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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Reviewer Name(s)	Eileen M. Craig, MD
Review Completion Date	06 November 2012
Established Name	Mipomersen sodium
(Proposed) Trade Name	Kynamro
Therapeutic Class	Lipid lowering; antisense inhibitor
Applicant	Genzyme Corp.
Formulation(s)	Injection
Dosing Regimen	200 mg SQ weekly
Indication(s)	to reduce LDL-C, apo B, TC, non-HDL-C and lipoprotein (a)
Intended Population(s)	Homozygous familial hypercholesterolemia

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends approval for the following indication:
Mipomersen is as an adjunct to maximally tolerated lipid-lowering medications and diet to reduce low-density lipoprotein (LDL-C), apoB, total cholesterol, and non-high-density-lipoprotein-cholesterol (non-HDL) in adult individuals with homozygous familial hypercholesterolemia (HoFH).

The indication should include the following limitations of use: (1) the effect of mipomersen on cardiovascular morbidity and mortality has not been determined and (2) mipomersen has not been adequately studied as an adjunct to LDL-apheresis; therefore, the use of mipomersen as an adjunct to LDL-apheresis is not recommended.

While the LDL-C reduction with mipomersen was modest and there were issues with high discontinuation rates in the open-label extension trial, lack of data in conjunction with LDL-apheresis, hepatic transaminase elevations and increases in hepatic fat, injection site reactions, flu-like symptoms and lingering immunogenicity concerns, the risk for cardiovascular events is extremely high in this HoFH population. In this HoFH population, my assessment is that the potential cardiovascular benefit outweighs the risk.

A risk evaluation and mitigation strategy (REMS) with elements to ensure safe use (ETASU) is needed to educate physicians and patients on the risks of mipomersen and restrict the use of mipomersen to the indicated population.

1.2 Risk Benefit Assessment

1.2.1 Efficacy

Exposure to Mipomersen
A total of 41 individuals with HoFH were exposed to mipomersen at 200 mg/week for at least 6 months, and 25 individuals with HoFH were exposed for at least 12 months. A total of 243 individuals were exposed to mipomersen at 200 mg/week for at least 6 months, 113 individuals were exposed for at least 12 months, 75 individuals were exposed for at least 18 months, and 54 individuals were exposed for at least 24 months.

This exposure to drug is consistent with other development programs for orphan drug products.

Discontinuations
In the pooled Phase 3 trials, a total of 391 individuals were randomized to double-blind treatment (261 mipomersen, 130 placebo). Discontinuations were higher in mipomersen-treated individuals (28.0%; 73/261) as compared with placebo-treated individuals (6.9%; 9/130). The most common reason for discontinuation was due to adverse events (AEs): 18.0% (47/261) of mipomersen-treated individuals and 2.3% (3/130) of placebo-treated individuals discontinued due to an AE or serious adverse event (SAE). In Trial ISIS 301012-CS5 (individuals with HoFH), 82% of individuals completed treatment and discontinuation rates due to AEs or SAEs were 11.8% (4/34) in mipomersen-treated individuals and 0.0% in placebo-treated individuals. Across the other three supportive trials, the percentage of mipomersen-treated individuals who discontinued treatment ranged from 12 to 43%, compared to placebo, which ranged from 0 to 15%. In the open-label extension (OLE) trial ISIS 301012-CS6, 77 of 141 (54.6%) individuals discontinued treatment: 43.3% (61/141) due to an AE or SAE, 11 (7.8%) withdrew consent, 2 (1.4%) due to lack of efficacy, 2 (1.4%) due to physician's decision, and 1 (0.7%) due to pregnancy. In individuals with HoFH treated in OLE trial ISIS 301012-CS6, 60.5% (23/38) of individuals discontinued treatment, 47.4% (18/38) due to an AE or SAE, 4 (10.5%) withdrew consent, and 1 (2.6%) due to pregnancy. Thus, the discontinuation rates in the HoFH extension trial are high with 23 of the 38 (61%) individuals discontinuing, of which 78% of the discontinuations (18/23) are from AEs or SAEs. The overall incidence of discontinuation in the pooled Phase 3 population is also high with 77 of the 141 (55%) individuals discontinuing, of which 79% of the discontinuations (61/77) were from AEs or SAEs. This high discontinuation rate from adverse events is problematic for a therapy that needs to be taken chronically.

