

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**202057Orig1s000**

**OFFICE DIRECTOR MEMO**

## Summary Basis for Regulatory Action

<b>Date</b>	January 29, 2013
<b>From</b>	Christine P. Nguyen, MD Acting Deputy Director, Office of Drug Evaluation II
<b>Subject</b>	Summary Review
<b>NDA/BLA #</b>	203568
<b>Applicant Name</b>	Genzyme Corporation
<b>Date of Submission</b>	3/29/12
<b>PDUFA Goal Date</b>	1/29/13
<b>Proprietary Name / Established (USAN) Name</b>	Kynamro/mipomersen sodium
<b>Dosage Forms / Strength</b>	200 mg subcutaneous injection once weekly
<b>Proposed Indication</b>	Adjunct to maximally tolerated lipid lowering medications and diet to reduce low density lipoprotein-cholesterol (LDL-C), apo B, total cholesterol, and non-high density lipoprotein-cholesterol (non-HDL-C) in patients with homozygous familial hypercholesteremia
<b>Regulatory Action:</b>	<i>Approval</i>

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
Reviews from the following disciplines:	
Clinical	Eileen Craig/Eric Colman
Statistics	Japobrata Choudhury/Jon T Sahlroot
Pharmacology Toxicology	Ronald Wange/ Karen Davis Bruno
Chemistry, Manufacturing, and Controls	Joseph Leginus/Eric Duffy
Division of Therapeutic Proteins	Jinhai Wang/Daniela Verthelyi
Clinical Pharmacology	Ritesh Jain/ Immo Zadezensky
Office of Scientific Investigations	Susan Leibenhaut/ Janice Pohlman
OSE/DEPI	Patricia Bright/ Diane Wysowski
OSE/DRISK	Joyce Weaver/Cynthia LaCivita
OSE/OPE	Leonard Seeff/John Senior

OSE= Office of Surveillance and Epidemiology  
 OPE= Office of Pharmacovigilance and Epidemiology  
 DEPI= Division of Epidemiology  
 DRISK=Division of Risk Management

### 1. Introduction and Background

This memo summarizes the basis of the regulatory action for this new drug application seeking an orphan indication of the treatment of homozygous familial hypercholesteremia (HoFH). In-depth review and analyses of specific issues can be found in the primary reviews of the respective disciplines and also in the summary review of Dr. Eric Colman, the Deputy Director of the Division of Metabolism and Endocrinology Products. This memo contains my summary, assessments, and conclusions of the major issues identified in the review of this application.

Mipomersen is a first-in-class, new molecular entity, antisense oligonucleotide (ASO) that

binds to the coding region for human apolipoprotein B (apo B) mRNA and inhibits apo B synthesis. Apo B is a major structural component of apo B-containing lipoproteins, including VLDL-C that gives rise to circulating LDL-C. In essence, mipomersen inhibits the production of LDL-C particles.

Homozygous familial hypercholesteremia (HoFH) is an autosomal dominant disease resulting from mutations in both alleles of the LDL receptor (LDL-r). These mutations render the LDL-r activity essentially absent, resulting in reduced clearance of LDL-C from circulation and marked elevation in serum LDL-C levels. Serum LDL-C levels in HoFH individuals are up to 4- to 8-fold higher than normal, ranging from 500 to 1000 mg/dL. Untreated HoFH patients die prematurely from severe accelerated atherosclerotic cardiovascular by the second or third decade of life. Even with contemporary treatment, the average life expectancy for HoFH patients is approximately 33 years.<sup>1</sup> In the U.S., the prevalence of HoFH is about 1 per million persons.

Treatment options for HoFH are limited (Table 1). High potency HMG-CoA reductase inhibitors (statins) with or without a cholesterol absorption inhibitor, and LDL apheresis have been the mainstay of treatment for HoFH. Statin therapy depends on functional LDL-r for most of its lipid lowering effects and, therefore, has limited efficacy in HoFH. Similar to dialysis, LDL apheresis is an extracorporeal procedure that selectively removes apo-B containing lipoproteins (VLDL-C, LDL-C, lipoprotein (a), and triglycerides) from circulation. The procedure, however, needs to be performed on a chronic, repetitive basis of every one to two weeks, and currently, there are only 35 apheresis centers in the U.S. Recently, lomitapide, a microsomal triglyceride protein inhibitor that lowers serum LDL-C by inhibiting the assembly of apo-B containing lipoproteins, was approved as an add-on therapy in HoFH patients. Liver transplantation has been used rarely as a last resort.

**Table 1: Non-surgical therapies for HoFH**

Therapy	Mechanism of action	LDL-C lowering effects (HoFH)
HMG-CoA reductase inhibitors*	LDLR activity	< 10 – 25%
Cholesterol absorption inhibitors	LDLR activity, inhibits cholesterol absorption	< 10%
LDL-apheresis**	LDL-C removal	~30 – 40% <sup>2</sup>
Lomitapide***	Microsomal triglyceride protein inhibitor	40-50%

\*Response depends on amount of functional LDL-r's

\*\* Response based on time averaged LDL-C levels; apheresis acutely lowers LDL-C by 50-75%

\*\*\* As add-on therapy to diet and lipid-lowering therapies, including LDL apheresis

Because HoFH patients have such elevated LDL-C at baseline (> 500 mg/dL), multiple treatment modalities are necessary to control LDL-C levels. Under the ideal circumstance of robust response and good tolerability and safety, some HoFH patients treated with a combination of therapies listed in Table 1 can approach target LDL-C levels. Not all HoFH individuals, however, have adequate response or acceptable tolerability, and some individuals

<sup>1</sup> Frederick J. Raal, Gillian J. Pilcher, Vanessa R. Panz, et al. Reduction in Mortality in Subjects With Homozygous Familial Hypercholesterolemia Associated With Advances in Lipid-Lowering Therapy. *Circulation*. 2011;124:2202-2207.

