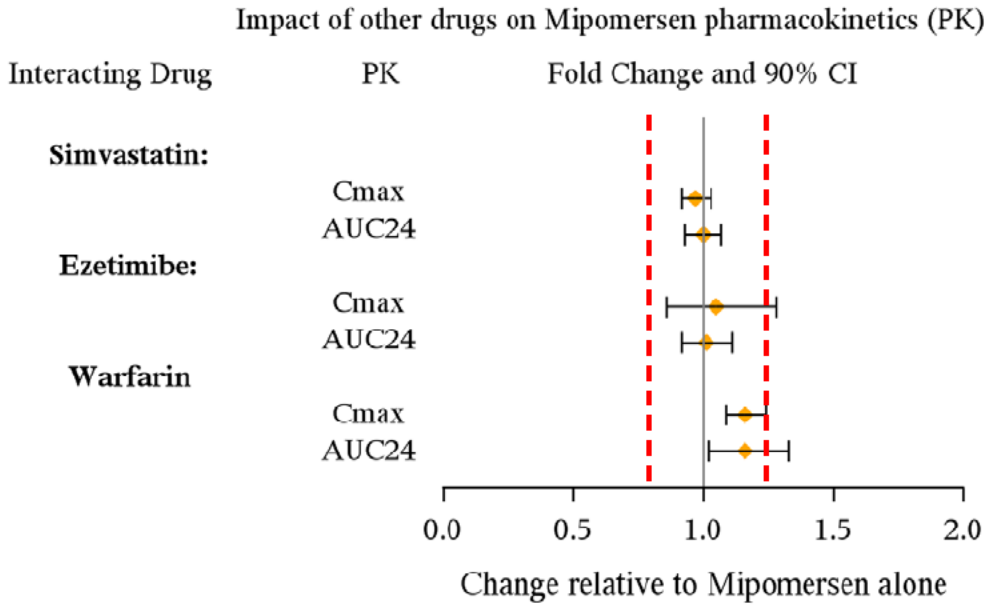

Figure 1: Impact of other drugs on the pharmacokinetics of mipomersen

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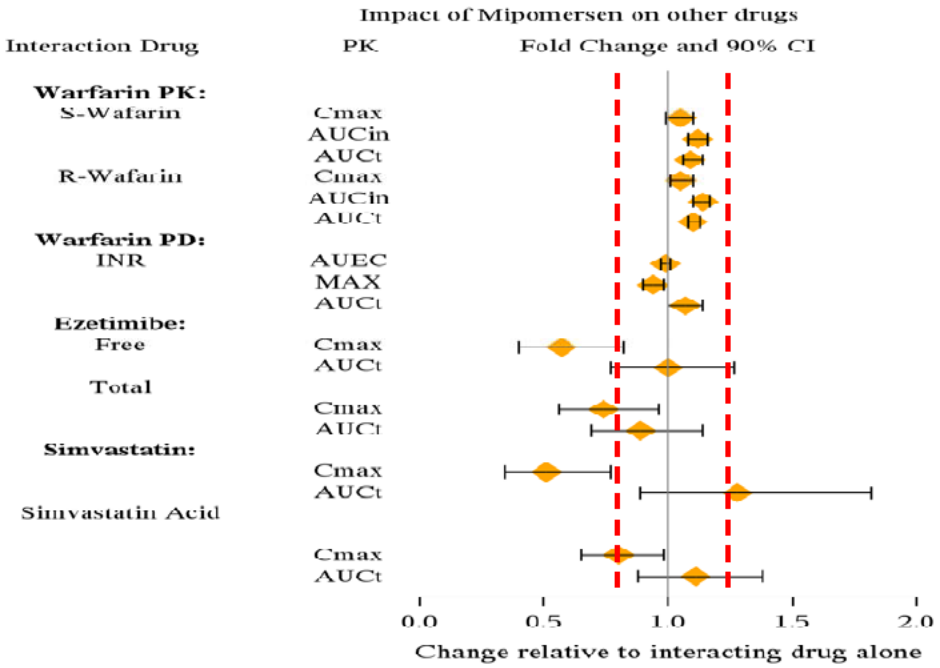

Geometric mean with 95% confidence intervals

Figure 2: Impact of mipomersen on the pharmacokinetics of other drugs

Pivotal Bioequivalence Trials

There were no pivotal BE studies in this application. The Sponsor used the to-be-marketed commercial formulation in their pivotal clinical pharmacology and Phase 3 trials.

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2 Question-Based Review (QBR)

2.1 General Attributes of the Drug and Drug Product

The sponsor Genzyme Corporation has submitted a 505(b)(1) application, seeking marketing approval for mipomersen sodium. Mipomersen sodium (ISIS 301012) is a 20-base, synthetic, oligonucleotide sodium salt and a antisense inhibitor of apolipoprotein B-100 (apo B) synthesis. Mipomersen is a first-in-class compound for LDL-c reduction via apo B inhibition. Unlike the statins, mipomersen is not dependent on LDL receptor (LDLr) up regulation, or on LDLr function for its pharmacodynamic effects.

Mipomersen is a phosphorothiolated oligonucleotide and therefore differs from naturally occurring oligonucleotides by substitution of the phosphate di-ester internucleotide linkage by a phosphorothioate diester. Other modifications include methylation of the cytosine bases at the 5-position and substitution in the 2′-position with a 2-methoxyethyl moiety for 10 of 20 nucleotides. These modifications are inteded to increase the stability of the oligonucleotides towards nucleases. Mipomersen is the first systemically administered phosphorothioate antisense oligonucleotide (PS ASO).

2.1.1 What pertinent regulatory background or history of this drug?

HoFH is a rare genetic disorder in which both LDL-receptor alleles are defective. According to the sponsor, the overall prevalence of HoFH in US is about 1 in 1,000,000 persons, which extrapolates to approximately 300 individuals in the US. Untreated HoFH individuals have very high concentrations of LDL-C, in the range of 650 to 1000 mg/dL. Mipomersen received Orphan Drug Designation (No.06-2214) for the treatment of HoFH on May 23, 2006.

2.1.2 What is the mechanism of action and therapeutic indication?

Mipomersen sodium is a first-in-class apolipoprotein B-100 (apo B) synthesis inhibitor, which binds to a specific segment of the coding region of the mRNA for apo B, thus inhibiting the synthesis of this target. The base sequence of mipomersen is complementary to a 20-nucleotide segment of the coding region of the messenger RNA (mRNA) for apoB, to which it binds by Watson and Crick base-pairing (Figure 3).

The hybridization (binding) of mipomersen to the cognate mRNA results in reduced translation of the mRNA to protein by multiple mechanisms including activation of RNase H-mediated degradation of the cognate mRNA. This leads to decreased synthesis of apo-B in the liver (the primary site of apo B generation), a reduction in transport of apo-B containing lipoprotein out of the liver and a reduction in circulating LDL cholesterol (LDL-C).

Mipomersen sodium is indicated as an adjunctive therapy to maximally tolerated lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol, apolipoprotein B, total cholesterol, non-high density lipoprotein-cholesterol and lipoprotein in patients with homozygous familial hypercholesterolemia.

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Figure 3: Figure showing the proposed mechanism of action

2.1.3 What are the proposed dosage and route of administration?

Mipomersen sodium drug product is a sterile solution for injection in vials and pre-filled syringes. The formulation consists of mipomersen sodium at 200 mg per mL in water, with pH adjustment as required to 7.5-8.5. The drug product is intended for subcutaneous injection of 200 mg dose once weekly

2.1.4 What are the highlights of the chemistry and physicochemical properties of the drug substance and the formulation of the drug product?

Highlights of the chemistry and physiological properties of the drug substance mipomersen sodium are shown in Table 1.

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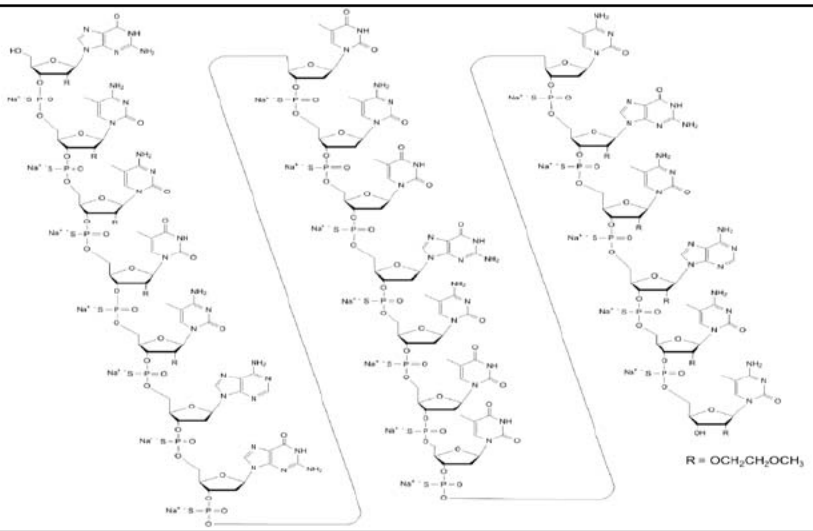
Table 1: Chemistry and physicochemical properties of the drug substance

	Mipomersen
Description	white to yellow, amorphous, hygroscopic solid
Chemical Name	2′-O- (2-methoxyethyl)-*P*-thioguanylyl-(3′-*O*→5′-*O*)-2′-O-(2-methoxyethyl)-5-methyl-*P*-thiocytidylyl-(3′-*O*→5′-*O*)-2′-O-(2-methoxyethyl)-5-methyl-*P*-thiocytidylyl-(3′-*O*→5′- *O*)-2′-O-(2-methoxyethyl)-5-methyl-*P*-thiouridylyl-(3′-*O*→5′-*O*)-2′-O-(2-methoxyethyl)- 5-methyl-*P*-thiocytidylyl-(3′-*O*→5′-*O*)-2′-deoxy-*P*-thioadenylyl-(3′-*O*→5′-*O*)-2′-deoxy- *P*-thioguanylyl-(3′-*O*→5′-*O*)-*P*-thiothymidylyl-(3′-*O*→5′-*O*)-2′-deoxy-5-methyl-*P*-thiocytidylyl-(3′-*O*→5′-*O*)-*P*-thiothymidylyl-(3′-*O*→5′-*O*)-2′-deoxy-*P*-thioguanylyl-(3′- *O*→5′-*O*)-2′-deoxy-5-methyl-*P*-thiocytidylyl-(3′-*O*→5′-*O*)-*P*-thiothymidylyl-(3′-*O*→5′- *O*)-*P*-thiothymidylyl-(3′-*O*→5′-*O*)-2′-deoxy-5-methyl-*P*-thiocytidylyl-(3′-*O*→5′-*O*)-2′- O-(2-methoxyethyl)-*P*-thioguanylyl-(3′-*O*→5′-*O*)-2′-O-(2-methoxyethyl)-5-methyl-*P*-thiocytidylyl-(3′-*O*→5′-*O*)-2′-O-(2-methoxyethyl)-*P*-thioadenylyl-(3′-*O*→5′-*O*)- 2′-O-(2- methoxyethyl)-5-methyl-*P*-thiocytidylyl-(3′-*O*→5′-*O*)-2′-O-(2-methoxyethyl)-5-methylcytidine, nonadecasodium
Molecular Formula	C230H305N67O122P19S19Na19
Molecular Weight	7594.9 g/mol
Structural Formula	
Solubility	Mipomersen sodium is freely soluble in water and in aqueous sodium acetate buffer (pH 3.5), soluble in methanol, and insoluble in acetone, ethanol, acetonitrile, isopropyl alcohol, and chloroform.

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Formulation: Mipomersen sodium injection, 200 mg/mL is a sterile, preservative-free, clear, and colourless to slightly yellow aqueous solution for subcutaneous injection. Table 2 shows the composition of Mipomersen Sodium Injection, 200 mg/mL, in vials.

Table 2: Composition of mipomersen sodium injection, 200 mg/mL, in vials

Component	Quality Standard	Function	Quantity per Vial[a]
Mipomersen sodium	In-house	Active Ingredient	200 mg
Water for injection	PhEur[b] USP-NF[c]	(b) (4)	
Sodium hydroxide (1 N)	PhEur USP-NF	pH adjustment	Sufficient to reach target pH
Hydrochloric acid (1 N)	PhEur USP-NF	pH adjustment	Sufficient to reach target pH

[a] These values are calculated for the label claim of 1.0 mL. (b) (4)
[b] European Pharmacopoeia
[c] United States Pharmacopoeia-National Formulary

Source: Sponsor's report on quality overall summary of drug product (2.3.P.1)

2.1.5 Is any OSI (Office of Scientific Investigation) inspection requested for any of the clinical studies?

No, OSI inspection was not requested from clinical pharmacology standpoint. The sponsor used proposed to-be-marketed formulation in the Phase 3 trials and hence there were no pivotal bioequivalence studies in this NDA.

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2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The clinical development program for mipomersen is comprised of 20 clinical studies, including 8 Phase 1 studies, 6 Phase 2 studies, 4 placebo-controlled Phase 3 studies, and 2 open label extension (OLE) studies (one Phase 2 and one Phase 3)

Efficacy and Safety Program (Phase 3 Program):

The safety and efficacy of mipomersen in the target population is demonstrated by results from 1 pivotal Phase 3 study in HoFH patients, 3 supportive Phase 3 studies in other high-risk hypercholesterolemic populations and ongoing OLE studies. Table 3 provides an overview of sponsor's Phase 3 development program.

Table 3: Overview of trials for efficacy evaluation

Study	Description
ISIS 301012-CS5	Phase 3 randomised, double-blind, placebo-controlled efficacy and safety study in patients with HoFH on lipid-lowering therapy. A total of 51 male and female subjects were enrolled in this study.
MIPO3500108	A randomised, double-blind, placebo-controlled efficacy and safety study in patients with Severe HeFH and on a maximally tolerated lipid-lowering regimen. A total of 58 male and female subjects were enrolled in this study
ISIS 301012-CS7	Phase 3 randomised, double-blind, placebo-controlled efficacy and safety study inpatients with HeFH and CAD on lipid-lowering therapy. A total of 124 male and female were enrolled in this study
ISIS 301012-CS12	Phase 3 randomised, double-blind, placebo-controlled efficacy and safety study in patients with high-risk hypercholesterolemia (CHD or CHD-risk equivalent) on lipid-lowering therapy. A total of 157 male and female were enrolled in this study
Open Label Extension Study ISIS 301012-CS6:	OLE to provide long-term safety and efficacy data in 141 patients who completed ISIS 301012-CS5, MIPO3500108, or ISIS 301012- CS7.

For all four Phase 3 trials, the primary efficacy endpoint was the percent change from baseline in LDL-C between treatment groups at week 28. Secondary efficacy endpoints include the percent change in apo B, TC and non-HDL-C from baseline.

Figure 4 shows the mean percent change in LDL-C over time in the pivotal phase 3 trials with HoFH patients (ISIS 301012-CS5). Furthermore, data from three supportive Phase 3

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studies (MIPO3500108, ISIS 301012- CS7, and ISIS 301012-CS12) demonstrated that mipomersen therapy resulted in a statistically significant mean percent reduction in LDL-C compared with placebo (Figure 5).

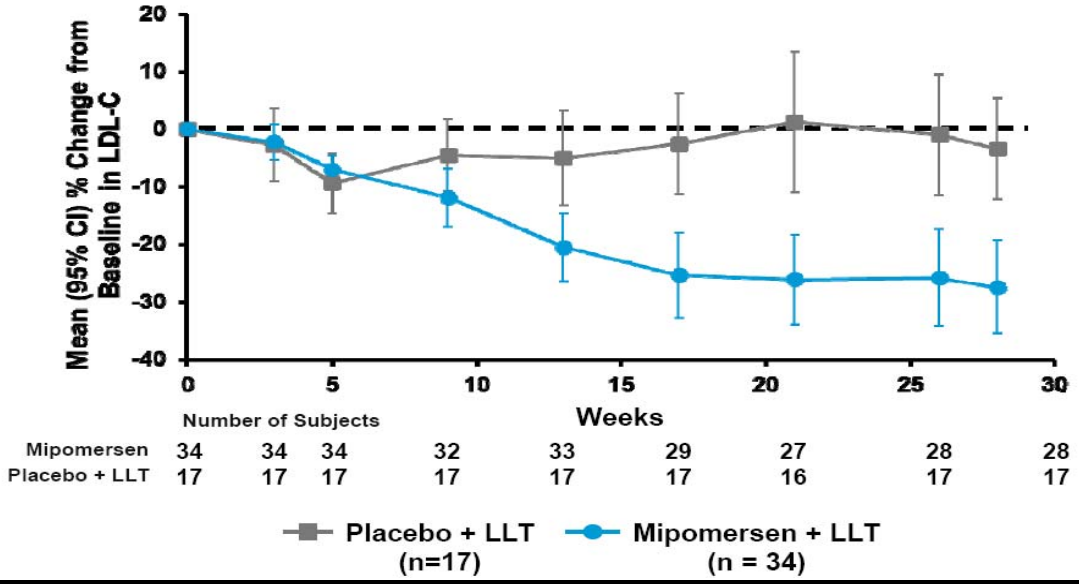
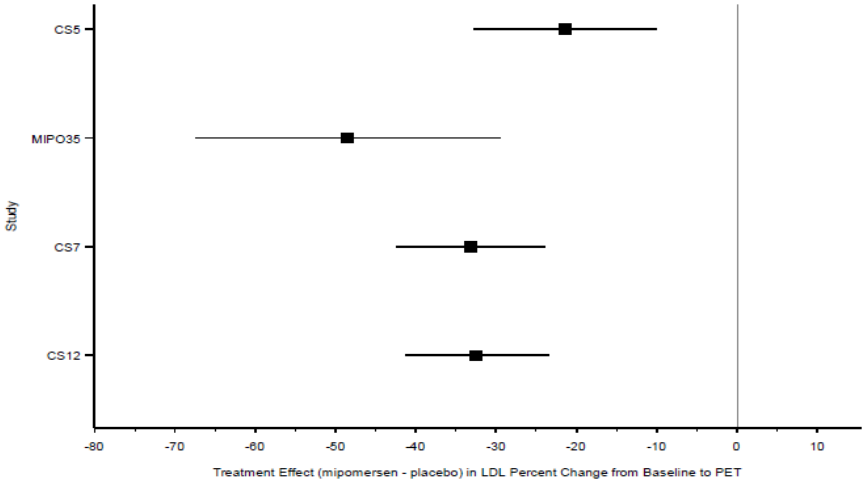


Figure 4: Mean percent change in LDL-C in patients in pivotal study

CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; Vertical bars indicate 95% confidence intervals

Source: Sponsor's AC briefing Document Pg 18.