Primary Endpoint: LDL-C Reduction
The primary efficacy parameter for the Phase 3 trials was the percent change in LDL-C from baseline to primary efficacy timepoint (PET) at 26 weeks (the post-baseline visit closest to 14 days after the last dose of study treatment for which LDL-C is assessed).

In Trial ISIS 301012-CS5 (individuals with HoFH), the mean percent change in LDL-C was -24.7% for individuals in the mipomersen group and -3.3% for individuals in the placebo group ($p<0.001$). The treatment difference from placebo was -21.4%. There was notable variability in the individual results for the mipomersen group, which ranged from a 2% increase in LDL-C to an 82% decrease in LDL-C. Fifty percent of individuals in the mipomersen group of ISIS 301012-CS5 had at least a 20% decrease in LDL-C levels from baseline to PET, compared with 12% of individuals in the placebo group. Four (11.8%) individuals in the mipomersen group had a >50% decrease in LDL-C levels from baseline to PET, compared with no individuals in the placebo group. Approximately 47% of individuals in the placebo group had an increase in LDL-C

compared with 6% of mipomersen-treated individuals. Efficacy results for the pivotal trial and the 3 supportive trials are summarized in the following table.

	ISIS 301012-CS5		MIPO3500108		ISIS 301012-CS7		ISIS 301012-CS12	
LDL-C (mg/dL)	**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%
Proportion of Subjects with Specified Change from Baseline to Week 26								
Increase	8 (47%)	2 (6%)	10 (56%)	3 (8%)	26 (63%)	8 (10%)	22 (44%)	11 (11%)
>20% decrease	2 (12%)	17 (50%)	3 (17%)	27 (69%)	2 (5%)	52 (63%)	10 (20%)	75 (74%)
>50% decrease	0	4 (12%)	0	10 (26%)	0	17 (20%)	3 (6%)	35 (35%)
<100 mg/dL	0	2 (6%)	0	6 (15%)	2 (5%)	37 (45%)	19 (38%)	77 (76%)

In Trial MIPO3500108 (individuals with severe hypercholesterolemia on maximum baseline therapy), the mean percent change in LDL-C was -35.9% for the mipomersen group and 12.5% for the placebo group (p<0.001). The treatment difference from placebo was -48.4%. Approximately 69% of individuals in the mipomersen group had at least a 20% decrease in LDL-C levels from baseline to PET, compared with 17% of individuals in the placebo group. Ten (25.6%) individuals in the mipomersen group had a >50% decrease in LDL-C levels from baseline to PET compared with no individuals in the placebo group.

In ISIS 301012-CS7 (individuals with HeFH and CAD on maximally tolerated statin), the mean percent change in LDL-C was -28.0% for individuals in the mipomersen group and 5.2% for individuals in the placebo group (p<0.001). The treatment difference from placebo was -33.2%. Approximately 63% of individuals in the mipomersen group had at least a 20% decrease in LDL-C levels from baseline to PET, compared with 5% of individuals in the placebo group. Seventeen (20.7%) individuals in the mipomersen group had a >50% decrease in LDL-C levels from baseline to PET compared with no individuals in the placebo group.

In ISIS 301012-CS12 (individuals with high CVD risk on maximally tolerated statin), the mean percent change in LDL-C was -36.9% for individuals in the mipomersen group

and -4.5% for individuals in the placebo group (p<0.001). The treatment difference from placebo was -32.4%. Approximately 74% of individuals in the mipomersen group had at least a 20% decrease in LDL-C levels from baseline to PET, compared with 20% of individuals in the placebo group. Thirty-five (34.7%) individuals in the mipomersen group and 3 (6.0%) individuals in the placebo group had a >50% decrease in LDL-C levels from baseline to PET.

In the four Phase 3 trials, a progressive decrease in LDL-C levels occurred in the mipomersen group over the first 16 weeks of treatment. From Week 17 to Week 28, the LDL-C levels remained generally stable.

Secondary Endpoints
Secondary efficacy parameters for all four Phase 3 trials included percent changes from baseline to PET in apo B, non-HDL-C, and TC levels. Inflation of type I error due to multiple secondary endpoints was controlled by use of sequential inferential approach in which statistical significance of the primary parameter was required before drawing inferential conclusions about the first secondary parameter. Inferential conclusions about each successive parameter required statistical significance of the prior one. Parameters were assessed in the following order: LDL-C; apo B; total cholesterol; and non-HDL-C. Statistically significant percent reductions with mipomersen compared to placebo were seen for apo B, TC, and non-HDL-C from baseline to PET in the four Phase 3 trials.