<sup>2</sup> Pfohl M, Naoumova RP, Klass C, Knisel W, Jakober B, Risler T, Thompson GR. Acute and chronic effects on cholesterol biosynthesis of LDL-apheresis with or without concomitant HMG-CoA reductase inhibitor therapy. *J Lipid Res*. 1994;35(11):1946.

have contraindications, to available therapies, including lomitapide, and additional therapeutic options are needed for HoFH patients.

This NDA supports the use of mipomersen 200 mg injected subcutaneously once weekly as add-on therapy to lipid-lowering medications and diet to reduce LDL-C in HoFH patients.

## **2. Recommendations of Review Disciplines regarding Approvability**

CMC: In his review signed on December 7, 2012, and in an addendum dated January 4, 2013, the primary reviewer (Joseph Leginus) recommended approval from a CMC perspective.

Division of Therapeutic Proteins: In the consult review signed on January 9, 2013, the primary reviewer (Jinhai Wang) stated that there were “no immune response induced issues that prevent Approval.” Safety concerns and recommended required postmarket evaluations related to mipomersen-induced immunological response are discussed in Section 4 (Safety) and Section 5 (Risk Management and Assessment).

Clinical Pharmacology: In his review signed on November 30, 2012, the primary reviewer (Ritesh Jain) recommended approval from a clinical pharmacology perspective.

Pharmacology Toxicology: In his review signed on December 3, 2012, the primary reviewer (Robert Wange) recommended approval from a pharmacology toxicology perspective. Safety concerns based on preclinical findings are discussed in Section 4 (Safety).

Statistics: In his review signed on November 12, 2012, the primary reviewer (Japobrata Choudhury) confirmed that efficacy has been demonstrated for mipomersen from a statistical perspective.

Clinical: In her review signed on November 26, 2012, the primary reviewer (Eileen Craig) recommended approval from a clinical perspective. Pertinent clinical findings and assessments are discussed in Section 3 (Efficacy) and Section 4 (Safety).

Dr. Eric Colman recommended approval of this application, and I concur with this overall recommendation.

## **3. Efficacy**

Efficacy of mipomersen was demonstrated in one Phase 3 trial in HoFH patients (“CS5”), with supportive evidence from three Phase 3 trials in non-HoFH patients with dyslipidemia (“MIPO108,” “CS7,” and “CS12”). All four trials were identical in design: multicenter, randomized, double-blind, placebo-controlled, parallel arm with a 2:1 randomization to mipomersen 200 mg subcutaneous once weekly or placebo as add-on therapy to maximally tolerated lipid lowering drugs (not including lomitapide or patients on apheresis) and diet. The duration of drug treatment was 26 weeks. The primary efficacy endpoint in all four trials was the change in percent of serum LDL-C from baseline to 2 weeks after the last dose (Week 28/end of treatment [ET]).

The surrogate endpoint of serum LDL-C has been an accepted primary efficacy measure in marketing applications for lipid-lowering therapies in the U.S. The relationship between reductions in LDL-C and decreased risk of adverse cardiovascular outcomes has been well established for statins. Although there are no data correlating LDL-C reduction and improved cardiovascular outcomes for antisense oligonucleotide therapy, there is no reason to believe that LDL-C would not be an acceptable primary target for cholesterol lowering therapy, such as mipomersen, in HoFH patients. Moreover, a definitive cardiovascular outcomes trial in HoFH patients is not feasible because of the rarity of the disease, and LDL-C is the most appropriate surrogate measure available.

The primary efficacy endpoint was analyzed using paired t-test and Wilcoxon rank-sum test performed on the full analysis set with last-observation-carried-forward (LOCF) imputation of missing data. Efficacy findings from the pivotal HoFH trial and supportive trials are shown below. It is notable that baseline LDL-C levels in HoFH patients were in the 400 mg/dL range despite being on maximally tolerated pharmacotherapy and diet. In HoFH patients, mipomersen treatment resulted in a mean placebo-adjusted LDL-C reduction of 21% from baseline to Week 28/ET. Although this magnitude of LDL-C reduction appears modest, it should be appreciated that this benefit is in addition to the lipid lowering effects of baseline therapies in a difficult-to-treat population, and that some statins, such as pravastatin, were approved based on a similar degree of LDL-C lowering effect.

**Table 2: Primary Endpoint\* – Percent change in LDL-C from baseline to Week 28/ET**

LDL-C (mg/dL)	ISIS 301012-CS5		MIPO3500108		ISIS 301012-CS7		ISIS 301012-CS12	
	Placebo (N=17)	Mipo (N=34)	Placebo (N=18)	Mipo (N=39)	Placebo (N=41)	Mipo (N=83)	Placebo (N=52)	Mipo (N=105)
Baseline - Mean	400	439	249	276	143	153	123	123
Min, Max	172, 639	190, 704	93, 427	112, 470	87, 392	36, 377	69, 265	65, 270
Percent change from baseline	-3.3	-24.7	12.5	-35.9	5.2	-28.0	-4.5	-36.9
Min, Max	-33.4, 43.1	-81.8, 2.1	-44.6, 175.3	-89.5, 13.5	-43.0, 41.4	-84.4, 86.1	-61.9, 63.2	-86.4, 38.8
Trt Diff. from Pbo (p<0.001)		-21.4%		-48.4%		-33.2%		-32.4%

Source: Adapted from primary clinical review (Eileen Craig), p. 12

\*Trial population - **CS5**: HoFH; **MIPO108**: severe hypercholesteremia (primarily HeFH); **CS7**: heterozygous familial hypercholesteremia with CAD; **CS12**: high cardiovascular disease risk (>20% risk over 10 years)

In all 4 trials, progressive reduction in LDL-C was seen during the initial 16 weeks of treatment with stabilization thereafter. Durability of treatment benefit in HoFH patients was observed at one year (mean LDL-C reduction -25%, N=27) and two years (mean LDL-C reduction -39%, N=3) of treatment in the open label extension study.