CS5, Study ISIS 301012-CS5; CS7, Study ISIS 301012-CS7; CS12, Study ISIS 301012-CS12; LDL, low-density lipoprotein cholesterol; MIPO35, Study MIPO3500108; PET, primary efficacy time point

Figure 5: Low-density lipoprotein cholesterol percent change from baseline to primary efficacy time point treatment effects (difference between mipomersen and placebo treatment) and 95% confidence intervals for Phase 3 clinical studies

Source: Sponsor's Clinical Overview, Figure 2, page 45

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Clinical Pharmacology Program:
The clinical pharmacology program for mipomersen is shown in Table 4.

Table 4: Overview of Clinical Pharmacology studies

Phase 1 Studies	Description
ISIS 301012-CS1	Dose ranging study in healthy volunteers with mild hypercholesterolemia
ISIS 301012-CS101	Proof-of-concept study to evaluate oral formulation in healthy volunteers with mild hypercholesterolemia
ISIS 301012-CS301	Study to investigate mechanism of injection site reactions (ISRs) in healthy volunteers
ISIS 301012-CS2	Drug-drug pharmacokinetic (PK) interaction study in healthy volunteers
MIPO2900210	A drug-drug interaction study to assess the effects of mipomersen on warfarin pharmacodynamics (PD) and PK in healthy adult subjects
MIPO2800209	A randomised, double-blind crossover study to define the ECG effects of mipomersen in healthy men and women
MIPO3200309	Relative bioavailability, PK, safety, and tolerability of three weeks of dosing with different SC regimens of mipomersen in healthy volunteers
MIPO3700710	A Phase 1 study to evaluate the pharmacokinetics, safety, and tolerability of single doses of mipomersen administered SC to Japanese healthy subjects

2.2.2 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

No. Please refer to the analytical section (Section 2.9) for further details.

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2.3 Exposure-Response

2.3.1 What are the characteristics of the exposure/dose-response relationship for effectiveness?

The sponsor conducted all Phase 3 trials using a 200 mg once weekly SC dose. The selection of 200 mg once weekly dose for the Phase 3 trials was based on several Phase 2 trials where increasing doses of up to 400 mg once weekly resulted in increase in change from baseline in LDL-lowering. However, doses above 200 mg resulted is increase safety related concerns such as increase hepatic enzyme elevation and flu like symptoms.

The sponsor studied only 200 mg once weekly dose in the pivotal Phase 3 trial in HoFH patients. Exposure response analysis for efficacy in patients with HoFH showed that % change from baseline LDL-C decreases with increasing steady state plasma trough concentration (Figure 6). However, this exposure response analysis is just for exploratory purposes and no definitive conclusion can be drawn from this analysis. Even though, this was an exploratory analysis, attempt was made to identify any baseline covariates that could explain the lower exposures and hence lower response in patients in the first two quartiles. None of the baseline covariates could explain the exposure difference among quartiles.

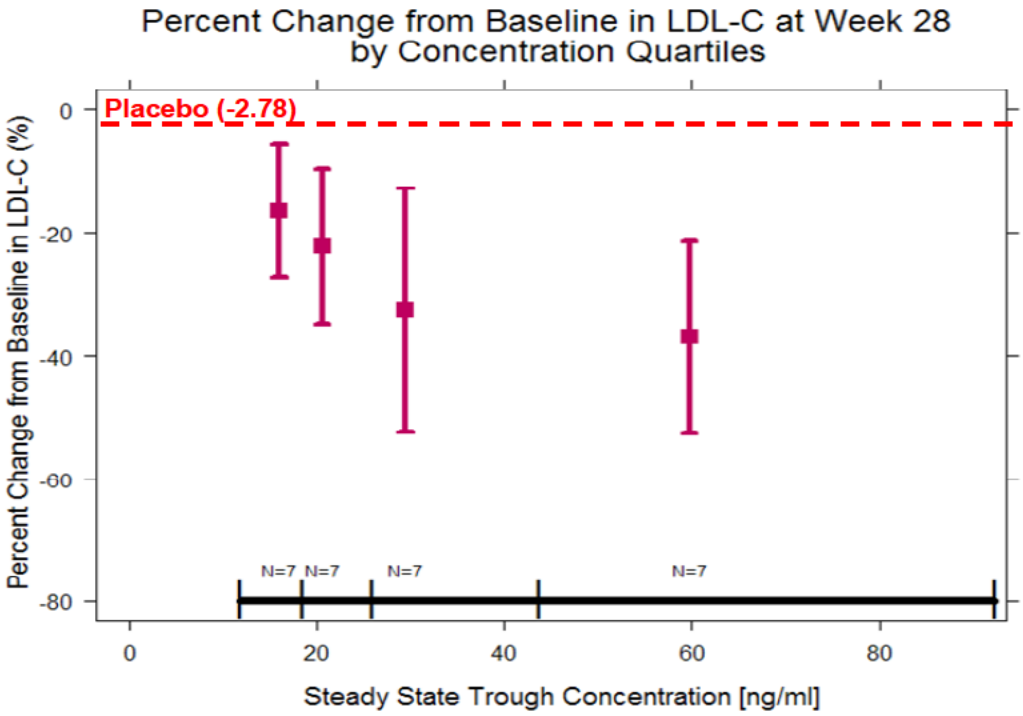

Figure 6: Percent change from baseline in LDL-c by concentration quartile in the pivotal Phase 3 trial.
The exposure range in each trough quartile is denoted by the horizontal black line along with the number of subjects in each quartile. Exposures are demonstrated as squares at the median exposure of each quartile. The vertical bars represent the mean change from baseline in LDL-c with 95% confidence interval.

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Reviewer's Comment: *During the review cycle it was found that the antidrug antibody can interfere with the bioanalytical method which was used to analyze the mipomersen concentration in the plasma. Therefore, the exposure data is not reliable. Given this limitation and the fact that approximately 33% subjects in this pivotal trial developed antidrug antibody during the course of treatment, the exposure response analysis shown here is just for exploratory purposes and no definitive conclusion can be drawn from it.*

2.3.2 ***What are the characteristics of the exposure/Dose-response relationship for Safety?***

The sponsor evaluated only one dose in the Phase 3 trials, so no dose-response relationship for safety can be conducted. However, based on safety from several Phase 2 trials (in patients with HeFH, patients with mild hypercholesterolemia, patients with HoFH and patient with primary hypercholesterolemia), the 200 mg once weekly dose was selected for the evaluation of Phase 3 trials. In the Phase 2 trials, where increasing doses of up to 400 mg once weekly resulted in increase in efficacy, doses above 200 mg resulted is increase safety related events such as increase hepatic enzyme elevation and flu like symptoms.

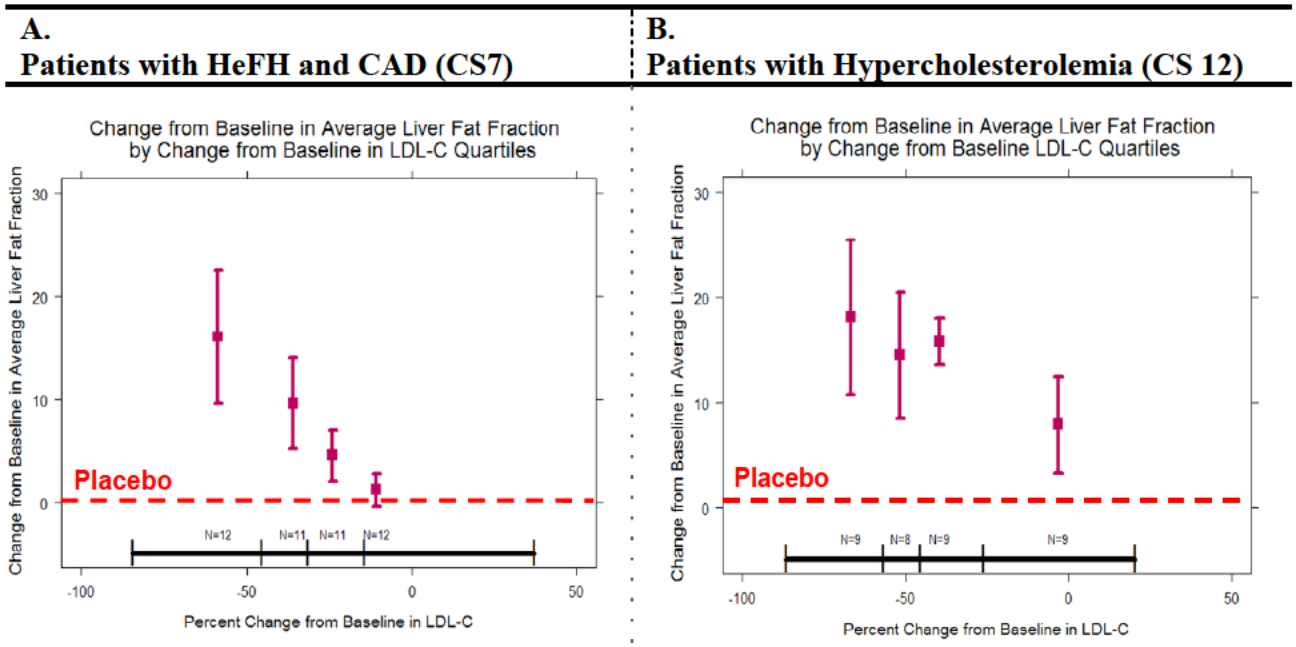

Figure 7: A) Percent change from baseline in average liver fat fraction by change from baseline in LDL-C quartile in patients with HeFH and CAD (Trial ISIS 301012-CS7). B) Percent change from baseline in average liver fat fraction by change from baseline in LDL-C quartile in patients with hypercholesterolemia (Trial ISIS 301012-CS12).

The change from base line in LDL-C is divided into four quartiles is denoted by the horizontal black line along with the number of subjects in each quartile. The change from base line in LDL-c is demonstrated as squares at the median exposure of each quartile. The vertical bars represent the mean change from baseline in average liver fat fraction with 95% confidence interval.

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Exposure-response analysis for safety was not conducted because the exposure measurements are not reliable due to the bioanalytical issues (See section 2.9 for further details). Some of the major safety concerns identified in the clinical program were liver fat accumulation, liver enzymes elevations, flu like symptoms and injection site reactions. We conducted an analysis investigating the effect of LDL-c lowering on liver fat accumulation. In two supporting Phase 3 trials the sponsor measured the fat accumulation in liver using MRI. Figure 7 showed that decrease in % change from baseline in LDL-C results in increase in liver fat accumulation. The results are consistent with the mechanism of action of the drug where apo-B inhibition is expected to result in liver fat accumulation.

2.3.3 Does mipomersen prolong the QT/QTc Interval??

The effect of mipomersen on the QT interval was assessed in a thorough ECG study (MIPO2800209 CSR) conducted in 60 healthy volunteers. The study was a Phase 1, randomized, double-blind, single-site, crossover study in healthy male and female subjects to determine if mipomersen administered as a single therapeutic (200 mg) SC and a single supratherapeutic (200 mg) IV dose delays cardiac repolarization as determined by the measurement of the QT/QTc interval.

FDA's interdisciplinary review team's thorough QT study (TQT) review concluded that no significant QTc prolongation effect of mipomersen (200-mg s.c. therapeutic dose and 200-mg i.v. 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 supratherapeutic dose (200 mg i.v.) produces mean Cmax and AUC values of 3.8-and 1.2- fold the mean Cmax and AUC for the therapeutic dose (200 mg s.c.). At these concentrations there are no detectable prolongations of the QT-interval.

2.4 What are the PK characteristics of the drug?

2.4.1 What are the single and multiple dose PK characteristic of mipomersen in healthy adult subjects?

Single Dose Pharmacokinetics

The single dose PK of mipomersen was characterized in Phase 1, placebo controlled, dose-ranging study following intravenous (IV) and SC administration to healthy volunteers with mild hypercholesterolemia (Study ISIS 301012-CS1). Twenty-nine (29) healthy volunteer subjects received either 50 mg (n = 8), 100 mg (n = 8), 200 mg (n = 9), or 400 mg (n = 4) mg per dose day and 7 subjects received placebo.

Figure 8 presents the pharmacokinetic profile and Table 5 summarizes the pharmacokinetic parameter of mipomersen following single dose. The mean time of maximum plasma concentration (T_{max}) following SC injection of mipomersen ranged from 2.6 h – 4.0 h. Absolute plasma bioavailability (BAV) of mipomersen following SC

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administration ranged from 54% to 78%, in comparison to i.v. infusion, and was independent of dose.

Table 5: Descriptive statistical summary of pharmacokinetic parameter estimates for mipomersen in healthy human volunteers following first s.c. injection (SD 1)

Dose (mg)	N	C_{max} (µg/ml)	T_{max} (hr)	$AUC_{0\text{-}48hr}$ (µg*hr/mL)	$AUC_{0\text{-}\infty}$ (µg*hr/mL)	Apparent Distribution $t_{1/2}$ (hr)	%F
50	3	1.40 ± 0.29	2.67 ± 0.58	7.27 ± 0.93	7.28 ± 1.01	1.85 ± 0.49	61.8 ± 0.7
100	3	1.45 ± 0.83	2.99 ± 0.99	14.5 ± 2.9	14.9 ± 2.8	4.22 ± 2.71	65.6 ± 12.8
200	4	3.14 ± 1.59	3.63 ± 2.98	38.0 ± 24.3	38.8 ± 24.9	3.58 ± 1.16	57.7 ± 34.6
400	4	7.60 ± 0.81	4.00 ± 1.63	106 ± 17	109 ± 18	5.18 ± 1.88	69.2 ± 7.3

Data are presented as Mean ± Standard Deviation

N	Number of subjects
C_{max}	Maximum plasma concentration
T_{max}	Time C_{max} observed
$AUC_{0\text{-}48hr}$	Partial area under the plasma concentration-time curve from time 0 to 48 hours after the start of dose administration
$AUC_{0\text{-}\infty}$	Area under the plasma concentration-time curve from time 0 to infinity
%F	Plasma bioavailability (%) following s.c. administration relative to i.v. (MD1)

Source: Sponsor's study report

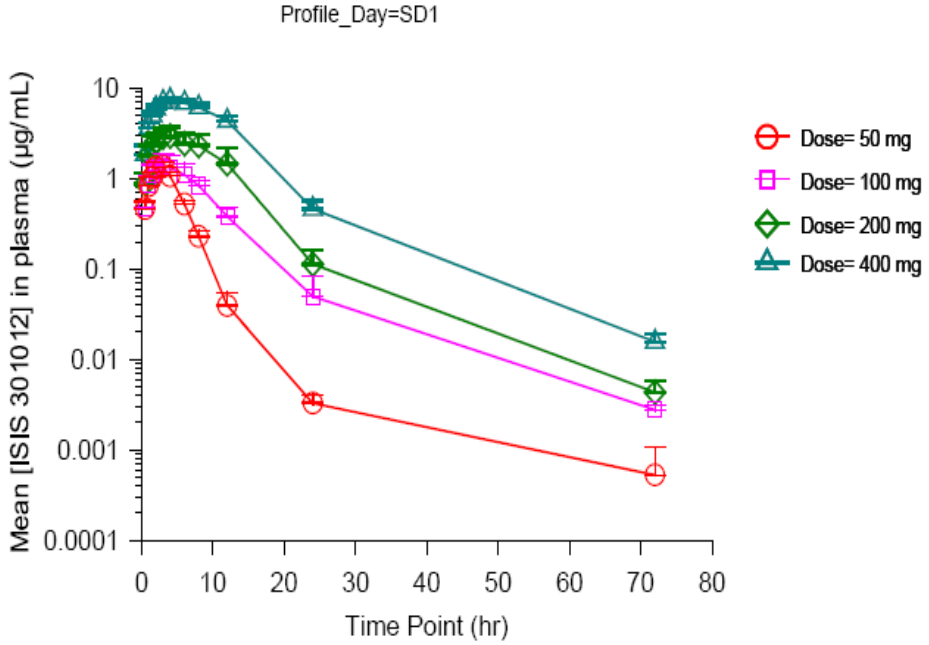

Figure 8: Mean plasma concentration-time profiles following single subcutaneous doses in healthy volunteers.

Source: Sponsor's summary of clinical pharmacology report.

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Multiple Dose Pharmacokinetics: Study (ISIS 301012-CS1)

The multiple dose PK of mipomersen was characterized in Phase 1, placebo controlled, dose-ranging study following intravenous (IV) and SC administration to healthy volunteers with mild hypercholesterolemia (Study ISIS 301012-CS1). In this study subjects after completing their single-dose period were continued into the multiple-dose (MD) period and received the same study drug (mipomersen or placebo) at the same dose, to which they had previously been randomised. The MD period consisted of three IV infusions (on day1, day 3 and day 5) over 2 hours every other day during the first week, followed by once weekly SC injections for 3 weeks (on day 8, day 15, and day 22) for a total of 6 doses over 22 days.

Figure 9 presents the pharmacokinetic profile and Table 6 summarizes the pharmacokinetic parameter of mipomersen following multiple doses. Following multiple doses the terminal elimination half life was approximately 23-46 days over a dose range of 50 mg to 200 mg following 22 days of treatment. The mean time of maximum plasma concentration (Tmax) following SC injection of mipomersen ranged from 3.2 h - 7.5 h.