Tertiary Endpoints
Tertiary efficacy parameters for all four Phase 3 trials included percent changes from baseline to PET in TG, Lp(a), VLDL-C, LDL/HDL ratio, apo A-I, and HDL-C. Of note, no adjustments for inflation of type I error due to multiple endpoints were made for tertiary parameters. In ISIS 301012-CS5, nominally statistically significant percent reductions occurred in Lp(a), TG, VLDL-C, and LDL/HDL ratio from baseline to PET. A nominally statistically significant increase in HDL-C was noted in mipomersen-treated individuals as compared with placebo-treated individuals. Changes in apo A-I were not statistically significant. In the 3 supportive Phase 3 trials (MIPO3500108, ISIS 301012-CS7, and ISIS 301012-CS12), nominally statistically significant reductions in Lp(a), and LDL/HDL ratio were noted in the mipomersen-treated group as compared with placebo. HDL-C did not decrease in these trials. However, apolipoprotein A-I (apo A-I) decreased from baseline and as compared to the placebo group in the mipomersen group in the three supportive trials. Reductions in TG and VLDL-C occurred but were not consistently statistically significant.

Cardiovascular Events
While the primary efficacy endpoint for this application is LDL-C reduction, LDL-C reduction is a surrogate endpoint for the ultimate goal of cardiovascular disease risk reduction. While it is relevant to look at cardiovascular events in the evaluation of efficacy for mipomersen, it is important to note that these trials were not powered to

evaluate cardiovascular morbidity and mortality and that these events were not prospectively defined or adjudicated across the four Phase 3 trials or the OLE trial.

At the System Organ Class (SOC) level, a slightly greater percentage of HoFH individuals in ISIS 301012-CS5 had Serious Adverse Events (SAEs) of Cardiac Disorders in the mipomersen-treated group (2.9%, 1/34) as in the placebo group (0%, 0/17). At the SOC level, more individuals in the pooled Phase 3 trials had Serious Adverse Events (SAEs) of Cardiac Disorders in the mipomersen-treated group (3.8%, 10/261) than in the placebo group (3.1%, 4/129).

At the SOC level, more individuals in the pooled Phase 3 trials had Cardiac Disorders in the mipomersen-treated group than in the placebo group (9.2% vs. 6.2%), respectively. In the Cardiac Disorders SOC, a greater number of disorders occurred in the mipomersen-treated group as compared to the placebo group in ISIS 301012-CS5 [4 (11.8%) vs 0] and in MIPO3500108 [5 (12.8%) vs 1 (5.3%)]. Of the 4 individuals in the mipomersen group in ISIS 301012-CS5, 2 experienced angina pectoris, and 1 patient each experienced acute coronary syndrome, palpitations, and aortic valve disease. The relevant preferred term events for MIPO108 were angina pectoris, coronary artery disease, acute myocardial infarction, angina unstable, cardiac failure, prinzmetal angina, and supraventricular extrasystoles.

There was no evidence for a decrease in cardiovascular events in the mipomersen group as compared to the placebo group in these trials. Based on the data submitted in this application, the possibility that mipomersen therapy increases the risk for cardiovascular events cannot be excluded. If approved, a limitation of use statement clarifying that the effect of mipomersen on cardiovascular morbidity and mortality has not been determined would be included.

1.2.2. Safety

The safety summary primarily focuses on the four Phase 3 trials. As the ISIS 301012-CS5 trial data represents the indicated patient population for this submission, those are discussed separately as needed.

The four Phase 3 trials were randomized, double-blind, six-month, placebo-controlled parallel group trials and employed a 2:1 (active:placebo) randomization. Mipomersen was dosed at 200 mg subcutaneously (SC) once weekly for up to 26 weeks, and was added to stable, maximally-tolerated lipid-lowering therapy. The trials consisted of a ≤ 4-week screening period, 26 weeks of treatment, and a 24-week post-treatment follow-up period (unless individuals enrolled into the OLE trial ISIS 301012-CS6). The long half-life of mipomersen made it necessary to have an extended duration in the post-treatment follow-up period. Most Phase 3 trials had an option for individuals to enter

OLE trial ISIS 301012-CS6 with up to 24 months of mipomersen treatment; ISIS 301012-CS12 and some sites in MIPO3500108 were not eligible.