An important shortcoming of the mipomersen clinical program was the lack of evaluation of mipomersen in conjunction with LDL-apheresis. Nevertheless, mipomersen is a valuable add-on therapy for HoFH patients, as not all patients have access to or can tolerate LDL-apheresis.

Categorical LDL-C responses: In trial CS5, a greater proportion of mipomersen-treated patients than placebo experienced an LDL-C reduction of at least 20% (50% mipomersen vs. 12% placebo) or 50% (12% mipomersen vs. 0% placebo). Two of 34 mipomersen-treated

patients had an LDL-C level < 100 mg/dL at the end of treatment. Therefore, I anticipate that there will be HoFH patients with a robust response to mipomersen.

Pediatric Patients: Trial CS5 enrolled 7 HoFH adolescent patients ages 12 to < 18 years old, 3 of whom were randomized to mipomersen. All 3 individuals weighed > 50 kilograms and were dosed with mipomersen 200 mg once weekly. LDL-C reduction from baseline to Week 28/ET for these 3 adolescents ranged from -31% to -62%, compared to -8% to +43% in the 4 adolescent patients randomized to placebo. During the open label extension trial CS6 (OLE CS6) where all 7 adolescent patients received mipomersen, LDL-C change from baseline to last drug dose ranged from -42% to +11%. These results were within the range of efficacy results seen in adult HoFH patients in CS5 and OLE CS6.

Secondary endpoints: Pre-specified secondary endpoints in all four phase 3 trials were change in percent of apo B, non-HDL-C, and total cholesterol from baseline to Week 28/ET. Statistically significant reductions in all of these parameters were seen with mipomersen in the four trials. Table 3 shows results for the secondary endpoints from trial CS5. These findings are consistent with LDL-C reduction, but they should not be interpreted as providing additional cardiovascular benefits beyond those expected from lowering of LDL-C.

**Table 3: Secondary efficacy endpoints (CS5-HoFH)**

Lipid Parameters	Relative Change from Baseline to Week 28 Mean change % (SD)*	
	Mipomersen (N=34)	Placebo (N=17)
Apo B	-27 (17)	-3 (13)
Total Cholesterol	-21 (18)	-2 (15)
Non-HDL-C	-25 (19)	-3 (16)

Source: Adapted from primary clinical review (Eileen Craig), Table 14

\*Statistical significance ( $p < 0.05$ ) for all 3 secondary endpoints tested sequentially to control for multiplicity

### **Efficacy conclusion**

Mipomersen was efficacious in reducing LDL-C in HoFH patients on background maximally tolerated lipid lowering drugs and diet, and efficacy was corroborated by findings in non-HoFH subjects with hypercholesterolemia. Drug effect on other lipid parameters (apo B, non-HDL-C, and total cholesterol) was consistent with the benefits observed with LDL-C. Treatment effect observed in a few HoFH adolescents studied was similar to that of adult HoFH patients.

Efficacy of mipomersen was not evaluated in patients on LDL-apheresis or those treated with lomitapide, which was only recently approved for HoFH patients.

## **4. Safety**

The safety findings of mipomersen have been thoroughly discussed in Dr. Eileen Craig's review. My safety assessment focuses on issues of interest identified by the review teams. This assessment draws from the placebo-controlled safety database pooled from the four phase 3 trials (CS5, MIP0108, CS7, and CS12). These trials were identical in design, with a 26-week treatment phase followed by a 24-week off-treatment follow up period due to the long half life of mipomersen (approximately 5 weeks). Subjects in the phase 3 trials, except for those in trial CS12 and some sites in trial MIP0108, were eligible to enter the open-label

safety extension study CS6 to receive up to an additional 24 months of mipomersen treatment. The safety findings in HoFH patients were similar to those in the pooled safety database and will not be discussed separately.

The pooled phase 3 database consisted of 391 patients, with 261 randomized to mipomersen and 130 to placebo. The open label extension study CS6 (OLE CS6) enrolled 141 patients and is ongoing.

**Deaths:** Four deaths (3 mipomersen, 1 placebo) were reported in the entire mipomersen clinical development program. The 3 mipomersen deaths (2 myocardial infarctions [MI], 1 hepatic failure with MI) occurred during the off-treatment follow up period; the 1 placebo death (MI) occurred during the on-treatment placebo-controlled period. The fatal case of hepatic failure in the setting of an acute myocardial infarction and possible acetaminophen overdose in a 68 year-old HeFH patient happened approximately 4 months after he completed his 26-week treatment with mipomersen. Both the clinical review team and FDA hepatologists concluded that the liver failure was most likely secondary to a myocardial infarction and not as a direct result of mipomersen-induced hepatic injury, and I concur with this assessment. Although drug-causality in the remaining 2 MI's in mipomersen patients (after 6 months and 18 months of treatment) could not be entirely excluded, I believe they were unlikely to have been directly caused by mipomersen after reviewing the narratives. No deaths occurred in HoFH patients.