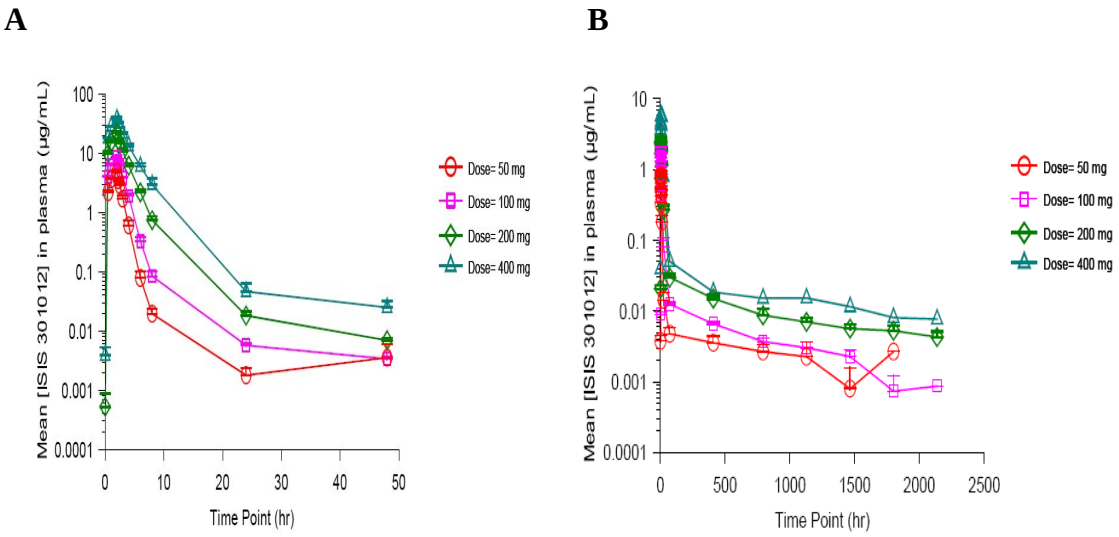

Figure 9: A) Mean plasma concentration-time profile following intravenous infusion (2-hour) in healthy volunteers (MD1) B) mean plasma concentration-Time profiles following multiple subcutaneous administration on day 22

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Table 6: Plasma pharmacokinetic parameters for mipomersen following 2-hour IV infusion (MD1) or final SC injection (MD22)

Dose in mg (mg/kg)	Route	N	Mean ± Standard Deviation					
			C_{max} (μg/mL)	T_{max} (hr)	AUC_{0-48hr} (μg*hr/mL)	Apparent Distribution $t_{1/2}$ (hr)	Terminal $t_{1/2}$ (days)	%F
50 mg (0.7±0.1)	IV	8	4.77 ± 1.08	1.96 ± 0.08	11.4 ± 2.9	0.67 ± 0.11	NC	NA
	SC	7	1.02 ± 0.26	3.58 ± 2.21	7.52 ± 1.59	3.50 ± 1.05	23.2	69.3 ± 8.8
100 mg (1.3±0.1)	IV	8	8.77 ± 1.01	1.95 ± 0.12	23.6 ± 3.1	0.84 ± 0.14	NC	NA
	SC	8	1.92 ± 1.00	3.75 ± 1.92	17.7 ± 3.5	4.77 ± 2.65	26.7 ± 12.4	76.2 ± 17.8
200 mg (2.7±0.5)	IV	8	21.5 ± 4.2	1.98 ± 0.21	68.2 ± 13.5	1.26 ± 0.16	NC	NA
	SC	8	2.68 ± 1.11	3.19 ± 2.17	35.2 ± 6.8	6.92 ± 3.24	31.1 ± 11.4	53.7 ± 11.1
400 mg (5.9±1.2)	IV	3	37.9 ± 5.0	2.02 ± 0.20	148 ± 14	1.67 ± 0.36	NC	NA
	SC	2	7.15	7.50	109	8.27	46.6	78.1

Source: Sponsor's summary report

Reviewer's Comment: During the review cycle it was found that the antidrug antibody can interfere with the bioanalytical method which was used to analyze the mipomersen concentration in the plasma. However, for this short term single and multiple dose studies no antidrug antibody formation is expected and thus bioanalytical analysis of pharmacokinetic samples can be estimated without any interference from antidrug antibodies.

Multiple Dose Pharmacokinetics: Study MIPO3200309:

Sponsor conducted another study to characterize the multiple dose pharmacokinetics of mipomersen. Study MIPO3200309 was a Phase 1, randomised, double-blind, placebo-controlled, parallel-group, single-center study to investigate the PK, safety, and tolerability of different SC dosing regimens of mipomersen in healthy volunteers. In this study subjects were randomised equally to 1 of the 3 treatment regimens and then further randomised in a 3:1 ratio to mipomersen vs. placebo:

- Cohort A/Test Treatment Regimen 1: 28 subjects received a 30 mg SC dose of study drug or matching volume of placebo daily for 3 weeks (21 doses; 630 mg total).
- Cohort B/Test Treatment Regimen 2: 28 subjects received a 70 mg SC dose of study drug or matching volume of placebo 3 times a week for 3 weeks (9 doses; 630 mg total).
- Cohort C/Reference Treatment Regimen: 28 subjects received a 200-mg SC dose of study drug or matching volume of placebo once a week for 3 weeks (3 doses; 600 mg total).

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Summary of the key plasma PK parameters for mipomersen is presented in Table 7. Figure 10 shows the mean concentration of mipomersen in plasma over 24 hours following the first and last doses of mipomersen. Peak concentration and total exposure were similar following single and repeat dosing. SC administration at 30-mg to 200-mg doses of mipomersen showed rapid absorption, with Cmax typically observed at 2 hours to 4 hours post dose. After reaching C_{max}, mean plasma concentrations of mipomersen declined in a multi-phasic fashion with time for all dose levels. The mean apparent half life following the last dose administration ranged from 32.6 days to 49.8 days.

Table 7: Key plasma pharmacokinetic parameters for mipomersen in study MIPO3200309

Parameter	Mipomersen 30 mg QD (N = 21)		Mipomersen 70 mg TIW (N = 21)		Mipomersen 200 mg QW (N = 21)	
	First Dose	Last Dose	First Dose	Last Dose	First Dose	Last Dose
C_{max} (µg/mL)	0.577 (0.374)	0.979 (1.64)	1.59 (0.451)	1.49 (0.405)	4.04 (1.42)	4.98 (2.84)
T_{max} (hr)	3.00 (2.00 – 8.00)	2.03 (1.00 – 4.08)	3.00 (1.00 – 8.00)	3.02 (1.00 – 8.02)	3.00 (2.00 – 8.00)	4.00 (1.12 – 12.0)
$AUC_{0\text{-}24hr}$ (µg*hr/mL)	3.80 (0.955)	5.25 (3.72)	12.2 (2.49)	12.3 (2.69)	43.4 (10.3)	50.2 (14.0)
$t_{1/2kz}$ (days)	N/A	39.5 (13.3)	N/A	49.8 (27.2)	N/A	32.6 (11.6)
$C_{Day\ 28}$ (ng/mL)	N/A	12.9 (7.99)	N/A	12.0 (3.77)	N/A	8.9 (3.33)
$C_{7\ days\ from\ last\ dose}$ (ng/mL)	N/A	12.9 (7.99)	N/A	13.2 (4.43)	N/A	12.7 (5.18)

Source: Sponsor's Clinical Pharmacology summary report

A **B**

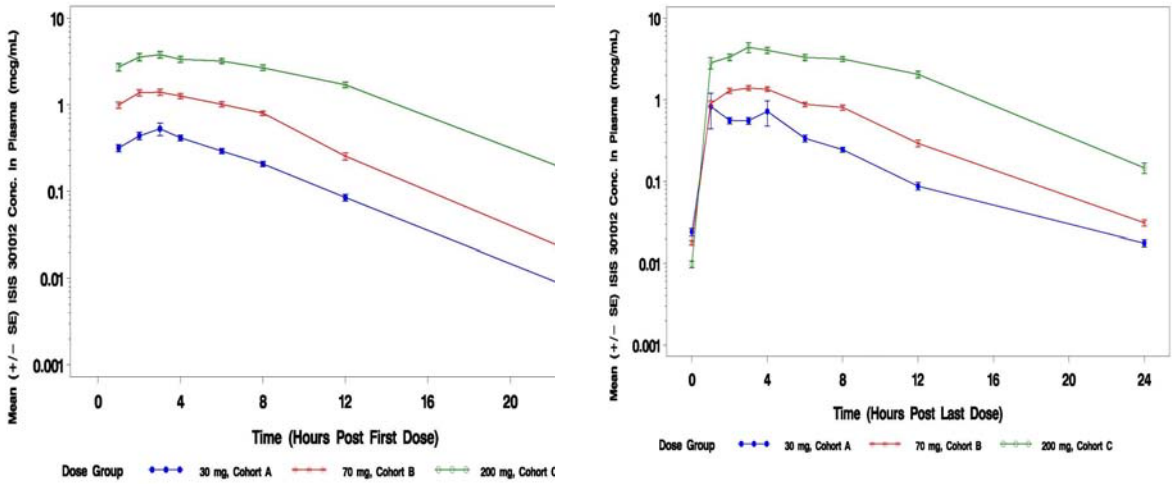

Figure 10: Mipomersen plasma concentrations-time profiles over 24 hours following first (A) and last (B) dose in study MIPO3200309
Source: Sponsor's Clinical Pharmacology summary report

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2.4.2 What are the characteristics of drug absorption??

Absolute plasma bioavailability of mipomersen following SC administration ranged from 54% to 78%, in comparison to i.v. infusion, and was independent of dose (Table 6 and Table 8). Please refer to section 2.4.1 for further details.

Table 8: Descriptive statistical summary of pharmacokinetic parameter estimates for mipomersen in healthy human volunteers following first s.c. injection (SD 1)

Dose (mg)	N	C_{max} (µg/ml)	T_{max} (hr)	AUC_{0-48hr} (µg*hr/mL)	$AUC_{0-\infty}$ (µg*hr/mL)	Apparent Distribution $t_{1/2}$ (hr)	%F
50	3	1.40 ± 0.29	2.67 ± 0.58	7.27 ± 0.93	7.28 ± 1.01	1.85 ± 0.49	61.8 ± 0.7
100	3	1.45 ± 0.83	2.99 ± 0.99	14.5 ± 2.9	14.9 ± 2.8	4.22 ± 2.71	65.6 ± 12.8
200	4	3.14 ± 1.59	3.63 ± 2.98	38.0 ± 24.3	38.8 ± 24.9	3.58 ± 1.16	57.7 ± 34.6
400	4	7.60 ± 0.81	4.00 ± 1.63	106 ± 17	109 ± 18	5.18 ± 1.88	69.2 ± 7.3

Data are presented as Mean ± Standard Deviation

N	Number of subjects
C_{max}	Maximum plasma concentration
T_{max}	Time C_{max} observed
AUC_{0-48hr}	Partial area under the plasma concentration-time curve from time 0 to 48 hours after the start of dose administration
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time 0 to infinity
%F	Plasma bioavailability (%) following s.c. administration relative to i.v. (MD1)

Source: Sponsor's study report

2.4.3 What are the characteristics of drug distribution?

In vitro plasma protein binding of mipomersen was ≥90% in human, rat, and monkey, and ≥85% in mouse at plasma mipomersen concentration between 8 and 152 µg/mL. Binding in human plasma was 95.87% at the lowest concentration (0.8 µg/mL) and 84.81% at the highest concentration (4556 µg/mL) tested.

2.4.4 What are the characteristics of drug metabolism?

In vitro studies in human liver microsomes suggest that mipomersen is not metabolized by CYP450. At concentration ranges of 1 to 500 µg/mL mipomersen was stable in human liver microsomes suggesting CYP does not play a major role in its metabolism. Preclinical analysis of mipomersen suggests that mipomersen is primarily metabolized by endonucleases hydrolysis at various positions within the gap of mipomersen, followed by subsequent 3'- and 5'-exonuclease hydrolysis of the deoxynucleoside ends of the formed hemimers. (Please refer to Review by Dr. Wange for further details).

2.4.5 What are the characteristics of mipomersen elimination?

Mipomersen is believed to be primarily eliminated via metabolism by endonucleases and exonucleases and excretion in urine. In Phase 1 clinical study there was a minimal amount of urinary excretion of parent compound (<5% of administered dose) or total oligonucleotide (<8% of administered dose) within the first 24 hours after dosing over the

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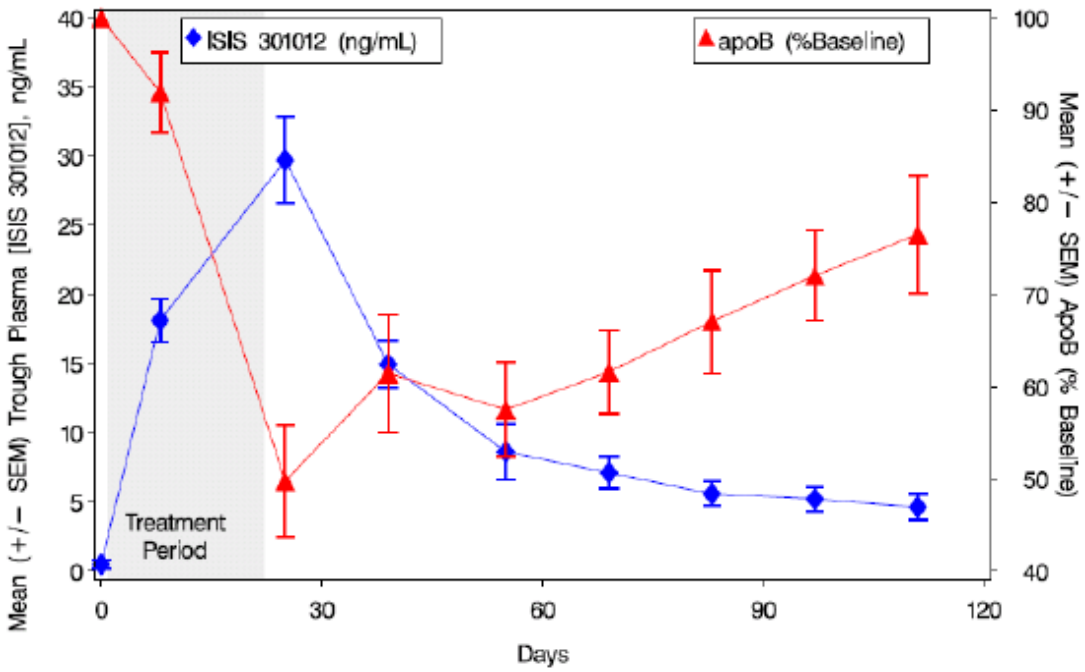
dose range studied (50 mg to 400 mg mipomersen by IV or SC administration). Also, excretion of chain-shortened metabolites was evident in urine, suggesting endonucleases followed by exonucleases mediated cleavage of the parent compound.

2.5 What are the Pharmacodynamic (PD) Characteristics of the Drug?

Mipomersen sodium is an apolipoprotein B (apo B) synthesis inhibitor, which binds to a specific segment of the coding region of the mRNA for apo B, thus inhibiting the synthesis of this target. The hybridization (binding) of mipomersen to the cognate mRNA results in reduced translation of the mRNA to protein by multiple mechanisms including activation of RNase H-mediated degradation of the cognate mRNA. This leads to decreased synthesis of apo-B100 in the liver (the primary site of apo-B100 generation), a reduction in transport of apo-B100 containing lipoprotein out of the liver and a reduction in circulating LDL cholesterol (LDL-C).

In Phase 1 and Phase 2 study sponsor measured the apo B concentrations. Figure 11, results from a Phase 1 study, showed that trough plasma concentrations (measured ≥72 hours post-dose) were highly correlated with serum apo B protein levels in healthy volunteers.



Source: Sponsor's summary of clinical pharmacology report.

Figure 11: Exposure-response relationships between median mipomersen trough plasma concentration and median serum apo B level (percent change from baseline) with time in study ISIS 301012-CS1

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2.6 Intrinsic Factors

2.6.1 What intrinsic factors (e.g., age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure

Renal Impairment:

No formal PK studies have been conducted in patients with renal impairment. The sponsor used results of a PopPK analysis suggesting that the impact of mild and moderate renal impairment on clearance of mipomersen is minimal.

PopPK analysis includes study results from short term Phase 1, Phase 2 trials and long term Phase 3 and extension trials. During the review cycle it was found that the antidrug antibody can interfere with the bioanalytical method which was used to analyze the mipomersen concentration in the plasma. According to the sponsor's analysis, 37.5 % of the Phase 3 patients are antidrug antibody positive and 72% patients are antidrug antibody positive in the extension trials. Given this affect of antidrug antibody on the bioanalytical method, the exposure data from these clinical trials are not reliable.

However, assuming that antidrug antibody takes some time to develop this reviewer reanalyzed the trough concentration data around week 13 of all the phase 3 trials to investigate the impact of renal impairment on the mipomersen exposure. Analysis of steady state dose normalized C_{trough} concentration data around week 13 showed that mild and moderate renally impaired subject have approximately 36% and 14% increase in mean trough concentrations, respectively. The results of this analysis demonstrate that there is no major impact of renal impairment on the pharmacokinetics of mipomersen (Figure 12).

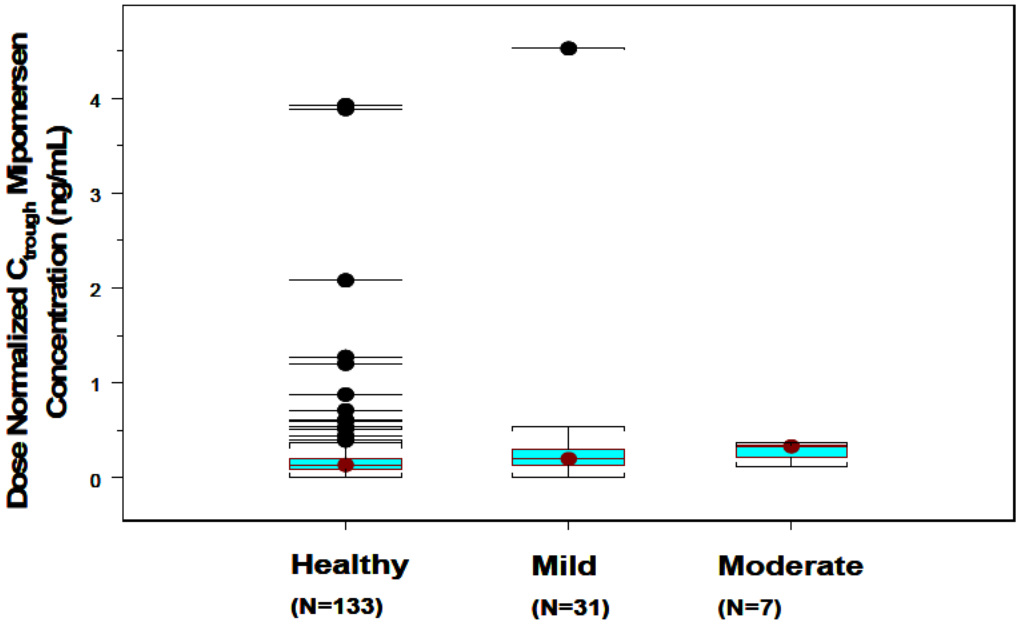

Figure 12: Effect of renal impairment on the dose normalized trough concentration around week 13.

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- **Hepatic Impairment:**

The effects of hepatic impairment on mipomersen PK have not been studied. *In-vitro* studies in human liver microsomes showed that mipomersen is not metabolized by CYP450 enzymes. Mipomersen is believed to be metabolized in tissues by endo- and exonucleases to form shorter oligonucleotides. Thus, from a clinical pharmacology perspective, the sponsor's recommendation of no dose adjustment for individuals with hepatic impairment is reasonable. However, based on the mechanism of action of this drug, where the liver is primary site of action, and the available safety and efficacy data from the Phase 3 trials applicant is recommending a contraindication of mipomersen in individuals with significant hepatic dysfunction, which may include persistent elevations of serum transaminases.

- **Age, Race Weight and Gender**

Sponsor's claim of no dose adjustment based on age, gender, race and weight is results from population pharmacokinetics (PopPK) analysis. PopPK analysis includes study results from short term Phase 1, Phase2 trials and long term Phase 3 and extension trials. During the review cycle it was found that the antidrug antibody can interfere with the bioanalytical method which was used to analyze the mipomersen concentration in the plasma. According to the sponsor's analysis, 37.5 % of the Phase 3 patients are antidrug antibody positive and 72% patients are antidrug antibody positive in the extension trials. Given this affect of antidrug antibody on the bioanalytical method, the exposure data from these clinical trials are not reliable and hence claim on age, race, gender and weight can not be made at this point.