Deaths
Four deaths have been reported across the mipomersen clinical program as of March 2012. Three deaths occurred in individuals in the mipomersen group and occurred during the 6-month post-treatment follow-up period. Two deaths were attributed to myocardial infarction and one to acute hepatic failure. One death due to acute myocardial infarction occurred in a patient in the placebo group during the 6-month on-treatment period.

The fulminant hepatic failure death occurred in a 68-year-old male with HeFH who received 26 injections of mipomersen and completed the treatment period of the trial. He developed elevated hepatic transaminases during the trial, which resolved by the end of the treatment period. He was found on MRI to have severe hepatic steatosis by the end of the trial. His death from hepatic failure was confounded by his presentation with a myocardial infarction event as well as his history of alcohol and acetaminophen use, but the potential for a contributing effect of mipomersen cannot be ruled out.

Serious Adverse Events
Eight percent (21/261) of mipomersen-treated individuals and 5% (7/129) of placebo-treated individuals experienced at least one SAE. The most frequently reported SAEs were Cardiac Disorders, occurring in 3.8% (10/261) of mipomersen-treated individuals and 3.1% (4/129) of placebo-treated individuals. One mipomersen-treated individual had SAEs of ALT and AST elevation and hepatic steatosis. Study drug was permanently discontinued due to the increase in ALT. An initial MRI scan showed incipient steatosis. The second MRI (93 days after starting mipomersen study treatment; 23 days after last dose) noted hepatomegaly and marked hepatosteatosis with changes from the previous examination. Total bilirubin, albumin, alkaline phosphatase, hsCRP, and coagulation parameters (aPTT, PT, and INR) remained within normal limits. Approximately 8 months after the ALT elevation SAE, the ALT and AST values had declined to less than 1.2 times the upper limit of normal.

Adverse Events that Led to Discontinuation
In the pooled Phase 3 population, 18% (47/261) of mipomersen-treated individuals and 2% (3/129) of placebo-treated individuals withdrew due to AEs. In the mipomersen individuals who discontinued due to an AE, injection site reactions (ISRs), flu-like symptoms (FLS), and abnormal hepatic transaminases were the major reasons. Discontinuations due to AEs were less common in ISIS 301012-CS5: 12% [4/34] of mipomersen-treated individuals and 0% of placebo-treated individuals. The AEs that most commonly leading to discontinuation in these individuals with HoFH (Rash, AST increase, Injection site pruritus, and Injection site pain) were similar to results in the pooled Phase 3 population.

Common Adverse Events
In the pooled Phase 3 trials, AEs that occurred notably more frequently in the mipomersen group as compared to the placebo group include Cardiac disorders (angina pectoris, palpitations); Gastrointestinal disorders (nausea, vomiting, abdominal pain); General disorders (ISRs, flu-like symptoms such as fatigue, pyrexia, chills, and peripheral edema); Hepatobiliary disorders (hepatic steatosis); Investigations (ALT, AST or hepatic enzyme increased, liver function test abnormal); Nervous system disorders (headache, dizziness); Psychiatric disorders (anxiety, insomnia); and Vascular disorders (hypertension). By far, ISRs were the most common AEs in individuals receiving mipomersen.

Targeted Safety Issues
Hepatic Issues
Adverse Events: In ISIS 301012-CS5 and the pooled Phase 3 trials, the mipomersen group had a greater number of AEs related to elevations in serum transaminase levels and hepatic steatosis as compared to the placebo group. For the individuals in the OLE trial ISIS 301012-CS6 (all subjects receive mipomersen), AEs of ALT increased occurred in 18% of the total population and in 32% of the HoFH population. For the entire ISIS 301012-CS6 population, 15 (11%) individuals had a treatment-emergent adverse event (TEAE) of Hepatic steatosis. Seven of the 15 individuals had corresponding elevations in ALT and/or AST.