**Non-fatal serious adverse events (SAEs):** In the pooled phase 3 database, 21 of 261 (8%) of mipomersen-treated patients and 7 of 129 (5%) of placebo patients reported at least one non-fatal SAE. The most common SAEs were Cardiac Disorders, reported by 3.8% (10/261) of patients on mipomersen compared to 3.1% (7/129) on placebo. This imbalance was primarily driven by a numerical imbalance in the number of patients with angina (5 mipomersen versus 0 placebo). A HeFH patient treated with mipomersen experienced SAE's of aminotransferase elevation (ALT 3.9X ULN after 9 weeks of treatment) and hepatic steatosis. Compared to an initial MRI showing incipient hepatic steatosis, her follow up MRI obtained 93 days after the first dose of mipomersen and 23 days since the last drug dose showed hepatomegaly and marked steatosis. Laboratory tests of hepatic function remained within normal limits. The aminotransferase elevations declined to < 1.2X ULN eight months after drug discontinuation. Dr. Craig believed this case to be drug-related, and I agree with her conclusion. Mipomersen's effects on the liver will be further discussed in the "Special Safety Issues" section.

**Drug discontinuation due to adverse events:**

In the pooled phase 3 database, 18% of mipomersen patients and 2% of placebo patients discontinued treatment due to adverse events (AEs). In the mipomersen treatment arm, the most common reasons leading to drug discontinuation were injection site reactions (ISRs), flu-like symptoms (FLS), and liver-related abnormalities, which together accounted for the significant majority of discontinuations. During the 2-year OLE CS6 trial, 44% of patients discontinued therapy due to AEs; FLS, ISR, and increases in aminotransferase were responsible for most of the discontinuations. Although one may find the poor tolerability of long-term mipomersen treatment troubling, approximately half of subjects did tolerate chronic treatment. In clinical practice, only approximately 50% of patients prescribed a lipid lowering

drug are still taking it at 6 months.<sup>3</sup> Because HoFH patients have few therapeutic options, I find the level of tolerability for mipomersen acceptable.

**Common adverse events:** In the pooled controlled phase 3 trials, common AEs that were reported more frequently in the mipomersen group than placebo were injection site reactions (84% mipomersen vs. 33% placebo), investigations (liver tests related) (30% vs. 15%), fatigue (15% vs. 8%), nausea (14% vs. 8%), influenza like illness (13% vs. 3%), headache (12% vs. 9%), hepatic steatosis (7% vs. 2%), and hypertension (7% vs. 3%).

In OLE CS6, the most common AEs were similar to those in the controlled trials and included injection site reactions (50-80%), flu like symptoms (41%), headache (31%), ALT/AST increased (30%), and nausea (21%).

### **Special Safety Issues**

- Liver abnormalities

***Serum aminotransferase (AT) elevations:***

Liver tests were evaluated every 4 weeks (phase 3 trials) or ~ 2 months (CS6). Serum ALT or AST  $\geq$  3X ULN triggered a prespecified evaluation that included laboratory tests and liver MRI. All phase 3 trials had stopping rules for ALT/AST elevations.

A summary of peak ALT elevations at various thresholds is shown in Table 4. Overall, 16% of mipomersen patients and 1% of placebo patients had at least one ALT value  $\geq$  3X ULN during the 26-week treatment period. There were no concurrent clinical or biochemical changes indicating impaired liver function, such as elevated serum total bilirubin or prothrombin time, in affected individuals, and no cases met the criteria for Hy's Law (ALT/AST  $\geq$  3X ULN, ALP  $<$  2X ULN, accompanied by total bilirubin  $\geq$  2X ULN in the absence of alternative explanations other than drug exposure).

**Table 4: Peak ALT elevations (CS5 and Pooled phase 3)**

Test	Incidence rate, n (%)	CS5 Placebo (N=17)	CS5 Mipo (N=34)	TOTAL Placebo (N=129)	TOTAL Mipo (N=261)
ALT maximum	> ULN and < 2 x ULN	7 (41.2)	12 (35.3)	42 (32.6)	95 (36.4)
	$\geq$ 2 x ULN and < 3 x ULN	2 (11.8)	12 (35.3)	6 (4.7)	61 (23.4)
	$\geq$ 3 x ULN and < 5 x ULN	0	1 (2.9)	1 (0.8)	31 (11.9)
	$\geq$ 5 x ULN and < 10 x ULN	0	3 (8.8)	0 (0.0)	9 (3.4)
	$\geq$ 10 x ULN and < 20 x ULN	0	0	0 (0.0)	3 (1.1)
	$\geq$ 20 x ULN	0	0	0	0
	<b>Total <math>\geq</math> 3x ULN</b>	<b>0</b>	<b>4 (12%)</b>	<b>1 (1%)</b>	<b>43 (16%)</b>
ALT	$\geq$ 3 x ULN, two consecutive results (at least 7 days apart), n (%)	0	1 (2.9)	0 (0.0)	22 (8.4)

Source: Adapted from primary clinical review (Eileen Craig), Table 25

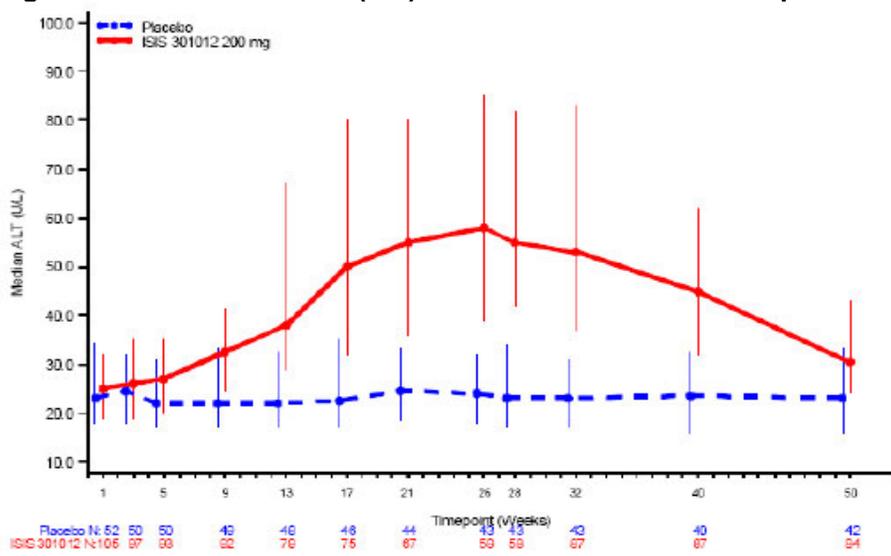
<sup>3</sup> Third report on National Cholesterol Education Program expert panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. IX Adherence. Circulation 2002 106: 3359-3366.