Reviewer's Comment:

- *During the review cycle the sponsor was asked to provide addition information on whether the antidrug antibody can interfere with the bioanalytical method which was used to analyze the mipomersen concentration in the plasma samples (See Appendix 4.1). The sponsor submitted a report investigating this and concluded that anti-drug antibodies can interfere with this assay methodology if present in similar amounts after dilution.*

- *According to the sponsor's analysis, 37.5 % of the Phase 3 patients are antidrug antibody positive and 72% patients are antidrug antibody positive in the extension trials. In current submission several labeling claim are based on the sponsor's PopPK analysis, which uses the data from several Phase 1, Phase 2 and Phase 3 studies. Given this effect of antidrug antibody on the bioanalytical method, the exposure data from these clinical trials are not reliable and hence these claims are not acceptable.*

- *Sponsor did capture the subjects which are antibody positive in the population PK data set. However, subjects were classified based on a previous antibody assay which was not as sensitive as the revised assay. Therefore, analysis excluding antibody positive subject can not be done since the data set does not capture antibody-positive subjects based on the revised assay.*

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- **Genetics**

Wide variability in mipomersen exposure and responses were observed in clinical trials. LDLR genotype, available for a subset of the pivotal trial participants (ISIS 301012-CS5), was not identified as a major predictor of clinical response (not confirmed by reviewer). A common polymorphism present in the binding region for mipomersen on APOB (chr2:21239518, G>A/G; frequency A/A 7.7%, A/G 11.5%, G/G 80.8%) that could affect mipomersen responses. However, the effect of this variant has not been formally evaluated and may be of limited clinical relevance.

Mipomersen and its metabolites may have alternate binding sites in tissues that account for inflammatory and other adverse effects observed in clinical trials, although it is not known whether such events result from off-target, hybridization-dependent mechanisms or hybridization-independent mechanism as proposed by the sponsor. BLAST searches to evaluate off-target binding of mipomersen identified four transcripts that matched mipomersen as follows: VPS37A, MDM2, PRKG2, and expressed sequence tag (EST) similar to B cell Growth Factor. Mipomersen did not modulate expression of these genes in human hepatocyte studies (study GT-348-EF-34). The sponsor's 2003 sequence alignment analysis was updated, confirming the sponsor's finding that no human genome regions other than APOB are 100% complementary to mipomersen; other alignments had multiple mismatches. However, patients may be exposed to all possible sequence lengths of mipomersen metabolites (based on Sponsor's study 301012-IS07) and we are unable to rule out off-target binding of other chain-shortened products of mipomersen.

2.7 Extrinsic Factors

2.7.1 What is the effect of LDL apheresis on the PK of mipomersen?

The effect of LDL apheresis on the pharmacokinetics of mipomersen has not been studied in this NDA. Also the effect of LDL apheresis on efficacy and safety is not studies in this NDA program.

2.7.2 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

The effects of lipid lowering drugs and warfarin on the exposure of mipomersen (and vice versa) are discussed in section 2.7.4. The effect of smoking, herbal products, and alcohol use were not evaluated by the sponsor.

2.7.3 Is mipomersen a substrate, inducer or inhibitor of CYP enzymes?

In vitro studies in human liver microsomes suggest that mipomersen is not metabolized by CYP450. *In vitro* studies (ISIS 301012-IS05) suggest that mipomersen is not an inhibitor of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 isoforms. The results from an *in-vitro* study (DMPK10-R015) also suggest that that mipomersen has a low

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potential to induce CYP1A2, CYP2B6, and CYP3A4 enzymes in plated cultures of cryopreserved human hepatocytes at the concentrations tested (1.0 to 500 µg/mL).

2.7.4 Is mipomersen a substrate, an inhibitor and/or an inducer of transporter processes?

In the *in-vitro* studies using MDCKII and MDCKII-MDR1 cell models, the sponsor demonstrated that mipomersen is not an inhibitor of P-gp as it did not affect the P-gp mediated efflux of digoxin, the positive control P-gp substrate at concentrations up to 100 mM (DMPK09-R037). Mipomersen did not cross the MDCKII cell monolayer and hence an assessment of mipomersen as a substrate for P-gp could not be determined. The sponsor didn't study the interaction potential of mipomersen to other transporters.

2.7.5 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Mipomersen is believed to be primarily eliminated via metabolism by endonucleases and exonucleases and excretion in urine. In this application drug-drug interaction studies were carried out with lipid lowering agents simvastatin and ezetimibe and with warfarin. Table 9 summarizes the effect of co-administered drugs on the pharmacokinetics of mipomersen. Table 10 summarizes the impact of mipomersen on the pharmacokinetics of co-administered drugs. In summary, mipomersen coadministration resulted in an increase in AUC for simvastatin and decrease in Cmax for simvastatin and ezetimibe. However, these changes were considered not to be clinically meaningful.

- **Drug-drug Interaction Study with Oral Hypolipidaemic Agents in Healthy Volunteers:**

A Phase 1, open-labeled, drug-drug interaction study was conducted to assess the DDI potential of mipomersen when co-administered with simvastatin and ezetimibe (oral hypolipidaemic agents) to healthy volunteers. The study design features were:

  - Cohort A: oral simvastatin (40 mg) on Days 1 and 11; IV mipomersen (200 mg) on Days 4, 6, 8 and 11; PK profile (0 to 24 hours) of simvastatin on Days 1 and 11; and PK profile (0 to 24 hours) of mipomersen on Days 8 and 11.

  - Cohort B: oral ezetimibe (10 mg) on Days 1 and 15; IV mipomersen (200 mg) on Days 8, 10, 12, and 15; PK profile (0 to 72 hours) of ezetimibe on Days 1 and 15; and PK profile (0 to 24 hours) of mipomersen on Days 12 and 15.

  - Mipomersen was administered by IV infusion over 2 hours.

- **Drug-drug Interaction Study with Warfarin in Healthy Volunteers**

A Phase 1, open-label, single-sequence, 2-period crossover study to determine the effect of multiple doses of mipomersen (200 mg SC administered every other day for a total of

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4 doses; total dose of 800 mg) on the pharmacodynamics and pharmacokinetics of a single oral 25-mg dose of warfarin. All subjects then received 200-mg SC doses of mipomersen administered every other day on Days 8, 10, 12, and 14 (total of 800 mg) with a single oral 25-mg dose of warfarin also administered on Day 14 (test treatment).

Table 9: Effect of co-administered drug on the pharmacokinetics of mipomersen

Co-administered Drug	Effect on Mipomersen Exposure GMR (90% CI)	
	$AUC_{0\text{-}24\ h}$	C_{max}
Simvastatin (40 mg)	1.00 (0.93, 1.07)	0.978 (0.92, 1.03)
Ezetimibe (10 mg)	1.01 (0.92, 1.11)	**1.05 (0.86, 1.28)**
Warfarin (25mg)	1.16 (1.09, 1.24)	**1.16 (1.02, 1.33)**

Bolded values indicate that the geometric mean ratio or 90 % CI is outside 80%-125% limit

Table 10: Effect of mipomersen on the pharmacokinetics of co-administered drugs

Co-administered Drug	Effect on Co-Administered Drug Exposure GMR (90% CI)	
	AUC_t	C_{max}
Simvastatin	**1.28 (0.89, 1.82)**	**0.51 (0.34, 0.77)**
Simvastatin Acid	**1.11 (0.89, 1.38)**	**0.80 (0.65, 0.98)**
Ezetimibe (Free)	**1.00 (0.77, 1.27)**	**0.58 (0.40, 0.82)**
Ezetimibe (Total)	**0.89 (0.69, 1.14)**	**0.74 (0.56, 0.96)**
Warfarin (PK)		
R-Warfarin	1.10 (1.08, 1.13)	1.05 (1.01, 1.10)
S-Warfarin	1.09 (1.06, 1.13)	1.05 (0.99, 1.10)
Warfarin (PD)	**AUEC**	**MAX**
INR	0.99 (0.97, 1.01)	0.94 (0.90,0.98)

Bolded values indicate that the geometric mean ratio or 90 % CI is outside 80%-125% limit

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***Reviewer's Comment**: Mipomersen is metabolized by endo- and exo-nucleases and is not affected by the cytochrome P450 system, The ability of mipomersen to inhibit the major CYP enzymes (namely CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) was evaluated in cryo-preserved human hepatocytes in vitro and it was demonstrated that mipomersen did not inhibit enzyme activities of all the CYP enzymes evaluated (study 301012-IS05).*

The DDI study showed that simvastatin, ezetimibe and warfarin has no impact on the pharmacokinetics of mipomersen. The result of the study also suggests that mipomersen alters the pharmacokinetic parameters for simvastatin and ezetimibe. The results on the DDI study should be interpreted with caution as several factor related to study design may have contributed these changes. The subjects were fasted fasting prior to dosing with simvastatin or ezetimibe alone but not when these agents were administered with mipomersen. While food was not expected to affect the PK of simvastatin, simvastatin acid or ezetimibe, the inconsistent food restrictions in this study could at least partly explain some of the apparent PK differences observed.

2.8 General Biopharmaceutics

An overview of the mipomersen drug products used in clinical trials during the development of mipomersen is presented in Table 11. Mipomersen formulation intended for marketing purposes (i.e., 200 mg/mL solution for SC administration) was used in most Phase 2 and all Phase 3 clinical studies to date.

Table 11: Clinical trials and mipomersen products used

Study Number	Solution		Lyophilised	Oral
	CONC (mg/mL)	Fill VOL (mL)	mg/vial	mg/capsule
ISIS 301012-CS1	250	0.5	n/a	n/a
ISIS 301012-CS2	n/a	n/a	100	n/a
ISIS 301012-CS3	n/a	n/a	100	n/a
ISIS 301012-CS4	200	1.0	n/a	n/a
ISIS 301012-CS5	200	1.0	n/a	n/a
ISIS 301012-CS6	200	1.0	n/a	n/a
ISIS 301012-CS7	200	1.0	n/a	n/a
ISIS 301012-CS8	200	1.0	n/a	n/a
ISIS 301012-CS9	200	1.0	n/a	n/a
ISIS 301012-CS10 (Cohort A-F)	250	0.5	n/a	n/a
ISIS 301012-CS10 (Cohort G)	200	1.0	n/a	n/a
ISIS 301012-CS12	200	1.0	n/a	n/a
ISIS 301012-CS17	200	1.0	n/a	n/a
ISIS 301012-CS19	200	1.0	n/a	n/a
ISIS 301012-CS301	250	0.5	n/a	n/a
ISIS 301012-CS101	n/a	n/a	100	100
MIPO2800209	200	1.0	n/a	n/a
MIPO2900210	200	1.0	n/a	n/a
MIPO3200309	200	1.0	n/a	n/a
MIPO3500108	200	1.0	n/a	n/a
MIPO3700710	200	1.0	n/a	n/a

CONC = concentration; VOL = volume; n/a = not applicable
NOTE: Studies MIPO1600810 and MIPO3801011 are not included in this table because no patients had been treated in these studies as of the cutoff date for this report.

Source: Sponsor report on Summary of Biopharmaceutic Studies and Associated Analytical Methods

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2.9 Analytical

2.9.1 How are the active moieties identified and measured in the plasma/serum?

In this NDA, mipomersen plasma levels were quantified by a specific sandwich enzyme linked immuno sorbent assay (ELISA). The CGE-UV method was used for the determination and quantitation of urine mipomersen concentrations.

2.9.2 What bioanalytical methods are used to assess Mipomersen concentrations?

(b) (4)

[redacted]

The initial hybridization-based ELISA method for quantitation of mipomersen in human plasma was validated by [redacted] (b) (4) (report #ISIS 301012-MV06) and [redacted] (b) (4) (ISIS 301012-MV11). The calibration ranges of these assays were from 1.52 to 48.6 ng/mL (200 to 6400 pM). To improve the sensitivity and dynamic range of the assay, the method was subsequently modified [redacted] (b) (4) (ISIS 301012-MV15) resulting in an improved calibration range of 0.230 to 30.4 ng/mL (30 to 4,000 pM). Dilutions up to 40,000-fold were validated for quantitation of samples exceeding the calibration range.

The CGE-UV method for determination and quantitation of urine mipomersen concentrations was validated by ISIS Pharmaceuticals (ISIS 301012-MV07). The calibration range of this assay was 0.076 to 7.6 µg/mL (0.01 to 1 µM).

Mipomersen was shown to be stable in plasma following up to 7 freeze/thaw cycles, freezer storage at -20 °C for up to 77 days (ISIS 301012-MV15 Amendment 5), and at -80 °C for up to 1,218 days (ISIS 301012-MV15 Amendment 3).

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Table 12: Mipomersen ELISA assay performance in human serum

Study Reference	Matrix	Assay	Assay Volume (µL)[a]	LLOQ (pM)	ULOQ (pM)	QC Levels (pM)	Intra-Run		Inter-Run		LTS (days)
							RE range (%)	CV range (%)	RE range (%)	CV range (%)	
ISIS 301012-MV06	Plasma	Hybridisation-ELISA	250	200 (1.52 ng/mL)	6,400 (48.6 ng/mL)	200, 300, 600, 2,000, 4,000, 5,000, 6,400, 16,000,000	-17.3 to 6.20	2.44 to 10.8	-20.9 to -4.66	5.81 to 43.5	85
ISIS 301012-MV11	Plasma	Hybridisation-ELISA	125	200 (1.52 ng/mL)	6,400 (48.6 ng/mL)	200, 600, 2,000, 4,000, 6,400, 2,000,000, 20,000,000	-19.7 to 13.8	7.7 to 23.4	N/A	N/A	128
ISIS 301012-MV15	Plasma	Hybridisation-ELISA	100	30 (0.230 ng/mL)	4,000 (30.4 ng/mL)	30, 50, 90, 800, 4,000, 5000, 17,650,000	-15.9 to-2.77	2.81 to 8.90	-21.8 to 1.65	8.33 to 14.9	1218
ISIS 301012-MV07	Urine	CGE-UV	500	10,000 (0.076 µg/mL)	1,000,000 (7.6 µg/mL)	10,000, 30,000, 150,000, 800,000, 15,000,000	-4 to 25	2 to 13	-17 to -3	3 to 10	413

Reviewer's Comment: *Several bioanalytical issues were identified during the review of this NDA which impact the acceptance of the mipomersen plasma data. Some of the issues are highlighted below:*

- *During the review cycle sponsor was asked to provide addition information on whether the antidrug antibody can interfere with the bioanalytical method which was used to analyze the mipomersen concentration in the plasma samples (See Appendix 4.1). The sponsor submitted a report investigating this and concluded that anti-drug antibodies can interfere with this assay methodology if present in similar amounts after dilution.*

- *According to the sponsor's analysis, 37.5 % of the Phase 3 patients are antidrug antibody positive and 72% patients are antidrug antibody positive in the extension trials. In current submission several labeling claim are based on the sponsor's PopPK analysis, which uses the data from several Phase 1, Phase 2 and Phase 3 studies. Given this effect of antidrug antibody on the bioanalytical method, the exposure data from these clinical trials are not reliable and hence these claims are not acceptable.*

- *Mipomersen is a 20 nucleic acid oligonucleotide and is believed to be metabolized by endonucleases and exonucleases hydrolysis at various positions within the gap of mipomersen to form hemimer of various lengths. Sponsor's cross-reactivity experiments showed no cross-reactivity for the putative 10-mer metabolite (less than 2.5%), but significant cross reactivity was seen for the putative 19-mer metabolite (51.4%). The cross reactivity studies suggest that the ELISA method may cross-react with long chain shortened oligonucleotide metabolites (e.g., 19-mer) if formed in the plasma. Although, the sponsor claims*

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that the long chain shortened oligonucleotide formation is not common with the second generation oligonucleotide such as mipomersen. However, the sponsor did not demonstrated that following mipomersen administration long chain shortened oligonucleotide are not present in the plasma and will not impact the study results. This reviewer consulted with the Pharm/Tox reviewer and was advised that the probability of formation of long chain shortened oligonucleotide following mipomersen administration is rare in human plasma samples based on available preclinical and literature information. Although the impact of this finding in the current evaluation is low, the sponsor should improve the bioanalytical method to avoid any kind of interferances.

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3 DETAILED LABELING RECOMMENDATION

The following are the labeling recommendations relevant to clinical pharmacology for NDA 203568. The ~~red strikeout font~~ is used to show the proposed text to be deleted and underline blue font to show text to be included or comments communicated to the sponsor.

7 DRUG INTERACTIONS

7.1 Interference with Other Drugs

[redacted] (b) (4) No clinically relevant pharmacokinetic interactions were reported between KYNAMRO and warfarin, or between KYNAMRO and simvastatin or ezetimibe. Additionally, coadministration of KYNAMRO with warfarin did not result in a pharmacodynamic interaction as determined by INR, aPTT and PT. [redacted] (b) (4)

8.6 Renal Impairment

The safety and efficacy of KYNAMRO treatment in patients with known renal impairment or in patients undergoing renal dialysis have not been established. [redacted] (b) (4)

12.3 Pharmacokinetics

Single- and multiple-dose pharmacokinetics of mipomersen sodium in healthy volunteers and patients with FH and non-FH have shown that mipomersen sodium plasma exposure increases with dose, and exhibits approximate dose proportionality across the studied dose range of 30 mg to 400 mg. Plasma concentrations decay with an initial distribution half-life in hours and a terminal elimination half-life of approximately 1-2 months. [redacted] (b) (4)

Absorption

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Following SC injection, peak concentrations of mipomersen sodium are typically reached in 3-4 hours. The estimated plasma bioavailability of mipomersen sodium following SC administration over a dose range of 50 mg to 400 mg, relative to IV administration, ranged from 54% to 78%.

Distribution

Mipomersen sodium is highly bound to human plasma proteins (≥ 90%) at clinically relevant concentrations (1-8 µg/mL). Mipomersen sodium has a rapid distribution plasma half-life of approximately 2 to 5 hours.

From animal studies it was demonstrated that mipomersen sodium is rapidly and broadly distributed to tissues, with the kidney and liver containing the highest concentrations. Little to no drug is distributed to cardiac muscle, skeletal muscle, or brain.

With once weekly dosing, plasma trough levels increase over time and approach steady-state, typically within 6 months. (b) (4)

(b) (4)

Metabolism

Mipomersen sodium is not a substrate for CYP450 metabolism, and is metabolized in tissues by endonucleases to form shorter oligonucleotides that are then substrates for additional metabolism by exonucleases.

Excretion

The elimination of mipomersen sodium involves both metabolism in tissues and excretion, primarily in urine. Prolonged metabolic elimination of mipomersen sodium from tissues has been observed in animals with a half-life in the range of 13 to 34 days in the primary organs involved (kidney and liver). Similar to that seen in animals, urinary recovery was limited in humans with less than 4% within the 24 hours post dose. Both mipomersen sodium and putative shorter oligonucleotide metabolites were identified in human urine.