Hepatic Transaminases: Across the pooled Phase 3 trials, 17% (43/261) of mipomersen-treated individuals as compared to one placebo-treated individual (1%; 1/129) had at least 1 ALT result that was ≥ 3 x ULN during the treatment period. In ISIS 301012-CS5 (HoFH subjects only), ALT increases 3xULN occurred in 4 of 34 (12%) individuals in the mipomersen group compared to none in the placebo group. A total of 8% (22/261) of mipomersen-treated individuals had ALT levels ≥ 3 x ULN on at least 2 consecutive occasions at least 7 days apart following initial dosing as compared to no placebo-treated individuals. No placebo-treated individuals in the Phase 3 trials had ALT levels ≥5 x ULN. No mipomersen-treated individuals in CS5 had ALT levels ≥8 x ULN. However, there were three (1%) mipomersen-treated individuals in the pooled supportive trials who had ALT levels ≥10 x ULN: one individual each in MIPO108 (peak ALT 604 U/L, 14.7 x ULN), CS7 (peak ALT 486 U/L, 11.9 x ULN) and CS12 (peak 415 U/L, 10.1 x ULN). Of note, these 3 individuals, as was the case with most subjects with significant ALT/AST elevations, met the liver chemistry-stopping rule (AST or ALT ≥ 8 x ULN for MIPO108, CS7 or CS12; ≥ 5 x ULN for CS5). Mipomersen was discontinued and the ALT elevations decreased off drug over a period of weeks. In general, when mipomersen therapy was stopped, ALT levels trended back to baseline values over a period of months. There were no cases of Hy's law (ALT increases ≥3 x ULN with concomitant elevations in total bilirubin ≥ 2 x ULN) during the treatment period in the mipomersen clinical program.

Hepatic Steatosis: In ISIS 301012-CS7 and ISIS 301012-CS12, hepatic fat fraction was assessed with MRI at baseline and Week 28 / Early Termination. A median increase in hepatic fat fraction of 9.6% in mipomersen-treated vs. 0.02% in placebo-treated individuals (mean increase 12.2% vs 0.4%) was observed. In ISIS 301012-CS7 and ISIS 301012-CS12, 62% of individuals in the mipomersen group had a ≥ 5 percentage point change from baseline in hepatic fat content. Of these 63 individuals, 16% had at least one ALT ≥ 3 x ULN. For the placebo group, 8% of individuals had a ≥ 5 % change from baseline in hepatic fat content and none had at least one ALT ≥ 3 x ULN. Approximately 84% of mipomersen-treated individuals with significant hepatic fat accumulation (defined by the applicant as ≥ 5 % change from baseline) did not have ALT abnormalities 3x ULN or greater.

In ISIS 301012-CS6, 16% had an average liver fat fraction >20% on at least 1 occasion. Forty-one percent had elevations in ALT ≥3 × ULN. Thus, the majority of individuals (~60%) with average liver fat fraction >20% on at least 1 occasion could not be indentified by monitoring ALT levels. As of March 2012, among individuals in ISIS 301012-CS6 with a measurement at baseline and at 12 months or longer on treatment, 25% (6 female, 10 male) had an average liver fat fraction > 20% on at least 1 occasion. All liver fat fractions were < 40%.

For individuals administered mipomersen, the accumulation of fat in the liver was varied. For some individuals, liver fat content increases continued over time. For other individuals who had an increase in liver fat and continued mipomersen treatment, extended treatment with mipomersen was associated with liver fat stabilization, or decrease.

Hepatic Biopsies: During the clinical development program, five individuals had liver biopsies prompted by increases in hepatic fat as seen on imaging studies. All patients had increases in hepatic fat on MRS or MRI, and 4 of 5 had elevations in ALT ≥ 3 x ULN. These five biopsies showed hepatic fat with minimal signs of inflammation and with minimal to no liver fibrosis. There was no evidence of necrosis or severe inflammation in the biopsies. Although these findings maybe reassuring, the mipomersen treatment duration was short and necrosis or fibrosis develops over time.

One of the concerns with mipomersen is that in some individuals mipomersen increases hepatic fat and it is not known what the long-term consequences are from this drug-induced hepatic steatosis in terms of progression to nonalcoholic steatohepatitis (NASH). Other questions include what is the best way to monitor for hepatic steatosis; whether there is an extent of hepatic steatosis that is sufficiently worrisome to warrant discontinuing the drug; is hepatic steatosis in the absence of elevated ALT levels of concern; and how to distinguish between fatty liver and nonalcoholic steatohepatitis (NASH)? In addition, non-drug induced nonalcoholic fatty liver disease (NAFLD) is characterized by an atherogenic lipid profile and there are data in the literature supporting an association of NAFLD with insulin resistance and increased

cardiovascular risk. It is unknown if drug-induced fatty liver could be associated with a similar potential for an increased risk of cardiovascular events.