Overall, 5% (14/261) of mipomersen-treated patients discontinued treatment due to protocol-specified stopping rules for ALT/AST elevations (CS5: confirmed values  $\geq 5X$  ULN; the other three phase 3 trials: confirmed values  $\geq 8X$  ULN or consecutive ALT/AST values  $\geq 5X$  ULN). In some patients with peak serum ALT levels greater than 3X ULN but less than liver stopping threshold (e.g., ALT  $\geq 3X$  ULN but  $< 5X$  ULN in CS5), ALT followed a variable course, falling below 3X ULN at certain time points, with continued treatment until the end of the controlled trial (Week 26). For a majority of these patients, however, normalization of AT levels did not occur until weeks to months after drug cessation.

In OLE CS6, 22% (31/141) of patients had at least one peak ALT value  $\geq 3X$  ULN. None of these patients had clinical signs/symptoms or concurrent laboratory abnormalities indicating hepatic functional impairment. Of the 31 patients, 9 discontinued mipomersen because of protocol-defined liver stopping rules.

In general, serum AT abnormalities trended towards baseline weeks to months after drug discontinuation, consistent with the long terminal half life of mipomersen. This reversibility is demonstrated by the findings of trial CS12, which measured serum AT levels during the 26-week treatment period (Weeks 0 – 26) and the 24-week off-treatment period (Weeks 26 – 50). The time course of ALT changes is shown below.

**Figure 1: Median ALT levels (U/L) on and off treatment with mipomersen (CS12)**



Vertical bars represent the interquartile range.

Last mipomersen dose was scheduled for Week 26.

ALT = alanine aminotransferase; ISIS 301012 = mipomersen.

Source: Primary clinical review (Eileen Craig), Figure 8

Patients who discontinued mipomersen were not re-challenged because of its prolonged half life (5 weeks). Therefore, no data exist to inform the rate of recurrence or the severity of liver enzyme abnormalities if a patient resumes mipomersen after drug interruption for elevated AT levels.

Mipomersen causes a clear shift in serum AT levels, as exemplified in Figure 1. No cases of Hy's Law were reported in the entire safety database, but the size of the database could only exclude a true rate of Hy's Law cases of greater than 1% (with 95% confidence).

In summary, mipomersen increases serum AT levels at a frequent rate. The mechanism of action for the hepatocellular injury is not well understood and may not be entirely related to drug-induced hepatic fat accumulation (see "hepatic steatosis" discussion below). However, it is reassuring that the hepatic enzyme elevations appear to be reversible with drug discontinuation. More modest AT elevations may intermittently improve, although not necessarily to baseline levels, with continued treatment. These hepatic enzyme abnormalities were not accompanied by clinical or biochemical evidence of impaired liver function, although the safety data are very limited. Moreover, serum AT levels can be readily monitored by available liver chemistry tests. For these reasons, I believe that this significant risk can be appropriately managed in clinical practice with the risk management strategies of labeling and REMS.

Mipomersen's ability to cause transaminitis alone (without evidence of altered hepatic function) is not a reliable predictor of its potential for severe drug-induced liver injury, but this risk unknown at this time. Nevertheless, defining mipomersen's potential for severe drug induced liver injury in the premarket setting would be infeasible given the large clinical database required to detect such a case in an orphan-size population of HoFH. Therefore, this risk will need to be characterized in the postmarket long-term observational study.

### *Hepatic steatosis*

Hepatic fat accumulation is an expected effect of mipomersen because mipomersen prevents the export of triglyceride from the liver. In trials CS7 and CS12, liver fat fraction (%) was measured by MRI at baseline and at the end of treatment (Week 28/ET). In addition, in trial CS12, liver MRI was also obtained at end of the 24 weeks off-treatment follow up period to evaluate for reversibility of hepatic fat accumulation after drug cessation. OLE CS6 measured hepatic fat at 6-month intervals and "for cause."

In the combined CS7 and CS12 trials, a median increase in hepatic fat of 10 percentage points from baseline to Week 28/ET was observed in mipomersen patients compared to 0% in placebo. Overall, 62% of mipomersen patients compared to 8% of patients on placebo had an increase of  $\geq 5\%$  points from baseline in hepatic fat content. Most individuals (84%) with hepatic fat increase  $\geq 5\%$  points did not have transaminase elevations  $\geq 3X$  ULN; therefore, one cannot rely on aminotransferase elevations alone for detecting the presence or monitoring the severity of hepatic steatosis.

In OLE CS6, 16% (22/141) of patients had a liver fat fraction  $>20\%$  on at least one occasion, with the largest fraction measuring at 39%. Among these 22 patients, only 41% had transaminase elevations  $\geq 3X$  ULN, reinforcing the concept that ALT/AST measurements alone are unreliable for screening or monitoring for hepatic steatosis. In OLE CS6, paired MRI assessments available for a limited number of patients provided information about the temporal trend of hepatic fat accumulation over an extended duration of use. The trend showed an initial rise in hepatic fat accumulation over the first year of use, with slight decline thereafter. The median increase in hepatic fat fraction peaked at 13% points at Week 52, and

persisted between 5% to 7% points between Weeks 76 and 130. These results should be interpreted with caution, because not the same patients were imaged at every time point. On the subject level, individual patients experienced an increase, stabilization, or decrease in hepatic fat accumulation with continued mipomersen treatment.