(b) (4)

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(b) (4)

[redacted]

Drug Interactions

Specific Populations

Renal Impairment
Pharmacokinetics of KYNAMRO in patients with renal impairment has not been established [*see Use in Specific Population (8.6)*].

Hepatic Impairment
Pharmacokinetics of KYNAMRO in patients with renal impairment has not been established [*see Use in Specific Population (8.7)*].

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4 APPENDIX

4.1 Assessment of Anti Drug Antibody Interference In Analysis of Mipomersen in PK Samples

Title: Assessment of ADA Interference in Mipomersen Quantitation PK Assay

In order to understand the potential interference of anti-drug antibodies (ADA) in the mipomersen PK ELISA , samples with varying levels of mipomersen in the presence of affinity purified rabbit anti-mipomersen antibodies (as a surrogate ADA) were generated and tested in the PK assay. The mipomersen levels ranged from 0.38 to 15.19 ng/mL (which fall within the quantitation range of this assay of 0.23-30.4 ng/mL) in the presence of 0.1 to 10 µg/mL of anti-mipomersen antibodies. The samples were prepared and incubated for 1 hour at 37°C to allow for complex formation prior to analysis of mipomersen levels in the PK assay.

The resulting data are shown in Table 1 and Figure 1 as interpolated mipomersen levels and further calculated for percent recovery from baseline (no ADA) in Table 2 and Figure 2.

The data illustrated in the following tables and figures indicate that within the quantifiable range of the assay, as the anti-drug antibody level increases, a commensurate decrease in detectable levels of mipomersen may occur. At 0.3 µg/mL or less of ADA, there was no impact seen on the quantitation of mipomersen between 0.38 and 15.19 ng/mL with acceptable recoveries of 80-120%. At the 0.6 µg/mL of antibody, acceptable recoveries were seen for mipomersen levels of 1.52 ng/mL and above. At the 1 µg/mL of antibody, acceptable recoveries were seen for mipomersen levels of 3.04 ng/mL and above. With antibody levels at and above 3 µg/mL, mipomersen at all levels showed under-recovery.

These data were generated using a surrogate ADA, affinity purified rabbit polyclonal antibodies generated by hyperimmunizing rabbits. Impact of ADA in vivo in patients on the quantitation of mipomersen may differ from what is observed in this study.

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Table 1. Mipomersen interpolated concentrations at varying concentrations with ADA

	ng/mL of Mipomersen detected							
Mipomersen Conc. (ng/mL)	ADA Concentration (µg/mL)							
Theoretical	0	0.1	0.3	0.6	1	3	6	10
0.38	0.499	0.52	0.434	0.306	0.236	0	0	0
0.76	1.01	0.946	0.851	0.757	0.582	0	0	0
1.52	1.76	1.776	1.677	1.557	1.156	0.341	0	0
3.04	3.837	3.597	3.379	N/A	3.637	1.117	0.409	0.247
6.07	7.36	6.388	6.566	6.573	6.391	4.124	1.762	0.606
15.19	16.012	17.051	15.763	16.208	14.521	11.959	9.289	4.771

N/A no data point reported

Figure 1. Mipomersen interpolated concentrations at varying concentrations with ADA

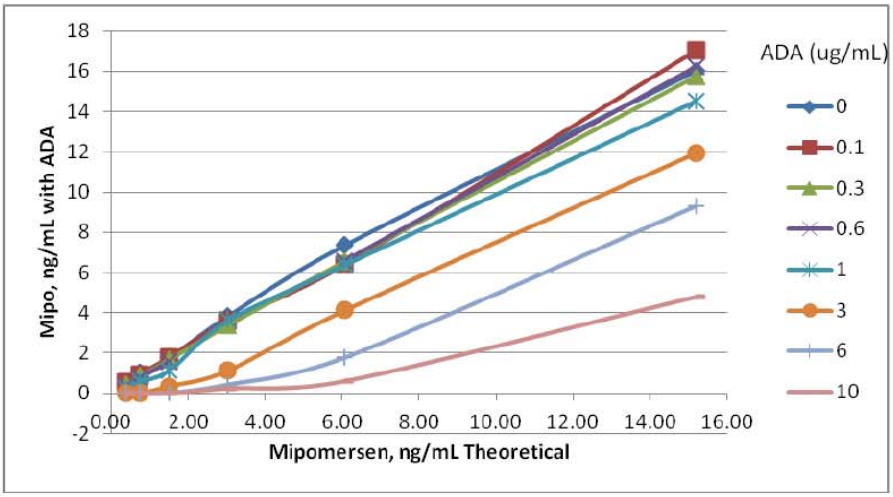

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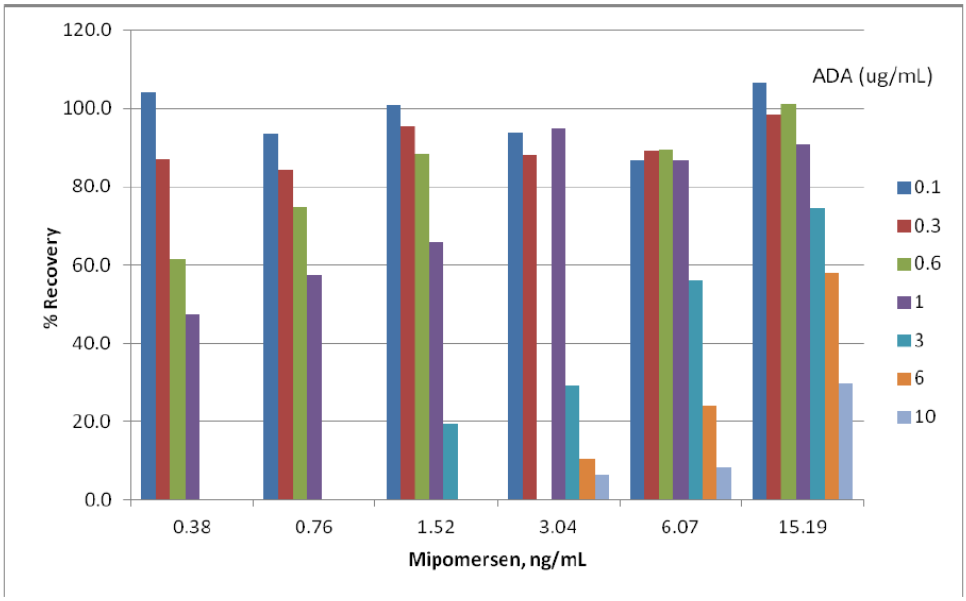
Table 2. Mipomersen % recoveries at varying concentrations with ADA

	% Recovery						
Mipomersen Conc. (ng/mL)	ADA Concentration (µg/mL)						
Theoretical	0.1	0.3	0.6	1	3	6	10
0.38	104.2	87.0	**61.3**	**47.3**	0	0	0
0.76	93.7	84.3	**75.0**	**57.6**	0	0	0
1.52	100.9	95.3	88.5	**65.7**	**19.4**	**0**	**0**
3.04	93.7	88.1	N/A	94.8	**29.1**	**10.7**	**6.4**
6.07	86.8	89.2	89.3	86.8	**56.0**	**23.9**	**8.2**
15.19	106.5	98.4	101.2	90.7	**74.7**	**58.0**	**29.8**

Bolded values are recoveries outside of 80-120%; N/A no data point reported

Figure 2. Mipomersen % recoveries at varying concentrations with ADA



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4.2 Genomics Group Review

NDA/BLA Number	203568
Submission Date	03/29/2012
Applicant Name	Genzyme Corporation
Generic Name	Mipomersen sodium
Proposed Indication	Homozygous Familial Hypercholesterolemia
Primary Reviewer	Lyle Canida, Pharm.D., M.S.
Secondary Reviewer	Mike Pacanowski, Pharm.D., M.P.H.

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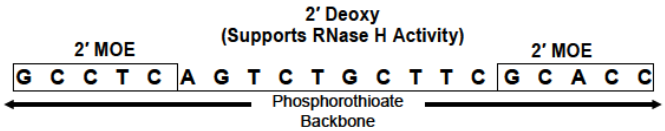
1 Background

Mipomersen is a 20-base, synthetic, antisense oligonucleotide inhibitor of apolipoprotein B (apo B) synthesis. The sequence, shown in the figure below, is specific for a region within the apo B gene. The applicant is seeking approval for the use of mipomersen as an adjunct to maximally tolerated lipid-lowering medications and diet to reduce LDL-C, apo B, total cholesterol, non-high density lipoprotein-cholesterol (non-HDL-C) and Lp(a) in patients with homozygous familial hypercholesterolemia (HoFH).

Mipomersen structure/sequence



Note: all cytodine residues are methylated at the 5-position

Source: ISIS 301012-ISO7 Mipomersen chimeric design

As an antisense oligonucleotide, mipomersen could potentially bind regions that are not the primary intended target, leading to various off-target toxicities. Additionally, genetic variations in the primary intended target could affect the extent to which mipomersen binds the target sequence, resulting in variable efficacy or clearance. The purpose of this review is to evaluate 1) potential safety issues related to off-target binding of mipomersen degradation products and 2) whether mutations/polymorphisms contribute to mipomersen exposure and/or response variability, particularly those in the binding region of the target mRNA.

2 Submission Contents Related to Genomics

The following reports submitted by the applicant are relevant from the perspective of the Genomics Group:

Materials Reviewed

Report ID	Title

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Report ID	Title
GT-348-EF-34	BLAST and Complimentary Gene Expression Analysis for ISIS 301012 (April 2003)
301012-CS5	RADICHOL I: A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of ISIS 301012 as Add-on Therapy in Homozygous Familial Hypercholesterolemia Subjects
301012-IS07	Mipomersen (ISIS 301012) Metabolites Identified by Ion-Pair HPLC- Electrospray/Mass Spectrometry (IPHPLC-ES/MS) in Liver and Kidney from Mice, Rats, and Monkeys and Urine from Rats, Monkeys, and Humans (August 2010)

No pharmacogenetic studies were submitted other than an assessment of response variability according to LDLR mutation status for subjects having such data available in trial ISIS 301012-CS5.

This review relies on data presented by the applicant unless otherwise specified.

3 Key Questions and Summary of Findings

3.1 What are potential safety issues related to off-target binding of mipomersen and its degradation products?

3.1.1 Summary of non-clinical and clinical safety

As an oligonucleotide, mipomersen is cleared in the urine as parent drug and smaller oligonucleotide fragments resulting from endonuclease hydrolysis. In applicant's study 301012-IS07, all possible sequence lengths of mipomersen metabolites from 5 to 19 nucleotides in length were detectable in liver and kidney samples of mice and monkeys. Potential safety issues with oligonucleotides, both of the parent and any degradation products, include clastogenic potential and off-target binding.

The applicant evaluated the clastogenic potential of mipomersen in study ISIS 301012-AS12. At doses up to 1200 mg/kg (the maximum tolerated), no evidence of clastogenicity was reported (Report ISIS 301012-AS12). Otherwise, nonclinical toxicities related to target-mediated effects (i.e., Apo B reduction) were not identified. Multi-organ inflammatory changes were observed in many animal studies (from *Nonclinical Overview*).

Clinical safety issues of interest for mipomersen based on review of the clinical trial data (see review from Eileen Craig, MD dated 11/26/12) include hepatic transaminase elevations (ALT/AST $\geq$3 x ULN at least once during trial; 16.5%), hepatic steatosis ($\geq$5% change from baseline in hepatic fat, 61.8% vs. 8.3%), flu-like symptoms (29.9% vs. 16.3%), inflammatory effects (i.e., hsCRP elevations to $\geq$ 3mg/L in 39.3% vs. 8.0%), and proteinuria (2.3% vs. 0.8%). Biomarker studies conducted in trial MIPO3200309 did not

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demonstrate significant effects on IL-1α, IL-13, IL-6, interferon alpha or beta or the chemokines MCP-1 and MIP-1α.

3.1.2 Applicant's analysis

The applicant states that effects of mipomersen on off-target RNA have been minimized insofar as no other perfectly homologous sequences are present in humans. To characterize the potential for off-target binding, the applicant conducted a database search for the mipomersen sequence matches using the NIH BLAST tool (report GT-348-EF-34). The applicant conducted an in-vitro analysis of the potential for off-target effects of mipomersen on the following four genes in human hepatocytes: hypothetical protein FLJ32642 (*VPS37A*), *MDM2*, expressed sequence tag similar to B cell Growth Factor, and protein kinase cGMP-dependent type 2 (*PRKG2*). As shown in the figure below, no consistent, dose-dependent gene expression changes were observed after mipomersen treatment.

Expression of potential cross-reactive genes in human hepatocytes (% control, mean ± SD)

Treatment	Hypothetical protein FLJ32642 mRNA*	MDM2 mRNA*	EST similar to B cell Growth Factor mRNA*	Protein kinase, cGMP-dependent, type 2 mRNA*
Untreated Control (n=12)	100 ± 50	100 ± 66	100 ± 85	100 ± 81
ISIS 301012-5 nM (n=3)	144 ± 27	191 ± 186	176 ± 136	170 ± 121
ISIS 301012-10 nM (n=3)	211 ± 89	324 ± 165	247 ± 130	255 ± 136
ISIS 301012-50 nM (n=3)	132 ± 93	131 ± 163	136 ± 153	145 ± 162
ISIS 301012-150 nM (n=2)	127 ± 4	99 ± 13	214 ± 1	222 ± 1

* None of the gene expression changes were significantly different from the untreated control using Dunnett's Multicomparison Test.

Source: Report GT-348-EF-34

3.1.3 Reviewer's analysis

An updated search (report was dated 2003) was conducted on mipomersen's sequence (GCCTCAGTCTGCTTCGCACC) using the NIH BLAST tool (BLASTN 2.2.27; RefSeq RNA). The BLAST search identified the APOB mRNA as the only location 100% complementary to mipomersen, consistent with the applicant's findings. Additional sequences identified in the BLAST search are listed in the table below; the next highest alignment had 6 mismatches.

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Sequence Alignment results (GCCTCAGTCTGCTTCGCACC)

Accession	Description	Max score	Total score	Query coverage	E value
NM_000384.2	Homo sapiens apolipoprotein B (including Aq(x) antigen) (APOB), mRN	40.1	40.1	100%	5e-04
NM_000788.2	Homo sapiens deoxycytidine kinase (DCK), mRNA	28.2	28.2	70%	2.1
XR_171159.1	PREDICTED: Homo sapiens uncharacterized LOC644083 (LOC644083)	26.3	26.3	65%	8.2
NM_001206696.1	Homo sapiens interferon regulatory factor 6 (IRF6), transcript varian	26.3	26.3	65%	8.2
NM_006147.3	Homo sapiens interferon regulatory factor 6 (IRF6), transcript varian	26.3	26.3	65%	8.2
NM_015409.4	Homo sapiens E1A binding protein p400 (EP400), mRNA	26.3	26.3	65%	8.2
XR_112044.1	PREDICTED: Homo sapiens uncharacterized LOC644083 (LOC644083)	26.3	26.3	65%	8.2
XR_108368.1	PREDICTED: Homo sapiens uncharacterized LOC644083 (LOC644083)	26.3	26.3	65%	8.2
NM_001193328.1	Homo sapiens zinc finger protein 692 (ZNF692), transcript variant 3,	26.3	26.3	65%	8.2
NM_017865.3	Homo sapiens zinc finger protein 692 (ZNF692), transcript variant 2,	26.3	26.3	65%	8.2

Source: Reviewer

The following chain shortened sequences of 13-mer to 15-mer starting from within the gap region as well as from the 3'- and 5'- ends were also queried in BLAST. 13-mer was the shortest sequence analyzed as it is likely to be the shortest sequence that is unique in the mRNA pool (PMID: 1380154); 15-mer length was the longest sequence analyzed due to the metabolic degradation process and structure of the oligonucleotide.

GCCTCAGTCTGCT
GCCTCAGTCTGCTT
GCCTCAGTCTGCTTC
AGTCTGCTTCGCACC
GTCTGCTTCGCACC
TCTGCTTCGCACC

E1A binding protein 400 (EP400) was the only sequence other than APOB that aligned with 100% complementarity. The degradation products aligned with numerous genes having $\leq$2 mismatches, although the E values were higher and scores were lower compared to the full mipomersen sequence against APOB (i.e., less relevant); results with 100% coverage for the first sequence are shown below.

Sequence Alignment results (GCCTCAGTCTGCT)

Accession	Description	Max score	Total score	Query coverage	E value
NM_001206696.1	Homo sapiens interferon regulatory factor 6 (IRF6), transcript varian	26.3	26.3	100%	3.3
NM_006147.3	Homo sapiens interferon regulatory factor 6 (IRF6), transcript varian	26.3	26.3	100%	3.3
NM_015409.4	Homo sapiens E1A binding protein p400 (EP400), mRNA	26.3	26.3	100%	3.3
NM_001193328.1	Homo sapiens zinc finger protein 692 (ZNF692), transcript variant 3,	26.3	44.6	100%	3.3
NM_017865.3	Homo sapiens zinc finger protein 692 (ZNF692), transcript variant 2,	26.3	44.6	100%	3.3
NM_001136036.2	Homo sapiens zinc finger protein 692 (ZNF692), transcript variant 1,	26.3	44.6	100%	3.3
NM_001242293.1	Homo sapiens acyl-CoA synthetase short-chain family member 2 (AC	26.3	26.3	100%	3.3
NM_001076552.2	Homo sapiens acyl-CoA synthetase short-chain family member 2 (AC	26.3	26.3	100%	3.3
NM_018677.3	Homo sapiens acyl-CoA synthetase short-chain family member 2 (AC	26.3	26.3	100%	3.3
NM_000788.2	Homo sapiens deoxycytidine kinase (DCK), mRNA	26.3	26.3	100%	3.3
NM_000384.2	Homo sapiens apolipoprotein B (including Aq(x) antigen) (APOB), mRN	26.3	26.3	100%	3.3
NM_001040660.1	Homo sapiens tetratricopeptide repeat domain 23 (TTC23), transcrip	26.3	26.3	100%	3.3
NM_001040659.1	Homo sapiens tetratricopeptide repeat domain 23 (TTC23), transcrip	26.3	26.3	100%	3.3
NM_001040658.1	Homo sapiens tetratricopeptide repeat domain 23 (TTC23), transcrip	26.3	26.3	100%	3.3
NM_001040657.1	Homo sapiens tetratricopeptide repeat domain 23 (TTC23), transcrip	26.3	26.3	100%	3.3
NM_001040656.1	Homo sapiens tetratricopeptide repeat domain 23 (TTC23), transcrip	26.3	26.3	100%	3.3
NM_022905.4	Homo sapiens tetratricopeptide repeat domain 23 (TTC23), transcrip	26.3	26.3	100%	3.3
NM_001040655.1	Homo sapiens tetratricopeptide repeat domain 23 (TTC23), transcrip	26.3	26.3	100%	3.3
NM_080792.2	Homo sapiens signal-regulatory protein alpha (SIRPA), transcript vari	26.3	26.3	100%	3.3
NM_001040023.1	Homo sapiens signal-regulatory protein alpha (SIRPA), transcript vari	26.3	26.3	100%	3.3
NM_001040022.1	Homo sapiens signal-regulatory protein alpha (SIRPA), transcript vari	26.3	26.3	100%	3.3

Source: Reviewer

3.2 Do genetic variants affect mipomersen pharmacokinetics and/or responses?

3.2.1 Summary of clinical PK and pharmacodynamics

In the pivotal study, the trough plasma concentrations showed high variability (CV >50%

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for most PK parameters), as shown in the table below.