Injection Site Reactions
ISRs were the most commonly reported AE in the clinical development program. In the pooled Phase 3 trials, 84% (220/261) of mipomersen-treated individuals experienced 3,683 ISR events and 33% (43/129) of individuals in the placebo group experienced 139 ISR events. ISRs were reported in 77% (26/34) of mipomersen-treated individuals in ISIS 301012-CS5 (individuals with HoFH). In the pooled Phase 3 trials, 13 of the 47 mipomersen-treated individuals (28%) who discontinued study treatment due to an AE did so because of an ISR. Thus, 5% (13/261) of all mipomersen-treated individuals discontinued due to an ISRs in these 6-month trials.

For all individuals in the open-label treatment extension trial, ISIS-301012-CS6, 138 (97.9%) had 2970 injection site-related events. Nine (6.4%) individuals had a severe injection site reaction. Thirteen (9.2%) individuals discontinued mipomersen due to an injection site reaction.

Flu-like Symptoms
Flu-like symptoms (FLS) were defined in the Mipomersen Pooled Data Analysis Plan by the preferred terms Influenza-like illness, Pyrexia, Chills, Myalgia, Arthralgia, Malaise, or Fatigue starting within 2 days after an injection. In ISIS 301012-CS5 (individuals with HoFH), 21% of the mipomersen group reported FLS at least once in the trial but none discontinued due to FLS. For HoFH individuals in the OLE trial CS6, FLS were reported by 66.0% (93/141) of individuals. Thirteen (9.2%) individuals had severe FLS. Approximately 25% (35/141) of individuals discontinued mipomersen due to FLS.

FLS were reported by 30% of mipomersen-treated individuals and 16% of placebo-treated individuals in the pooled Phase 3 trials. Fifteen percent of the mipomersen-treated individuals who discontinued study treatment due to an AE did so because of FLS. Thus, 3% of all mipomersen-treated individuals discontinued due to FLS in these 6-month trials.

The cause of the FLS is not known. In the dose-escalation trial ISIS 301012-CS3, there was a suggestion of an increased incidence of flu-like symptoms at the higher doses. Although the patient numbers are small, FLS were reported in a higher percentage of individuals with the highest trough plasma levels of mipomersen, as compared to the overall patient population. FLS do not seem to correlate with changes in plasma cytokines (IL-1β, IL-13, IL-6, interferon alpha or beta) or chemokines (MCP-1 and MIP-1α) as assessed in Protocol MIPO3200309.

Inflammatory and Immunological Issues
High Sensitivity C-reactive Protein (hsCRP) Effects

Chronic changes in hsCRP over time (from study baseline to the primary efficacy time point) were not seen in either mipomersen-treated individuals or placebo-treated individuals in the 6-month Phase 3 trials. After 26 weeks of therapy, the proportion of individuals with shifts in hsCRP levels from <3 mg/L pre-dose to ≥3 mg/L post-dose in the mipomersen group as compared to the placebo group was notably higher in trial ISIS 301012-CS12 (mipomersen 14% vs placebo 2%) but not in the other 3 trials.

Protocol MIPO3200309 was a Phase 1 trial evaluating 3 weeks of dosing with different subcutaneous (SC) regimens of mipomersen (200 mg once weekly, 70 mg thrice weekly, and 30 mg daily), in healthy volunteers. This trial assessed hsCRP, complement activation (Bb and C5a), and inflammatory markers (interleukin [IL]-1β, IL-6, IL-13, Interferon-α, Interferon-β, monocyte chemotactic protein [MCP]-1, and macrophage inflammatory protein-1α). Acute transient elevations in hsCRP were seen post-dosing with a peak approximately 2 days after the administration of a 200 mg once weekly dose (median change; IQR: 3.8 mg/L; 0.8-9.8, n=21) with less effect on hsCRP seen at the lower doses (70 mg dose: 0.4 mg/L; 0.2-1.7, n=21 and 30 mg dose: 0.3 mg/L; -0.2-1.2, n=21). Changes did occur in IL-6 in the 200 mg mipomersen group, but they were not generally associated with hsCRP increases. Similar changes in IL-6 occurred across treatment groups, including placebo. Most changes in hsCRP were <10 mg/L or only slightly above; most changes in IL-6 were below or only slightly above the ULN. No increases in the cytokines IL-1β, IL-13, IL-6, interferon alpha or beta or the chemokines MCP-1 and MIP-1α were observed in mipomersen-treated subjects compared to placebo-treated subjects after the first or last dose in this 3-week trial.