MRI hepatic fat measurement obtained off-treatment in CS12 indicated that hepatic steatosis appears to be reversible after stopping mipomersen. After 24 weeks off-treatment, the median change from baseline in hepatic fat declined from 15% points at Week 28/ET to 4% points at Week 50 (compared to median change from baseline of 0% at Week 28/ET and 1% point at Week 50 in the placebo group). In the OLE CS6, paired MRI assessments available for 28 individuals also suggested that the hepatic steatosis was reversible off treatment, with a mean change of hepatic fat content of 0.3% from baseline to 24 weeks after mipomersen discontinuation.

Liver biopsies: Liver biopsies were not protocol-mandated in mipomersen trials. Five subjects in the entire safety database had “for-cause” liver biopsies, prompted by increases in hepatic fat and serum aminotransferase levels, after 3 to 14 months of mipomersen treatment. These biopsies showed moderate to severe steatosis, with none to slight inflammation and fibrosis and without evidence of necrosis or severe inflammation. Biopsies from 2 of the 5 patients (obtained after 5 and 8 months on treatment) showed a “minor steatohepatic component.” It is difficult to determine drug-related changes in these 2 biopsies, because the patients’ confounding co-morbidities (diabetes, chronic alcohol use) and the lack of baseline biopsy precluded a reliable assessment as to what histological changes could be ascribed to mipomersen.

Our understanding of non-alcoholic fatty liver disease (NAFLD), a primary disease not secondary to other known causes of hepatic fat accumulation, sheds some light on the natural history of chronic liver injury from hepatic fat accumulation. Simple steatosis of NAFLD generally has a benign course, whereas steatosis associated with inflammation and necrosis (non-alcoholic steatohepatitis, or NASH) can progress to cirrhosis in up to 10 to 20% of the cases. Currently, there are no non-invasive biomarkers that could reliably predict the progression from simple steatosis to NASH or allow for early detection of NASH. At present, only a liver biopsy can be relied upon to distinguish between simple steatosis and NASH.

The risk of chronic liver injury, including steatohepatitis, from mipomersen-induced hepatic fat accumulation is unknown at this time. Whether the clinical course of hepatic steatosis caused by mipomersen follows a similar path as NAFLD is uncertain. Published literature on marketed drugs implicated in chronic steatosis and steatohepatitis (e.g., amiodarone) is not likely to be generalizable, as the risks may be drug-, patient-, or disease-specific. No evidence currently exists to inform the routine use of biomarkers or imaging studies to screen for steatohepatitis or to guide treatment decisions, such as when to contraindicate or discontinue treatment.

Regardless of the knowledge gaps, for mipomersen-treated patients, hepatic fat content could be monitored by imaging studies, and a liver biopsy could be performed to inform histopathological changes and provide an opportunity to discontinue treatment prior to the

development of more serious liver injury. Reversal of mipomersen-induced fat accumulation measured by imaging study was noted with drug discontinuation.

- Injection site reactions (ISRs)

Injection site reactions (injection site erythema, pain, hematoma, pruritus, swelling, and/or discoloration) were the most common adverse reactions. In the pooled phase 3 trials, 84% of mipomersen patients and 33% of placebo patients reported ISRs. ISRs led to premature discontinuation in 5% of mipomersen-treated subjects compared to 0% of placebo in the 6-month controlled trials. In OLE CS6, ISRs were almost universal, being reported by 98% of patients, 6% of whom had severe reactions. Approximately 10% of patients discontinued drug in the open label extension due to ISRs. Co-administration with corticosteroids did not alter the dermatological responses induced by mipomersen. Although ISRs adversely affected tolerability, it can be adequately managed through labeling to inform the risk/benefit decision for an individual patient.

- Flu-like symptoms (FLS)

FLS included influenza-like illness, pyrexia, chills, myalgia, arthralgia, malaise, or fatigue starting within 2 days after an injection. In the pooled phase 3 trials, FLS occurred in 30% of mipomersen-treated patients and 16% of placebo patients. This adverse reaction led to premature drug discontinuation in 3% of mipomersen patients compared to 0.8% in placebo patients. In OLE CS6, FLS was the second most common adverse reaction (66%), and 9% were reported as severe. FLS was the most common reason for drug discontinuation in the open label extension; approximately 25% (35/141) of patients discontinued mipomersen because of FLS. FLS significantly hinders long term tolerability, but this risk can be managed through labeling.

- Inflammatory and Immunological Issues:

**High sensitivity C-reactive protein (hsCRP):** Chronic increase in hsCRP over the 26-week of treatment in the controlled phase 3 trials were not observed in mipomersen-exposed or placebo subjects. A phase 1 study in healthy volunteers that specifically evaluated changes in hsCRP showed that mipomersen caused transient elevations in hsCRP level after each injection. These data mitigate my concern that mipomersen induces persistent increases in hsCRP that could adversely affect cardiovascular outcomes.

**Anti-drug antibody:** Mipomersen appears to be highly immunogenic. In the pooled phase 3 trials, approximately 40% of mipomersen-exposed patients developed antibodies to mipomersen. During the 2-year OLE CS6, 72% of patients had developed antidrug antibodies. Compared to antibody-negative patients, those who were antibody positive were more likely to experience FLS (71% vs. 53%) and discontinue treatment due to AEs (49% vs. 40%). Otherwise, no other differences were noted between antibody positive and negative patients, including serum AT elevations or LDL-C reduction.