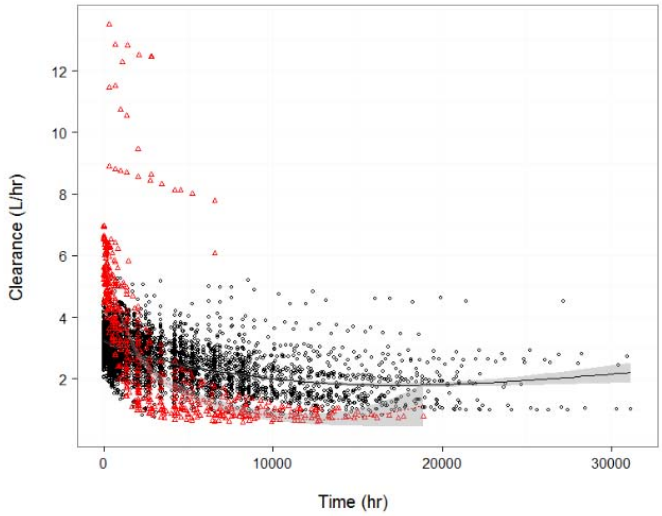
Statistical Summary of Trough Plasma Mipomersen Concentrations

Dose (mg)	Nominal Week	Nominal Day	N	Trough Plasma Mipomersen Concentrations (ng/mL) Mean	SD	SE	Min	Median	Max	CV%
160	1	1	4	0.00	0.00	0.00	0.00	0.00	0.00	NA
	3	15	4	10.5	7.12	3.56	2.89	9.81	19.6	67.7
	5	29	4	12.9	6.31	3.16	7.90	11.1	21.6	48.9
	9	57	4	21.0	6.41	3.21	15.6	19.4	29.3	30.6
	13	85	4	28.4	14.3	7.15	15.6	25.5	46.9	50.5
	17	113	3	31.0	17.8	10.3	18.7	22.9	51.4	57.4
	21	141	3	37.9	21.4	12.4	25.4	25.6	62.6	56.5
	26	176	3	36.9	25.4	14.7	22.0	22.4	66.2	68.9
	28	190	3	27.2	14.5	8.38	15.8	22.2	43.5	53.5
	36[a]	246	1	4.78	NA	NA	4.78	4.78	4.78	NA
	50[a]	344	1	0.79	NA	NA	0.79	0.79	0.79	NA
200	1	1	30	0.00	0.00	0.00	0.00	0.00	0.00	NA
	3	15	30	8.37	4.54	0.83	3.40	7.06	28.0	54.3
	5	29	29	13.0	3.99	0.74	4.97	13.2	24.8	30.7
	9	57	28	16.9	4.88	0.92	8.82	16.3	27.7	28.9
	13	85	27	21.9	7.57	1.46	7.34	21.3	43.3	34.5
	17	113	26	29.2	14.5	2.85	4.04	25.1	72.6	49.9
	21	141	25	36.2	18.3	3.66	15.6	35.4	92.1	50.6
	26	176	25	45.6	25.0	5.01	13.3	36.5	109	54.9
	28	190	25	34.1	22.2	4.45	11.7	26.6	92.3	65.3
	36[a,b]	246	4	20.2	13.5	6.74	7.19	20.1	33.5	66.7
	50[a,b]	344	4	8.70	11.7	5.83	1.67	3.52	26.1	134

Source:301012-CS5

The pharmacokinetics of mipomersen follows a two compartment linear model with first order elimination from the central compartment. A "fast decay" clearance group (11.4% of patients) and a "slow decay" clearance group (88.6% of patients) were described as shown in the figure below. Both groups have a clearance that decreases over time.

Effect of Time on Clearance by Population



Open black circles are population 1, solid black line is the trend for clearance in population 1, open red triangles are population 2, dashed red line is the trend for clearance in population 2, the grey shaded areas are the 95% confidence intervals of the trends.

Source: Genzyme Population PK-PD Analysis Report

Reviewer comment: Because of issues with the analytical validity of the mipomersen

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assay resulting from antidrug antibodies, PK results should be viewed with caution.

Wide variation was also evident in LDL-C reductions in the mipomersen-treated patients; 14 (41%) patients in the mipomersen group had LDL-C reductions <15% in the pivotal study (ISIS 301012-CS5).

LDL-C Responses in Pivotal and Supportive Trials

	ISIS 301012-CS5 [a]		MIPO3500108 [b]		ISIS 301012-CS7 [b]		ISIS 301012-CS12 [b]	
Parameter	**Placebo (N=17)**	**Mipomersen (N=34)**	**Placebo (N=18)**	**Mipomersen (N=39)**	**Placebo (N=41)**	**Mipomersen (N=83)**	**Placebo (N=52)**	**Mipomersen (N=105)**
LDL-C (mg/dL)	**Mean (SD)**		**Mean (SD)**		**Mean (SD)**		**Mean (SD)**	
Baseline	400.2 (141.5)	438.9 (138.6)	249.4 (84.3)	276.1 (72.1)	142.9 (51.6)	152.9 (48.7)	122.7 (38.6)	122.6 (31.7)
PET	388.2 (150.5)	326.2 (121.3)	263.9 (102.0)	174.9 (82.8)	146.4 (43.4)	103.9 (33.0)	113.3 (35.1)	75.3 (32.4)
% change from baseline	-3.3 (17.06)	-24.7 (19.85)*	12.5 (46.87)	-35.9 (24.71)*	5.2 (18.02)	-28.0 (26.99)*	-4.5 (24.22)	-36.9 (26.85)*
Apo B (mg/dL)	**Mean (SD)**		**Mean (SD)**		**Mean (SD)**		**Median (Q1, Q3)**	
Baseline	259.2 (84.4)	283.1 (78.4)	182.8 (48.6)	202.1 (49.1)	126.8 (33.2)	132.8 (33.9)	106 (98, 132)	114 (102, 129)
PET	252.6 (85.0)	205.4 (70.0)	193.7 (54.2)	126.8 (49.6)	133.8 (32.6)	95.0 (29.7)	108 (91, 122)	64 (52, 95)
% change from baseline	-2.5 (12.56)	-26.8 (17.04)*	11.4 (36.80)	-35.9 (22.95)*	7.0 (16.52)	-26.3 (22.16)*	-1.7 (-12.6, 7.5)	-40.6 (-53.0, -22.6)*
TC (mg/dL)	**Mean (SD)**		**Mean (SD)**		**Mean (SD)**		**Mean (SD)**	
Baseline	460.5 (132.0)	502.4 (144.5)	320.6 (87.2)	356.8 (77.0)	213.4 (54.6)	225.3 (51.5)	200.0 (42.1)	202.6 (36.8)
PET	452.1 (144.6)	389.7 (125.3)	341.5 (100.5)	251.5 (82.2)	219.0 (49.0)	176.0 (35.9)	192.2 (38.3)	147.4 (39.9)
% change from baseline	-2.0 (14.82)	-21.2 (17.69)*	11.1 (34.74)	-28.3 (20.43)*	3.9 (12.84)	-19.4 (19.25)*	-2.7 (14.58)	-26.4 (18.65)*
Non-HDL-C (mg/dL)	**Mean (SD)**		**Mean (SD)**		**Mean (SD)**		**Median (Q1, Q3)**	
Baseline	418.9 (144.5)	464.3 (145.4)	277.5 (88.3)	305.6 (78.3)	165.3 (54.5)	175.5 (51.1)	144 (125, 175)	144 (132, 171)
PET	409.1 (156.6)	345.8 (126.6)	296.7 (103.8)	198.1 (85.3)	168.2 (47.5)	125.2 (37.8)	140 (115, 165)	90 (67, 116)
% change from baseline	-2.9 (16.32)	-24.5 (19.17)*	14.2 (47.75)	-34.0 (23.80)*	3.7 (16.04)	-25.1 (25.71)*	-1.2 (-13.6, 11.5)	-38.7 (-54.0, -24.2)*
Lp(a) (mg/dL)	**Mean (SD)**		**Mean (SD)**		**Median (Q1, Q3))**		**Mean (SD)**	
Baseline	66.3 (53.1)	64.3 (41.0)	32.4 (28.5)	61.3 (68.4)	53 (17, 108)	45 (13, 93)	51.1 (48.6)	54.3 (57.0)
PET	61.6 (52.6)	43.8 (32.1)	32.1 (28.1)	43.3 (54.3)	51 (18, 108)	35 (9, 56)	49.5 (47.3)	39.6 (47.0)
% change from baseline	-7.9 (21.87)	-31.1 (23.02)*	-1.5 (25.74)	-32.7 (32.98)*	0.0 (-8.0, 13.0)	-21.1 (-37.9, 0.0)*	2.3 (28.09)	-24.0 (24.47)*

Apo, B, apolipoprotein B; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(s); PET, primary efficacy time point; Q1, first quartile; Q3, third quartile; SD, standard deviation; TC, total cholesterol

Data presented as mean and SD unless the result of the Kolmogorov Smirnov test was ≤0.05 (indicating non-normal distribution), in which case data are presented as median and interquartile range.

* The percent changes from baseline in the mipomersen group was statistically significant (p<0.001 based on the Wilcoxon signed rank test) for all 4 studies.

[a] Pivotal study.

[b] Supportive study.

Source: ISIS 301012-CS5 CSR Section 11.1; MIPO03500108 CSR Section 11.1; ISIS 301012-CS7 CSR Section 11.1; and ISIS 301012-CS12 CSR Section 11.1

Source: ISIS 301012-CS5, MIPO03500108, ISIS 301012-CS7, ISIS 301012-CS12

3.2.2 Applicant's analysis

The four Phase 3 studies submitted included a genetically diverse population. The pivotal trial (ISIS 301012-CS5) included HoFH patients of which 42 out of the 51 in the trial had confirmed LDL-R gene mutations. These mutations were a combination of true homozygotes (n=27) and complex heterozygotes (n=11). D206 was the most common allele (14 homozygous, 7 heterozygous). Other patients included in the pivotal trial that met the inclusion criteria may have mutations in other genes that contribute to the phenotype (APOB, PCSK9). The supportive studies (MIPO3500108, ISIS 301012-CS7, ISIS 301012-CS12) included patients with HeFH and/or primary hypercholesterolemia. The applicant's analyses suggest that responses did not vary significantly as a function of LDLR genotype.

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Reviewer comment: The aforementioned findings are based on the applicant's assessment and no specific data were presented. Analyses regarding effects of LDLR mutation on mipomersen responses were not reproduced by the reviewer as LDLR is not the direct target of mipomersen. The applicant also referred to an analysis based on an APOB binding site mutation, although these data were not presented.

3.2.3 Reviewer's analysis

Because of the high variability in exposures and responses, we evaluated the APO B sequence (b) (4) for polymorphisms (b) (4) (b) (4)

4 SUMMARY AND CONCLUSIONS

Mipomersen and its metabolites may have alternate binding sites that account for inflammatory and other adverse effects observed in clinical trials, although it is not known whether such events result from off-target, hybridization-dependent mechanisms or hybridization-independent mechanism as proposed by the sponsor. BLAST searches to evaluate off-target binding of mipomersen identified four transcripts that matched mipomersen as follows: VPS37A, MDM2, PRKG2, and expressed sequence tag (EST) similar to B cell Growth Factor. Mipomersen did not modulate expression of these genes in human hepatocyte studies (study GT-348-EF-34). The sponsor's 2003 sequence alignment analysis was updated, confirming the sponsor's finding that no human genome regions other than APOB are 100% complementary to mipomersen; other alignments had multiple mismatches. However, patients may be exposed to all possible sequence lengths of mipomersen metabolites (based on Sponsor's study 301012-IS07) and we are unable to rule out off-target binding of other chain-shortened products of mipomersen.

Wide variability in mipomersen exposure and responses were observed in clinical trials. LDLR genotype, available for a subset of the pivotal trial participants (ISIS 301012-CS5), was not identified as a major predictor of clinical response (not confirmed by reviewer). (b) (4) However, the effect of this variant has not been formally evaluated and may be of limited relevance.

Future clinical trials should include an assessment of changes in the expression of interferon and related transcripts that were identified in sequence alignment searches, to the extent that this could be a mechanistic basis for the observed inflammatory adverse reactions. Additionally, future clinical studies should also include an assessment of APOB gene variants, (b) (4), that are present in the binding region for

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mipomersen.

5 RECOMMENDATIONS

No post-marketing studies or labeling revisions are necessary from the perspective of the Genomics Group.

5.1 Post-marketing studies

None.

5.2 Labeling

None.

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4.3 OCP FILING MEMO

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	203568	**Brand Name**	KYNAMRO
OCP Division (I, II, III, IV, V)	DCP2	**Generic Name**	Mipomersen sodium
Medical Division	DMEP	**Drug Class**	antisense oligonucleotide
OCP Reviewer	Immo Zadezensky, Ph.D.	**Indication(s)**	as an adjunct to maximally tolerated lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol, apolipoprotein B, total cholesterol, non-high density lipoprotein-cholesterol and lipoprotein (a) in patients with homozygous familial hypercholesterolemia
OCP Team Leader	Jaya Vaidyanathan, Ph.D. (acting)	**Dosage Form**	1. Single-use vial containing 1 mL of a 200 mg/mL solution 2. Single-use pre-filled syringe containing 1 mL of a 200 mg/mL solution.
Pharmacometrics Reviewer	TBD	**Dosing Regimen**	Once weekly
Date of Submission	03/29/2012	**Route of Administration**	subcutaneous
Estimated Due Date of OCP Review	12/01/2012	**Sponsor**	Genzyme Corporation
Medical Division Due Date	12/04/2012	**Priority Classification**	Standard
PDUFA Due Date	01/29/2013		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	**X**	**1**		**301012-IS04**
Pharmacokinetics (e.g., Phase I) -	**X**			
Healthy Volunteers-				
single dose:	**x**	**1**		MIPO3700710 –in Japanese

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multiple dose:	x	4		ISIS301012-CS1 ISIS301012-CS101 ISIS301012-CS301 (with topical corticosteroid cream) MIPO3200309 (relative BA study)
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:	x	2		Lipid lowering drugs: ISIS301012-CS2 Warfarin: MIPO2900509 (Clinical summary mentions this study as MIPO2900210!)
In-vitro:	x	5		CYP450 inhibition: 301012-IS05 CYP450 induction: DMPK10-R015 In vitro metabolism: 301012-IS07 In vitro metabolism: DMPK10-R024 P-gp interaction: DMPK09-R037
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -		1		
Phase 2:	X			
Phase 3:	X			
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -		1		
Data rich:	X			
Data sparse:	X			
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	x	1		MIPO3200309 (evaluated three SC regimens)
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				

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Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		16		

Filability and QBR comments		
	"X" if yes	Comments
Application filable?	X	Yes, it is filable.
Comments sent to firm?		None
QBR questions (key issues to be considered)	• Is there an exposure response relationship for mipomersen? • Is dose adjustment required based on covariates? • Is there exposure response for safety? • Is the dose and dose regimen appropriate? • What is the interaction potential with other lipid lowering drugs?	
Other comments or information not included above	•None	
Primary reviewer Signature and Date	Immo Zadezensky, Ph.D.	
Secondary reviewer Signature and Date	Jaya Vaidyanathan, Ph.D.	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA_or_Supplement_090808

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8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?		X		
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
__Yes_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Immo Zadezensky, Ph.D.
Reviewing Clinical Pharmacologist Date

Jaya Vaidyanathan, Ph.D.
Team Leader/Supervisor (acting) Date

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The purpose of this document is to identify refuse to file and special issues, describe the materials needed for review but not included in the application, and summarize the application relevant to clinical pharmacology.

1. Identify refuse to file issues

Are there any refuse to file issues?

- No, the application is fileable.

Does the applicant provide sufficient data to support the labeling claims?

- Yes.

2. Identify special issues

What are the specific issues regarding this application?

1. Is there and exposure response relationship for mipomersen?
2. Is dose adjustment required based on covariates?
3. Is there exposure response for safety?
4. Is the dose and dose regimen appropriate?
5. What is the interaction potential with other lipid lowering drugs?

3. Identify materials needed for review but not included in the application

What are the materials needed for review but not included in the application?

None.

4. Summary of the application relevant to clinical pharmacology

The sponsor Genzyme Corporation is submitting a 505(b)(1) new drug application (NDA 203-568) seeking marketing approval for mipomersen sodium. The sponsor's intended indication is an adjunct to maximally tolerated lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol, apolipoprotein B, total cholesterol, non-high density lipoprotein-cholesterol and lipoprotein (a) in patients with homozygous familial hypercholesterolemia. Familial hypercholesterolaemia (FH), including HoFH, is a genetic disorder characterized by mutations in the low-density lipoprotein receptor (LDLr) gene, high LDL-C levels, and premature cardiovascular disease.
The chemical structure of mipomersen is shown in Figure 1.