Thus, mipomersen causes predominantly short-term elevations in the inflammatory marker hsCRP. It is not known what the clinical significance of these elevations is and whether these changes in hsCRP negatively influence cardiovascular morbidity.

Complement Effects
In the Phase 1 trial MIPO3200309, there was no evidence of complement activation (an increase in C5a or Bb) in subjects who received mipomersen. Circulating levels of an intact complement factor, C3, were measured in Phase 3 trials (excluding ISIS 301012-CS5) pre-dose and at specified post-dose times (a week after selected doses). Decreases in C3 occurred in both placebo and mipomersen treatment groups in the pooled Phase 3 placebo-controlled trials but the decreases were somewhat greater in the mipomersen group (median percent change in C3 in mipomersen-treated individuals was -7.2 vs. -3.0 in placebo-treated individuals at Week 28/ET, corresponding to median values of 1.31 g/L and 1.38 g/L, respectively; normal range 0.9 to 1.8 g/L).

Immunogenicity Effects
In ISIS 301012-CS5, 30 (60%) of the 50 mipomersen-treated individuals across ISIS 301012-CS5 and OLE ISIS 301012-CS6 tested positive for anti-mipomersen antibodies at some point during one of the trials. In ISIS 301012-CS5, no placebo-treated individuals were positive for anti-mipomersen antibodies. Among the 30 individuals who

tested positive for anti-mipomersen antibodies in either ISIS 301012-CS5 or ISIS 301012-CS6, 16 individuals (53%) discontinued from treatment. The reasons for these discontinuations were similar to those seen in the general mipomersen-treated population and included FLS (7 individuals), nausea, vomiting and/or abdominal pain (3 individuals), withdrawal of patient or loss to follow up (3 individuals), hepatic transaminase tests (2 individuals), ISRs (1 patient), urticaria (1 patient), pregnancy (1 patient), depression (1 patient), and non-cardiac chest pain (1 patient). There is a possible relationship with urticaria in antibody-positive individuals as two individuals tested positive for antibodies around the time of the urticaria adverse event. There were no cases of anaphylaxis in CS5. There was one case of hypersensitivity reaction with angioedema that was reported in July 2012 in a 46-year old male individual with HeFH in OLE trial CS6. The patient had previously participated in trial CS17 and received treatment from July 2007 to February 2011. Prior to CS17, the patient was enrolled in trial CS9 and received 15 doses of 300 mg mipomersen from March 2007 to May 2007.

Renal Issues
There was more proteinuria (≥ 1+ by dipstick measurement at Week 28/ET) occurring in the pooled mipomersen-treated group (23/256; 9%) compared to placebo (4/128; 3%). The differences in reported AEs of proteinuria in the Pooled Phase 3 analysis was smaller than the differences in the dipstick results (6/261 mipomersen-treated individuals; 2%, vs. 1/129 placebo-treated individuals; 1%).

There was no consistent trend for worsening GFR when assessed by shift analysis (baseline to end of treatment) between mipomersen and placebo individuals in these 6-month trials.

One SAE of glomerular nephritis occurred in a 48-year-old male HeFH patient with a history of Reynaud's phenomena, intermittent microscopic hematuria and proteinuria in the OLE trial ISIS 301012-CS6. This reviewer concludes that there is no compelling evidence that mipomersen was the precipitating or causative factor in this adverse event but it cannot be excluded as a possible factor in the case.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

DMEP and the Division of Risk Management propose that the REMS for mipomersen have the following goals:

- To educate prescribers about the approved indication for use of mipomersen, the potential risk of hepatotoxicity associated with the use of mipomersen, the lack of data in pediatric patients and the need to monitor patients during treatment with mipomersen as per product labeling

- To limit access to therapy with mipomersen to patients with a clinical or laboratory diagnosis of HoFH

The REMS should have the following components:

1) Elements to assure safe use that include:
    a. Health care professionals (HCP) who prescribe mipomersen are specially certified
    b. Pharmacies that dispense mipomersen are specially certified
    c. Mipomersen will be dispensed to patients with evidence or other documentation of safe-use conditions.
2) An implementation system
3) A timetable for submission of assessments

For HCPs to be certified, they would be required to read educational materials and enroll in the mipomersen REMS program by acknowledging understanding of the risks of mipomersen therapy; the need to monitor serum transaminases during treatment; and the approved indication for use. They would also agree to counsel patients about the risk of hepatotoxicity and the need to have regular blood tests performed to monitor for evidence of liver injury or dysfunction.