One HeFH subject developed a hypersensitivity reaction with angioedema in May 2012 after being treated with mipomersen for 5 years. This subject became antibody positive in July 2011 but had tested negative for mipomersen antibodies since November 2011. Although the

subject was on mipomersen when he developed the hypersensitivity reaction, I believe that the causal role of mipomersen or antidrug antibodies is questionable, in light of the fact that the subject had been treated for 5 years and had been antibody-negative for 10 months prior to the hypersensitivity reaction.

Because mipomersen induces a vigorous anti-drug antibody response, a theoretical, but plausible, concern exists that mipomersen could induce the production of antibodies that bind to native double-strand DNA, which then can lead to autoimmune diseases, such as lupus erythematosus. This concern will be further addressed in the required postmarket evaluations.

- Renal Issues:

In the pooled phase 3 database, a greater proportion of mipomersen patients compared to those on placebo had an AE of “proteinuria” (mipomersen 2.3% vs. placebo 0.8%) or a urine dipstick of  $\geq 1+$  protein (9% vs. 3%). No mipomersen-related adverse effect on urine beta-2-microglobulin or GFR was noted, however. Because proteinuria, especially mild or transient, on urine dipstick may be due to multiple factors (e.g., urine concentration) and there was no evidence of renal tubular damage or impaired renal function with mipomersen, I do not believe that these data support a clear drug-related safety signal for significant renal injury. This proteinuria signal of uncertain significance will be further evaluated in the postmarket setting.

- Cardiovascular Issues:

The Applicant determined post-hoc the frequency of major adverse cardiovascular events (MACE), based on adverse events data and without adjudication, for the pooled phase 3 trials. The incidence of serious MACE was slightly numerically higher for the mipomersen group (3.4%) compared to placebo (3.1%). FDA independently analyzed MACE data from the placebo controlled phase 3 trials using broad and narrow MedDRA cardiovascular SMQ searches and concluded that there were no statistically significant differences in risk between mipomersen and placebo. I consider these preliminary seemingly neutral findings as exploratory, and caution against any overarching inference regarding cardiovascular risk, or lack thereof, with mipomersen use. Information on cardiovascular outcomes will be obtained in the required long-term postmarket surveillance study to further characterize potential off-target toxicity of mipomersen.

In the pooled phase 3 database, angina, palpitations, and hypertension were reported more frequently in the mipomersen group (angina: mipomersen 5% vs. placebo 2%; palpitations: mipomersen 3% vs. placebo 0%; hypertension: mipomersen 7% vs. placebo 4%). Because angina and palpitations were not pre-defined or adjudicated, and could be secondary to multiple factors, I am unable to comment on the clinical importance, if any, of these reported imbalances. Mean and median measures of blood pressure were similar between the mipomersen and placebo patients reporting AEs of hypertension. Measurements of central tendency for change from baseline systolic and diastolic blood pressure were similar between mipomersen and placebo treatment groups. Categorical analyses did not show differences between mipomersen-treated patients and those receiving placebo. I do not believe the imbalances in hypertension represent a drug related safety signal.

- Neoplasms

Carcinogenic potential of mipomersen was evaluated in standard 2-year carcinogenicity studies in mice and rats, and a species-specific surrogate. The FDA Executive Carcinogenicity Assessment Committee concluded that there was a statistically significant increase in fibrohistiocytic tumors of the skin/subcutis (male mice, male/female rats), hemangiosarcoma (female mice), and hepatocellular adenomas and carcinoma (female mice) at clinically relevant exposures based on body surface area allometric scaling. Plausible species-specific mode of action exists for hemangiosarcoma and fibrohistiocytic tumors that may alleviate some clinical concerns for these neoplasms. The clinical relevance of hepatocellular neoplasms, however, remains a concern for a variety of reasons, such as the lack of rodent-specific mechanism of action and the liver being the primary site of drug action.

In the entire safety database, 9 of 749 (1.2%) of mipomersen-exposed patients developed a malignancy (gastric cancer; breast cancer; lung squamous cell carcinoma stage unspecified; rectal cancer; prostate cancer; malignant melanoma in situ; and 3 events of basal cell carcinoma) and 1 of 221 (0.5%) placebo patient reported a malignancy (basal cell carcinoma). Review of the individual cancer cases indicated that 4 of the 9 malignancies were unlikely to be drug related, for reasons such as more compelling competing etiologies (e.g., long history of smoking and lung cancer) and improbable short duration of drug use to cause the cancer (22 days of treatment prior to the diagnosis of gastric cancer). The remaining 5 cases were common background cancers in the older population (e.g., prostate cancer in a 77 year old man, rectal cancer in a 63 year old man), such that the occurrence of these cancers cannot be readily attributed to mipomersen. Furthermore, there were no imbalances in a specific type of cancer. Although the safety database is limited, the safety data do not suggest an obvious malignancy signal. A long term postmarket observational study will be in place to monitor for development of cancers seen in animal studies, especially hepatocellular carcinomas.

### **Safety conclusion**

The most important safety concerns are mipomersen-induced significant elevations of serum aminotransferase and hepatic steatosis at frequent rates. These liver abnormalities can be screened for and monitored by available laboratory and radiographic studies, and appear to reverse with drug cessation. No evidence of liver functional impairment was observed in the small safety database. The risks of severe acute and/or chronic drug-induced liver injury with mipomersen are unknown at this time and will be further characterized in the postmarket setting.

Injection site reactions and flu like symptoms are significant tolerability issues that could be adequately addressed in labeling to inform individual risk/benefit decision of mipomersen use.

Finally, potential safety signals related to inflammatory and immunological responses, renal and cardiovascular events, and neoplasms can be communicated through labeling and will be further defined in the postmarket long term observational study.