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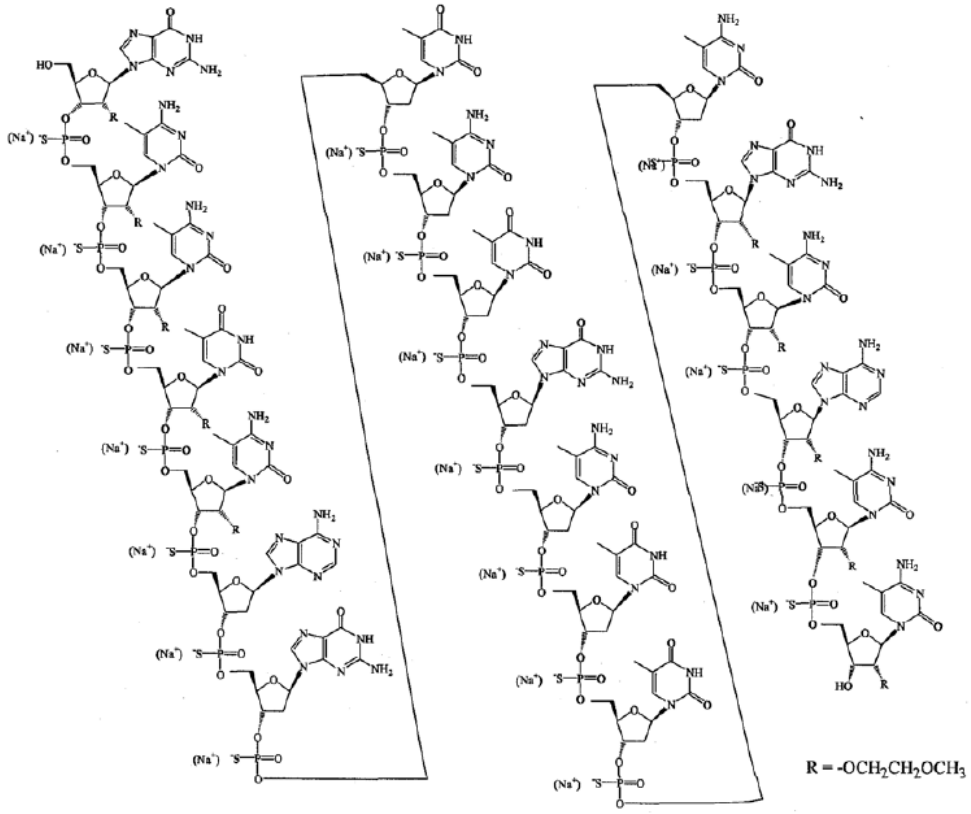
Figure 1 Chemical Structure of Mipomersen Sodium



Source: Sponsor proposed label, Figure 1

According to the sponsor the overall prevalence of HoFH in the US is approximately 1:1,000,000 based on the frequency of HeFH of 1:500, and extrapolates to 300 patients. Mipomersen received Orphan Drug Designation (No.06-2214) for the treatment of homozygous familial hypercholesterolemia on May 23, 2006.

The sponsor intends to market two separate presentations of the drug product:

1. Single-use vial containing 1 mL of a 200 mg/mL solution
2. Single-use pre-filled syringe containing 1 mL of a 200 mg/mL solution.

The proposed dose of mipomersen is 200 mg once weekly as subcutaneous (SC) injection.

Mipomersen is the first in its therapeutic class. The sponsor describes the mechanism of action as an antisense oligonucleotide targeted to human messenger ribonucleic acid (mRNA) for apo B-

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100, the principal apolipoprotein of LDL and its metabolic precursor, VLDL. Mipomersen sodium is complementary to the coding region of the mRNA for apo B-100, and binds by Watson and Crick base pairing. The hybridization of mipomersen sodium to the cognate mRNA results in RNase H-mediated degradation of the cognate mRNA thus inhibiting translation of the apo B-100 protein and results in reductions of apo B and LDL-C in patients with HoFH.

The clinical database for mipomersen includes 20 clinical studies. Of the 20 studies, one long term extension study is still ongoing. Two additional studies have recently been initiated; interim data was not available for the NDA.

The efficacy of mipomersen for the proposed indication is evaluated in one pivotal placebo-controlled, double-blind Phase 3 clinical study conducted in patients with HoFH (ISIS 301012-CS5) and three supportive similarly designed Phase 3 studies:

- in patients with Severe HeFH (MIPO3500108)
- in patients with HeFH and CAD (ISIS 301012-CS7)
- and in patients with high risk hypercholesterolaemia with and without Type 2 diabetes (ISIS 301012-CS12).

The following studies provided data for the NDA :

Phase 1 Studies		**Phase 2 Studies**		**Phase 3 Studies**	
Study #	Description	Study #	Description	Study #	Description
ISIS 301012-CS1	Dose ranging study in healthy volunteers with mild hypercholesterolaemia	ISIS 301012-CS3	Phase 2 placebo-controlled dose-ranging study in patients with mild hypercholesterolaemia not on lipid-lowering therapy	ISIS 301012-CS5	Phase 3 randomised, double-blind, placebo-controlled efficacy and safety study in patients with HoFH on lipid-lowering therapy
ISIS 301012-CS2	Drug-drug pharmacokinetic (PK) interaction study in healthy volunteers	ISIS 301012-CS4	Phase 2 placebo-controlled dose-escalation study in patients with primary hypercholesterolaemia on stable statin therapy	MIPO3500108	patients with Severe HeFH
ISIS 301012-CS101	Proof-of-concept study to evaluate oral formulation in healthy volunteers with mild hypercholesterolaemia	(ISIS 301012-CS8	Phase 2 open label dose-escalation add-on therapy study in patients with HoFH	ISIS 301012-CS7	Phase 3 randomised, double-blind, placebo-controlled efficacy and safety study in patients with HeFH and CAD on lipid-lowering therapy

Reference ID: 3224357

(ISIS 301012-CS301	Study to investigate mechanism of injection site reactions (ISRs) in healthy volunteers	ISIS 301012-CS9	Phase 2 dose-escalation add-on therapy study in patients with HeFH	(ISIS 301012-CS12	Phase 3 randomised, double-blind, placebo-controlled efficacy and safety study in patients with high-risk hypercholesterolaemia (CHD or CHD-risk equivalent) on lipid-lowering therapy
MIPO2800209	A randomised, double-blind crossover study to define the ECG effects of mipomersen in healthy men and women	ISIS 301012-CS10	Phase 2 placebo-controlled study in patients with varying degrees of hyperlipidaemia		
MIPO2900210	A drug-drug interaction study to assess the effects of mipomersen on warfarin pharmacodynamics (PD) and PK in healthy adult subjects	ISIS 301012-CS19	Placebo-controlled study in high risk (NCEP-ATP III) patients intolerant to statins		
MIPO3200309	Relative bioavailability, PK, safety, and tolerability of three weeks of dosing with different SC regimens of mipomersen in healthy volunteers				
MIPO3700710	A Phase 1 study to evaluate the pharmacokinetics, safety, and tolerability of single doses of mipomersen administered SC to Japanese healthy subjects				

Reference ID: 3224357

Additionally, there are the following open label extensions:

- **Ongoing Open-Label Extension (OLE) Study:**
  - Long-term efficacy and safety: ISIS 301012-CS6 (ongoing) includes patients from three Phase 3 studies (ISIS 301012-CS5, MIPO3500108, and ISIS 301012-CS7).
- **Completed Open-Label Extension Study:**
  - Long-term efficacy and safety: ISIS 301012-CS17 includes patients from two Phase 2 studies (ISIS 301012-CS8 and ISIS 301012-CS9).

Three different formulations of mipomersen were evaluated in clinical studies:

(1) a 200 mg/mL solution, which was the formula used in the vast majority of the clinical studies and all Phase 3 studies

and two early development formulations:

(2) a 250 mg/mL solution; and,

(3) a 100 mg/vial lyophilised powder for reconstitution

Different Forms of Drug Product Utilized in Mipomersen Studies

Study Number	Solution		Lyophilised	Oral
	CONC (mg/mL)	Fill VOL (mL)	mg/vial	mg/capsule
ISIS 301012-CS1	250	0.5	n/a	n/a
ISIS 301012-CS2	n/a	n/a	100	n/a
ISIS 301012-CS3	n/a	n/a	100	n/a
ISIS 301012-CS4	200	1.0	n/a	n/a
ISIS 301012-CS5	200	1.0	n/a	n/a
ISIS 301012-CS6	200	1.0	n/a	n/a
ISIS 301012-CS7	200	1.0	n/a	n/a
ISIS 301012-CS8	200	1.0	n/a	n/a
ISIS 301012-CS9	200	1.0	n/a	n/a
ISIS 301012-CS10 (Cohort A-F)	250	0.5	n/a	n/a
ISIS 301012-CS10 (Cohort G)	200	1.0	n/a	n/a
ISIS 301012-CS12	200	1.0	n/a	n/a
ISIS 301012-CS17	200	1.0	n/a	n/a
ISIS 301012-CS19	200	1.0	n/a	n/a
ISIS 301012-CS301	250	0.5	n/a	n/a
ISIS 301012-CS101	n/a	n/a	100	100
MIPO2800209	200	1.0	n/a	n/a
MIPO2900210	200	1.0	n/a	n/a
MIPO3200309	200	1.0	n/a	n/a
MIPO3500108	200	1.0	n/a	n/a
MIPO3700710	200	1.0	n/a	n/a

CONC = concentration; VOL = volume; n/a = not applicable

NOTE: Studies MIPO1600810 and MIPO3801011 are not included in this table because no patients had been treated in these studies as of the cutoff date for this report.

No formal comparative bioavailability or bioequivalence studies were conducted to compare the 250 mg/mL and 200 mg/mL of drug product. According to the sponsor, the mipomersen formulation intended for marketing purposes (i.e., 200 mg/mL solution for SC administration) was used in most Phase 2 and all Phase 3 clinical studies.

rence ID: 3135183

Reference ID: 3224357

Reviewer comment: During the Pre-NDA review stage the Clinical Pharmacology program appeared acceptable to the Clinical Pharmacology Previewer (for detail please see Dr. Jee Eun Lee's review, DARRTS date 12/09/2010)

According to the sponsor, the PK of mipomersen was well described by a 2-compartment linear model with first order elimination from the central compartment. In a Population PK Analysis, clearance of mipomersen was found to decrease over time with two subpopulations exhibiting different rates of clearance decay over time.

In population 1 (the slow decay clearance group, representing the majority or 88.6% of patients), mipomersen clearance is predicted to decrease from 2.76 L/h on the first day of dosing to 2.07 L/h after 1 year of dosing; a decrease of approximately 25%. In population 2 (the fast decay clearance group representing 11.4% of patients), mipomersen clearance is predicted to decrease from 5.65 L/hr on the first day of dosing to 0.79 L/hr after 1 year of dosing; a decrease of approximately 86%. According to the sponsor, there is an overlap in patients between the "fast decay" clearance group and an observed high trough drug level group.

According to the sponsor, no clear clinical sequelae or consistent pattern of clinical findings on efficacy or safety were noted in the 29 patients with the highest trough levels but a larger proportion of these patients appeared to have Flu Like Symptoms (FLS) compared to the overall population, particularly in the OLE study ISIS 301012-CS6.

In the population PK analysis, the effects of disease type, creatinine clearance, age, weight, gender, and race were investigated as potential covariates of PK variability for mipomersen. Except for creatinine clearance, none of these covariates were identified as being predictive of variability for mipomersen PK. No dose adjustment is recommended based on these factors by the sponsor.

The sponsor also proposes contraindication in patients with significant hepatic dysfunction.

According to the sponsor, Mipomersen is not a substrate, an inhibitor, or an inducer of major cytochrome P450 (CYP450) isozymes, and is not an inhibitor of and likely not a substrate for P-glycoprotein.

Two dedicated drug-drug interactions studies conducted in healthy volunteers evaluated the potential for drug interactions between mipomersen and 2 oral hypolipidemic agents (simvastatin and ezetimibe), and between mipomersen and warfarin. According to the sponsor, modest changes in PK parameters were observed for simvastatin, its metabolite (simvastatin acid), and ezetimibe upon co-administration of mipomersen.

In the population PK analysis, coadministration of mipomersen with 3-hydroxyl-3-methylglutaryl-coenzyme A (HMG CoA) reductase inhibitors, lipid modifying agent (ezetimibe), nicotinic acid, and derivatives of vasopressors, selective beta blocking agents, angiotensin converting enzyme (ACE) inhibitors, and platelet aggregation inhibitors (excluding heparin) did not alter the PK of mipomersen.

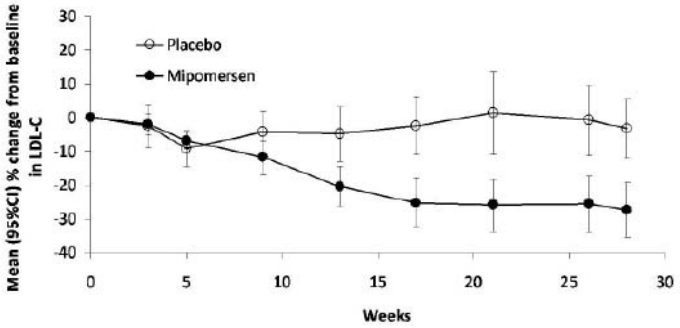
Reference ID: 3224357

Clinical Efficacy and Safety:

In the six-month Phase 3 pivotal clinical trial of mipomersen in patients with HoFH (ISIS 301012-CS5, Figure 2), who were already taking stable, maximally tolerated doses of statins and other lipid-lowering medications, the addition of mipomersen reduced LDL-C by a mean of 24.7%, corresponding to an absolute mean reduction of LDL-C of 112.7 mg/dL (2.92 mmol/L) compared with 3.3% corresponding to a mean reduction of 12.0 mg/dL (0.31 mmol/L) for the placebo group. In this study, the mean treated baseline LDL-C levels were 438.9 mg/dL (11.37 mmol/L) for the mipomersen group and 400.2 mg/dL (10.37 mmol/L) for the placebo group.

Furthermore, data from three supportive Phase 3 studies (MIPO3500108, ISIS 301012- CS7, and ISIS 301012-CS12) demonstrated that mipomersen therapy resulted in a clinically meaningful and statistically significant mean percent reduction in LDL-C compared with placebo in patients with Severe HeFH or with HeFH and CAD (-35.9% versus 12.5% in MIPO3500108; -28.0% versus 5.2% in ISIS 301012-CS7) and in patients with hypercholesterolaemia at high risk for CHD (-36.9% versus 4.5% in ISIS 301012-CS12). As presented by the sponsor, the addition of mipomersen to statins and other lipid-lowering medications substantially reduced LDL-C levels in patients with HoFH.

Figure 2 Mean Percent Change in LDL Cholesterol in Patients in Pivotal Study ISIS 301012-CS5 – Full Analysis Set

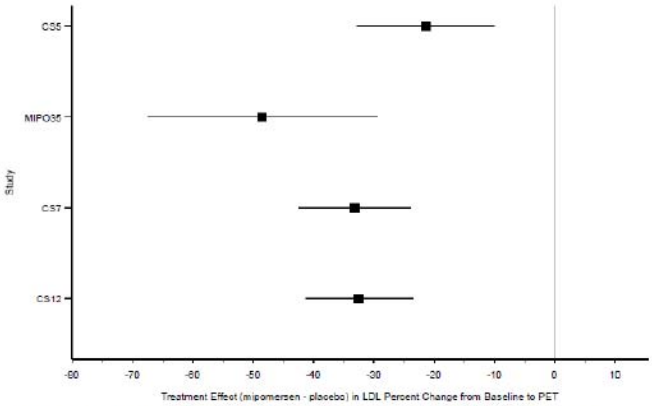


CI, confidence interval. LDL-C, low-density lipoprotein cholesterol
Vertical bars indicate 95% confidence intervals.

Source: Sponsor's Clinical Overview, Figure 1, page 43

Reference ID: 3224357

Figure 3 Low-Density Lipoprotein Cholesterol Percent Change from Baseline to Primary Efficacy Time Point Treatment Effects (Difference Between Mipomersen and Placebo Treatment) and 95% Confidence Intervals for Phase 3 Clinical Studies



CS5, Study ISIS 301012-CS5; CS7, Study ISIS 301012-CS7; CS12, Study ISIS 301012-CS12; LDL, low-density lipoprotein cholesterol; MIPO35, Study MIPO3500108; PET, primary efficacy time point

Source: Sponsor's Clinical Overview, Figure 2, page 45

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/s/

IMMO ZADEZENSKY
05/23/2012

Reference ID: 3224357

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/s/

RITESH JAIN
11/30/2012

LYLE CANIDA
11/30/2012

MICHAEL A PACANOWSKI
11/30/2012

NITIN MEHROTRA
11/30/2012

IMMO ZADEZENSKY
11/30/2012

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	203568	**Brand Name**	KYNAMRO
OCP Division (I, II, III, IV, V)	DCP2	**Generic Name**	Mipomersen sodium
Medical Division	DMEP	**Drug Class**	antisense oligonucleotide
OCP Reviewer	Immo Zadezensky, Ph.D.	**Indication(s)**	as an adjunct to maximally tolerated lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol, apolipoprotein B, total cholesterol, non-high density lipoprotein-cholesterol and lipoprotein (a) in patients with homozygous familial hypercholesterolemia
OCP Team Leader	Jaya Vaidyanathan, Ph.D. (acting)	**Dosage Form**	1. Single-use vial containing 1 mL of a 200 mg/mL solution 2. Single-use pre-filled syringe containing 1 mL of a 200 mg/mL solution.
Pharmacometrics Reviewer	TBD	**Dosing Regimen**	Once weekly
Date of Submission	03/29/2012	**Route of Administration**	subcutaneous
Estimated Due Date of OCP Review	12/01/2012	**Sponsor**	Genzyme Corporation
Medical Division Due Date	12/04/2012	**Priority Classification**	Standard
PDUFA Due Date	01/29/2013		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	**X**	**1**		**301012-IS04**
Pharmacokinetics (e.g., Phase I) -	**X**			
Healthy Volunteers-				
single dose:	**x**	**1**		MIPO3700710 –in Japanese

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

multiple dose:	**x**	**4**		**ISIS301012-CS1 ISIS301012-CS101 ISIS301012-CS301 (with topical corticosteroid cream) MIPO3200309 (relative BA study)**
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:	**x**	**2**		**Lipid lowering drugs: ISIS301012-CS2 Warfarin: MIPO2900509 (Clinical summary mentions this study as MIPO2900210!)**
In-vitro:	**x**	**5**		**CYP450 inhibition: 301012-IS05 CYP450 induction: DMPK10-R015 In vitro metabolism: 301012-IS07 In vitro metabolism: DMPK10-R024 P-gp interaction: DMPK09-R037**
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -		**1**		
Phase 2:	**X**			
Phase 3:	**X**			
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -		**1**		
Data rich:	**X**			
Data sparse:	**X**			
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**x**	**1**		**MIPO3200309 (evaluated three SC regimens)**
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**16**		

Filability and QBR comments

	"X" if yes	Comments
Application filable?	**X**	**Yes, it is filable.**
Comments sent to firm?		**None**
QBR questions (key issues to be considered)	• Is there an exposure response relationship for mipomersen? • Is dose adjustment required based on covariates? • Is there exposure response for safety? • Is the dose and dose regimen appropriate? • What is the interaction potential with other lipid lowering drugs?	
Other comments or information not included above	•None	
Primary reviewer Signature and Date	**Immo Zadezensky, Ph.D.**	
Secondary reviewer Signature and Date	**Jaya Vaidyanathan, Ph.D.**	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	**Yes**	**No**	**N/A**	**Comment**
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?		X		
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
__Yes_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Immo Zadezensky, Ph.D.
Reviewing Clinical Pharmacologist Date

Jaya Vaidyanathan, Ph.D.
Team Leader/Supervisor (acting) Date

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

The purpose of this document is to identify refuse to file and special issues, describe the materials needed for review but not included in the application, and summarize the application relevant to clinical pharmacology.

1. Identify refuse to file issues

Are there any refuse to file issues?

- No, the application is fileable.

Does the applicant provide sufficient data to support the labeling claims?

- Yes.

2. Identify special issues

What are the specific issues regarding this application?