## **5. Risk Management and Assessment**

The review teams and the Office of Surveillance (OSE) considered the following to be appropriate approaches to risk management and assessment of known and potential safety concerns for mipomersen:

Risk Management:

1. Risk Evaluation and Mitigation Strategies (REMS) program: The REMS program consisting of elements to assure safe use (ETASUs) was discussed with the REMS Oversight Committee and the Office of Chief Counsel. The goals of the REMS are to educate prescribers about mipomersen's risk of hepatotoxicity and the need to monitor patients during treatment with mipomersen as per product labeling. A further goal is to restrict access to mipomersen therapy to the intended HoFH population because of hepatotoxicity concerns. The ETASU includes prescriber certification, dispensing pharmacy certification, and documentation of safe-use conditions, consisting of a prescriber authorization form affirming that the patient has a clinical or laboratory diagnosis consistent with HoFH. The clinical database supporting the approval of mipomersen is very limited and significant toxicities have been identified already. At this time, the benefit/risk of drug treatment is expected to be favorable only in patients with severe familial disease consistent with HoFH. Such physician affirmation balances the need to have mipomersen available to patients with the most severe disease with preventing its use in patients with a very different risk/benefit profile, such as those with primary hypercholesterolemia who are intolerant to statin therapy. The REMS program can be modified as more safety data become available for mipomersen in the postmarket setting. I agree with the content of the REMS program.
2. Labeling, which includes a Medication Guide outside of the REMS, will have a Boxed Warning for the risk of hepatotoxicity. Labeling will include recommendations for screening and monitoring with liver chemistry tests. Because of the absence of data correlating hepatic fat findings on imaging study to clinical outcomes, no specific recommendations can be made in labeling regarding the use of imaging in the surveillance and management of hepatic steatosis. At this time, whether to follow and how to manage changes in hepatic steatosis should be left to clinicians as they continually reassess risk and benefit for individual patients.

Risk Assessment:

3. Postmarket requirement: As a condition of approval, the applicant will be required to conduct the following postmarket studies (PMRs) to better define the risks of mipomersen:
  - a. A 10-year, prospective, observational cohort study (product exposure registry) in HoFH patients to characterize the long-term effect of mipomersen on the liver; malignancies (including hepatocellular adenomas or carcinomas, fibroma/fibrosarcoma/fibrous histiocytoma of the skin/subcutis); and new diagnoses of autoimmune disorders. I agree with the review teams that this study is the most feasible mechanism to obtain long-term safety information for mipomersen.
  - b. Implementation of an enhanced pharmacovigilance program for serious reports hepatic abnormalities, malignancies, and immune-mediated reactions for 10 years from the date of approval.
  - c. To address the concern that mipomersen could induce the production of antibodies that bind to native double-stranded DNA that may then lead to autoimmune diseases, the applicant will:

- Develop and validate a sensitive assay to assess for the presence of antibodies to double stranded DNA
- Conduct a study to assess for the presence of antibodies that bind to native double stranded DNA from stored serum samples of mipomersen-treated patients in the completed clinical trials.

## 6. Advisory Committee Meeting

This application was discussed at the Endocrinologic and Metabolic Drugs Advisory Committee meeting on October 18, 2012. The pertinent discussions are provided in Dr. Craig's review. Regarding whether there is sufficient evidence of efficacy and safety to support the marketing approval of mipomersen, the vote was 9 versus 6 in favor of approval.

## 7. Conclusions and Recommended Regulatory Action

HoFH is a life-shortening disease associated with premature death from accelerated atherosclerosis secondary to severely elevated LDL-C. Available therapies may be suboptimal due to limited efficacy, availability, and/or unacceptable tolerability or morbidity, and there is an unmet medical need for this rare disease.

Mipomersen is a first in class, new molecular entity, antisense oligonucleotide targeted at blocking the assembly of lipoproteins that give rise to LDL-C. Mipomersen 200 mg subcutaneously once weekly was efficacious in lowering LDL-C by approximately 21% in HoFH patients already on maximally tolerated lipid lowering medications and diet. By providing incremental LDL-C lowering effects beyond lipid-altering medications, mipomersen is an important adjunctive therapeutic option for HoFH patients.

The principal safety concerns with mipomersen are the frequent rates of serum aminotransferase elevations and significant liver fat accumulation. These hepatic abnormalities can be screened for and monitored in clinical practice and appear to be reversible with drug discontinuation. The risks of severe acute or chronic drug-induced liver injury with mipomersen are unknown at this time. Other potential safety issues are related to immunological response, renal and cardiovascular effects, and preclinical findings of neoplasms at clinically relevant exposures.

Risk management will include a REMS program to mitigate the risk of hepatotoxicity and to restrict the use of mipomersen to patients with a clinical or laboratory diagnosis of HoFH, where the benefits appear to outweigh the serious risks. Labeling will contain a Boxed Warning for hepatotoxicity, along with recommendations for monitoring with liver chemistry tests, and a Medication Guide will be available to directly inform patients of the risks of mipomersen. The postmarketing requirement of a long term observational study will help to better define the safety profile of mipomersen when used in clinical practice.

The risk-benefit consideration for mipomersen is distinct from that of other lipid lowering drugs due to the serious nature of HoFH, the lack of adequate treatment options, and the demonstrated drug efficacy in a treatment-resistant population. Because the risk tolerance for HoFH patients is unique and HoFH is a rare disease, I can accept the small clinical database supporting the use of mipomersen in HoFH patients. Overall, I believe that the benefit and

risk balance is favorable for the indicated population, and recommend that mipomersen be approved as an adjunct to lipid-lowering medications and diet to reduce LDL-C, apo B, total cholesterol, and non-HDL-C in patients with HoFH.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CHRISTINE P NGUYEN  
01/29/2013