1. Is there and exposure response relationship for mipomersen?
2. Is dose adjustment required based on covariates?
3. Is there exposure response for safety?
4. Is the dose and dose regimen appropriate?
5. What is the interaction potential with other lipid lowering drugs?

3. Identify materials needed for review but not included in the application

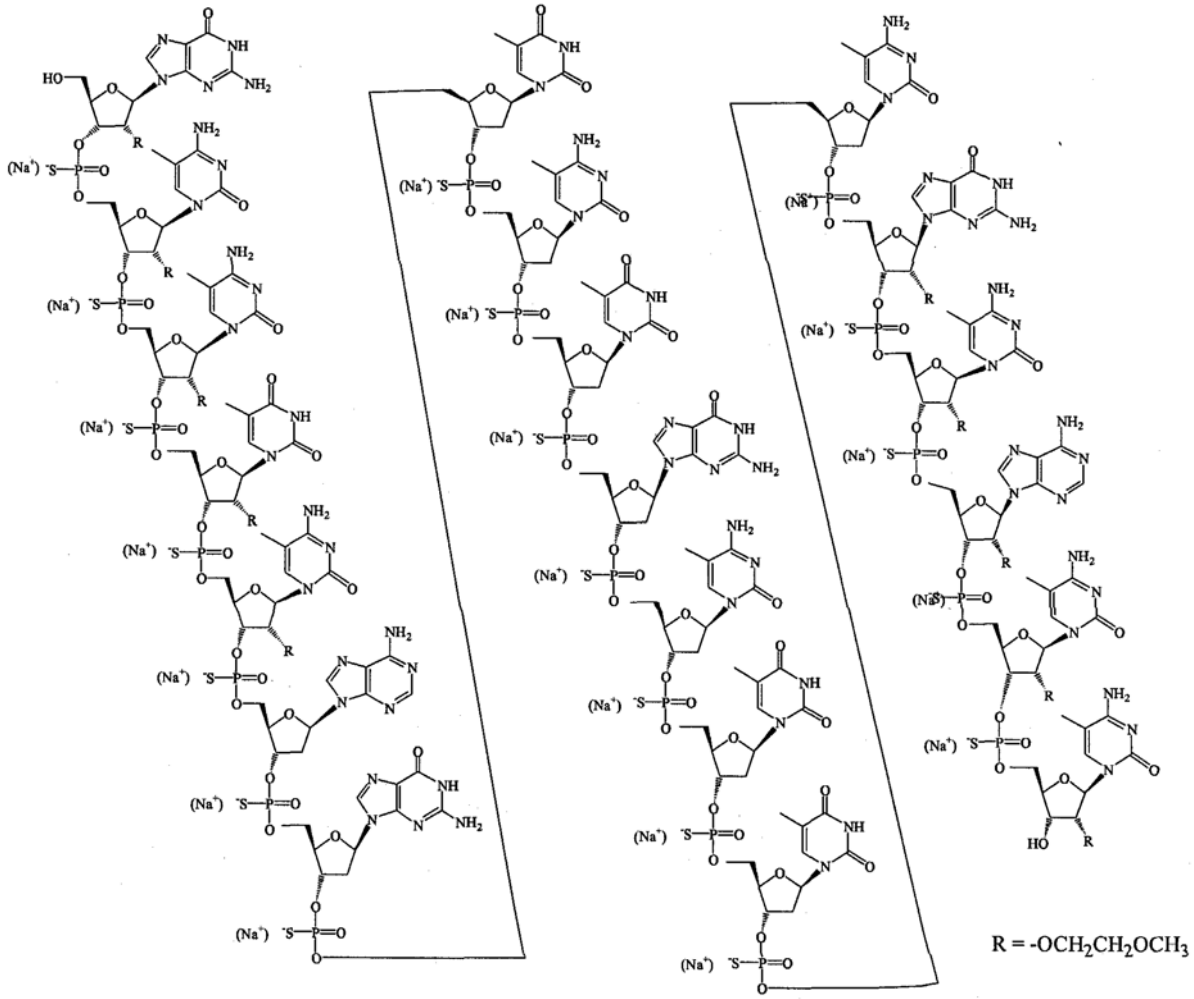
What are the materials needed for review but not included in the application?

None.

4. Summary of the application relevant to clinical pharmacology

The sponsor Genzyme Corporation is submitting a 505(b)(1) new drug application (NDA 203-568) seeking marketing approval for mipomersen sodium. The sponsor's intended indication is an adjunct to maximally tolerated lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol, apolipoprotein B, total cholesterol, non-high density lipoprotein-cholesterol [redacted] (b) (4) in patients with homozygous familial hypercholesterolemia. Familial hypercholesterolaemia (FH), including HoFH, is a genetic disorder characterized by mutations in the low-density lipoprotein receptor (LDLr) gene, high LDL-C levels, and premature cardiovascular disease.
The chemical structure of mipomersen is shown in Figure 1.

Figure 1 Chemical Structure of Mipomersen Sodium



Source: Sponsor proposed label, Figure 1

According to the sponsor the overall prevalence of HoFH in the US is approximately 1:1,000,000 based on the frequency of HeFH of 1:500, and extrapolates to 300 patients. Mipomersen received Orphan Drug Designation (No.06-2214) for the treatment of homozygous familial hypercholesterolemia on May 23, 2006.

The sponsor intends to market two separate presentations of the drug product:

1. Single-use vial containing 1 mL of a 200 mg/mL solution
2. Single-use pre-filled syringe containing 1 mL of a 200 mg/mL solution.

The proposed dose of mipomersen is 200 mg once weekly as subcutaneous (SC) injection.

Mipomersen is the first in its therapeutic class. The sponsor describes the mechanism of action as an antisense oligonucleotide targeted to human messenger ribonucleic acid (mRNA) for apo B-

100, the principal apolipoprotein of LDL and its metabolic precursor, VLDL. Mipomersen sodium is complementary to the coding region of the mRNA for apo B-100, and binds by Watson and Crick base pairing. The hybridization of mipomersen sodium to the cognate mRNA results in RNase H-mediated degradation of the cognate mRNA thus inhibiting translation of the apo B-100 protein and results in reductions of apo B and LDL-C in patients with HoFH.

The clinical database for mipomersen includes 20 clinical studies. Of the 20 studies, one long term extension study is still ongoing. Two additional studies have recently been initiated; interim data was not available for the NDA.

The efficacy of mipomersen for the proposed indication is evaluated in one pivotal placebo-controlled, double-blind Phase 3 clinical study conducted in patients with HoFH (ISIS 301012-CS5) and three supportive similarly designed Phase 3 studies:

- in patients with Severe HeFH (MIPO3500108)
- in patients with HeFH and CAD (ISIS 301012-CS7)
- and in patients with high risk hypercholesterolaemia with and without Type 2 diabetes (ISIS 301012-CS12).

The following studies provided data for the NDA :

Phase 1 Studies		**Phase 2 Studies**		**Phase 3 Studies**	
Study #	Description	Study #	Description	Study #	Description
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ISIS 301012-CS2	Drug-drug pharmacokinetic (PK) interaction study in healthy volunteers	ISIS 301012-CS4	Phase 2 placebo-controlled dose-escalation study in patients with primary hypercholesterolaemia on stable statin therapy	MIPO3500108	patients with Severe HeFH
ISIS 301012-CS101	Proof-of-concept study to evaluate oral formulation in healthy volunteers with mild hypercholesterolaemia	(ISIS 301012-CS8	Phase 2 open label dose-escalation add-on therapy study in patients with HoFH	ISIS 301012-CS7	Phase 3 randomised, double-blind, placebo-controlled efficacy and safety study in patients with HeFH and CAD on lipid-lowering therapy

(ISIS 301012-CS301	Study to investigate mechanism of injection site reactions (ISRs) in healthy volunteers	ISIS 301012-CS9	Phase 2 dose-escalation add-on therapy study in patients with HeFH	(ISIS 301012-CS12	Phase 3 randomised, double-blind, placebo-controlled efficacy and safety study in patients with high-risk hypercholesterolaemia (CHD or CHD-risk equivalent) on lipid-lowering therapy
MIPO2800209	A randomised, double-blind crossover study to define the ECG effects of mipomersen in healthy men and women	ISIS 301012-CS10	Phase 2 placebo-controlled study in patients with varying degrees of hyperlipidaemia		
MIPO2900210	A drug-drug interaction study to assess the effects of mipomersen on warfarin pharmacodynamics (PD) and PK in healthy adult subjects	ISIS 301012-CS19	Placebo-controlled study in high risk (NCEP-ATP III) patients intolerant to statins		
MIPO3200309	Relative bioavailability, PK, safety, and tolerability of three weeks of dosing with different SC regimens of mipomersen in healthy volunteers				
MIPO3700710	A Phase 1 study to evaluate the pharmacokinetics, safety, and tolerability of single doses of mipomersen administered SC to Japanese healthy subjects				

Additionally, there are the following open label extensions:

- **Ongoing Open-Label Extension (OLE) Study:**
  - Long-term efficacy and safety: ISIS 301012-CS6 (ongoing) includes patients from three Phase 3 studies (ISIS 301012-CS5, MIPO3500108, and ISIS 301012-CS7).
- **Completed Open-Label Extension Study:**
  - Long-term efficacy and safety: ISIS 301012-CS17 includes patients from two Phase 2 studies (ISIS 301012-CS8 and ISIS 301012-CS9).

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(1) a 200 mg/mL solution, which was the formula used in the vast majority of the clinical studies and all Phase 3 studies

and two early development formulations:

(2) a 250 mg/mL solution; and,

(3) a 100 mg/vial lyophilised powder for reconstitution

Different Forms of Drug Product Utilized in Mipomersen Studies

Study Number	Solution		Lyophilised	Oral
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ISIS 301012-CS2	n/a	n/a	100	n/a
ISIS 301012-CS3	n/a	n/a	100	n/a
ISIS 301012-CS4	200	1.0	n/a	n/a
ISIS 301012-CS5	200	1.0	n/a	n/a
ISIS 301012-CS6	200	1.0	n/a	n/a
ISIS 301012-CS7	200	1.0	n/a	n/a
ISIS 301012-CS8	200	1.0	n/a	n/a
ISIS 301012-CS9	200	1.0	n/a	n/a
ISIS 301012-CS10 (Cohort A-F)	250	0.5	n/a	n/a
ISIS 301012-CS10 (Cohort G)	200	1.0	n/a	n/a
ISIS 301012-CS12	200	1.0	n/a	n/a
ISIS 301012-CS17	200	1.0	n/a	n/a
ISIS 301012-CS19	200	1.0	n/a	n/a
ISIS 301012-CS301	250	0.5	n/a	n/a
ISIS 301012-CS101	n/a	n/a	100	100
MIPO2800209	200	1.0	n/a	n/a
MIPO2900210	200	1.0	n/a	n/a
MIPO3200309	200	1.0	n/a	n/a
MIPO3500108	200	1.0	n/a	n/a
MIPO3700710	200	1.0	n/a	n/a

CONC = concentration; VOL = volume; n/a = not applicable

NOTE: Studies MIPO1600810 and MIPO3801011 are not included in this table because no patients had been treated in these studies as of the cutoff date for this report.

No formal comparative bioavailability or bioequivalence studies were conducted to compare the 250 mg/mL and 200 mg/mL of drug product. According to the sponsor, the mipomersen formulation intended for marketing purposes (i.e., 200 mg/mL solution for SC administration) was used in most Phase 2 and all Phase 3 clinical studies.

Reviewer comment: During the Pre-NDA review stage the Clinical Pharmacology program appeared acceptable to the Clinical Pharmacology Previewer (for detail please see Dr. Jee Eun Lee's review, DARRTS date 12/09/2010)

According to the sponsor, the PK of mipomersen was well described by a 2-compartment linear model with first order elimination from the central compartment. In a Population PK Analysis, clearance of mipomersen was found to decrease over time with two subpopulations exhibiting different rates of clearance decay over time.

In population 1 (the slow decay clearance group, representing the majority or 88.6% of patients), mipomersen clearance is predicted to decrease from 2.76 L/h on the first day of dosing to 2.07 L/h after 1 year of dosing; a decrease of approximately 25%. In population 2 (the fast decay clearance group representing 11.4% of patients), mipomersen clearance is predicted to decrease from 5.65 L/hr on the first day of dosing to 0.79 L/hr after 1 year of dosing; a decrease of approximately 86%. According to the sponsor, there is an overlap in patients between the "fast decay" clearance group and an observed high trough drug level group.

According to the sponsor, no clear clinical sequelae or consistent pattern of clinical findings on efficacy or safety were noted in the 29 patients with the highest trough levels but a larger proportion of these patients appeared to have Flu Like Symptoms (FLS) compared to the overall population, particularly in the OLE study ISIS 301012-CS6.

In the population PK analysis, the effects of disease type, creatinine clearance, age, weight, gender, and race were investigated as potential covariates of PK variability for mipomersen. Except for creatinine clearance, none of these covariates were identified as being predictive of variability for mipomersen PK. No dose adjustment is recommended based on these factors by the sponsor.

The sponsor also proposes contraindication in patients with significant hepatic dysfunction.

According to the sponsor, Mipomersen is not a substrate, an inhibitor, or an inducer of major cytochrome P450 (CYP450) isozymes, and is not an inhibitor of and likely not a substrate for P-glycoprotein.

Two dedicated drug-drug interactions studies conducted in healthy volunteers evaluated the potential for drug interactions between mipomersen and 2 oral hypolipidemic agents (simvastatin and ezetimibe), and between mipomersen and warfarin. According to the sponsor, modest changes in PK parameters were observed for simvastatin, its metabolite (simvastatin acid), and ezetimibe upon co-administration of mipomersen.

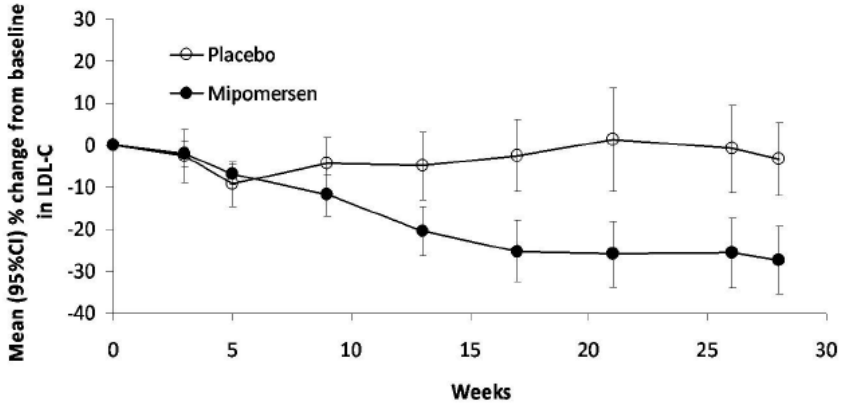
In the population PK analysis, coadministration of mipomersen with 3-hydroxyl-3-methylglutaryl-coenzyme A (HMG CoA) reductase inhibitors, lipid modifying agent (ezetimibe), nicotinic acid, and derivatives of vasopressors, selective beta blocking agents, angiotensin converting enzyme (ACE) inhibitors, and platelet aggregation inhibitors (excluding heparin) did not alter the PK of mipomersen.

Clinical Efficacy and Safety:

In the six-month Phase 3 pivotal clinical trial of mipomersen in patients with HoFH (ISIS 301012-CS5, Figure 2), who were already taking stable, maximally tolerated doses of statins and other lipid-lowering medications, the addition of mipomersen reduced LDL-C by a mean of 24.7%, corresponding to an absolute mean reduction of LDL-C of 112.7 mg/dL (2.92 mmol/L) compared with 3.3% corresponding to a mean reduction of 12.0 mg/dL (0.31 mmol/L) for the placebo group. In this study, the mean treated baseline LDL-C levels were 438.9 mg/dL (11.37 mmol/L) for the mipomersen group and 400.2 mg/dL (10.37 mmol/L) for the placebo group.

Furthermore, data from three supportive Phase 3 studies (MIPO3500108, ISIS 301012- CS7, and ISIS 301012-CS12) demonstrated that mipomersen therapy resulted in a clinically meaningful and statistically significant mean percent reduction in LDL-C compared with placebo in patients with Severe HeFH or with HeFH and CAD (-35.9% versus 12.5% in MIPO3500108; -28.0% versus 5.2% in ISIS 301012-CS7) and in patients with hypercholesterolaemia at high risk for CHD (-36.9% versus 4.5% in ISIS 301012-CS12). As presented by the sponsor, the addition of mipomersen to statins and other lipid-lowering medications substantially reduced LDL-C levels in patients with HoFH.

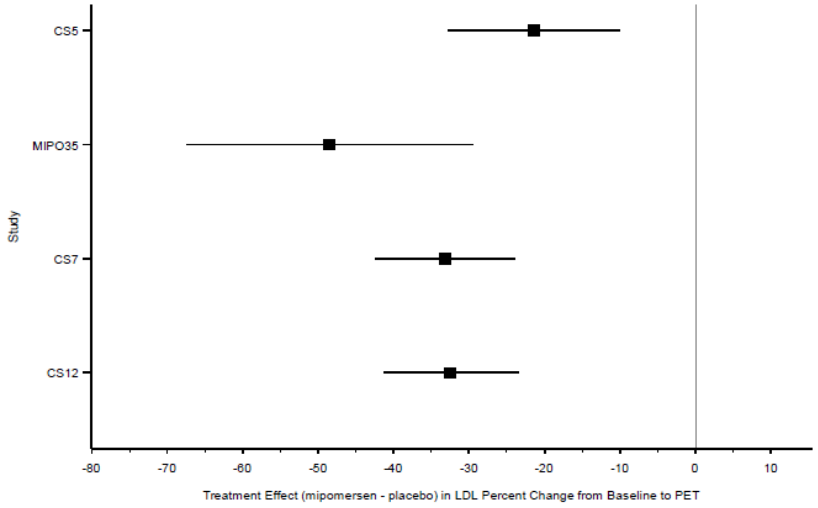
Figure 2 Mean Percent Change in LDL Cholesterol in Patients in Pivotal Study ISIS 301012-CS5 – Full Analysis Set



CI, confidence interval; LDL-C, low-density lipoprotein cholesterol
Vertical bars indicate 95% confidence intervals.

Source: Sponsor's Clinical Overview, Figure 1, page 43

Figure 3 Low-Density Lipoprotein Cholesterol Percent Change from Baseline to Primary Efficacy Time Point Treatment Effects (Difference Between Mipomersen and Placebo Treatment) and 95% Confidence Intervals for Phase 3 Clinical Studies



CS5, Study ISIS 301012-CS5; CS7, Study ISIS 301012-CS7; CS12, Study ISIS 301012-CS12; LDL, low-density lipoprotein cholesterol; MIPO35, Study MIPO3500108; PET, primary efficacy time point

Source: Sponsor's Clinical Overview, Figure 2, page 45

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/s/

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05/23/2012

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