In addition, the prescriber will need to attest on an authorized prescription form, for each prescription, that he/she is aware that mipomersen is indicated for patients with homozygous familial hypercholesterolemia and the drug is medically appropriate for the patient. The authorized prescription form, completed and signed by the prescriber only, would be sent directly to the certified pharmacy; the form would not require a patient signature. Certified pharmacies would need to have systems in place to verify that only certified prescribers prescribe mipomersen to patients in whom therapy with mipomersen is medically appropriate.

1.4 Recommendations for Postmarket Requirements and Commitments

A pediatric clinical study to evaluate the efficacy and safety of mipomersen in children with HoFH is recommended. A pharmacokinetic study may also be necessary to explore the appropriate dose(s) in children.

A trial to explore the efficacy and dosing regimen when mipomersen is used in conjunction with LDL-apheresis is recommended. During the advisory committee meeting, the applicant referred to a pilot study that is underway in Germany to evaluate mipomersen use in patients on LDL-apheresis. This trial may be adequate to address our concerns.

The proposed trial is a Phase II, monocenter, prospective, randomized, controlled trial in patients with severe hypercholesterolemia and atherosclerosis treated with maximally tolerated lipid lowering drug therapy and regular apheresis.[1] The study will consist of 2 phases. In the first phase (6 months) patients will be treated with mipomersen (12 mipomersen and 5 control subjects) and unchanged weekly apheresis therapy in order to evaluate safety and efficacy during regular apheresis. In the second phase (3 months) mipomersen will be continued and apheresis conditions will be adjusted according to clinical necessity (change in apheresis duration, change in between-apheresis intervals, discontinuation of apheresis) to evaluate whether treatment with mipomersen affects clinically important aspects of apheresis therapy.

The goal of the first phase is to demonstrate that 6 months of mipomersen treatment reduces LDL-cholesterol in patients on regular LDL-apheresis and with similar side effects as reported in patients not treated by concomitant apheresis therapy and to estimate the extent of reduction. The goal of the second phase is to evaluate the clinical significance of the reduction in terms of possible adaptations in apheresis therapy, i.e. to evaluate in how many patients apheresis duration can be shortened, intervals between two consecutive apheresis treatments can be stretched or apheresis can be discontinued.

The applicant should be encouraged to do clinical studies on the concomitant use of mipomersen and lomitapide as these two agents will likely be used together in patients with HoFH. Drug-drug interactions are unlikely with mipomersen as it is not metabolized by liver microsomes or hepatocytes, but is metabolized in tissues by endonucleases to form shorter oligonucleotides that are then substrates for additional metabolism by exonucleases. However, both agents cause transaminase elevations and hepatic steatosis and the concern is that the risk for increased hepatotoxicity could be greater when these agents are used concomitantly. In addition to the safety concerns, it would be informative to know what the overall effect on lipids is when these agents are combined versus used as monotherapy.

The applicant has proposed the following post-marketing study: (b) (4)

(b) (4)

1 ClinicalTrials.gov Identifier: NCT01598948; A total number of 17 patients will be randomized (12 patients allocated to mipomersen arm; 5 patients allocated to control). M or F ≥ 18 years of age; the patient fulfils German criteria for regular LDL-apheresis: a. Established atherosclerosis, b. LDL-cholesterol >/=130 mg/dl despite maximal possible drug therapy; fasting pre-apheresis LDL-C >/= 130 mg/dL at screening; and maximally tolerated statin treatment greater than zero, unless the patient has a documented history of statin intolerance, stable for at least 12 weeks prior to screening. Time schedule per patient: 4 weeks screening + 38 weeks treatment + 26 weeks follow-up = 68 weeks; Study start date: June 2012; Estimated study completion date: Feb 2014

(b) (4)

2 Introduction and Regulatory Background

HoFH is a rare genetic disorder in which both LDL-receptor alleles are defective and has a US prevalence of about 1 in 1,000,000 persons[2,3] which extrapolates to approximately 300 individuals in the US and 455 in the European Union. Untreated HoFH individuals have very high concentrations of LDL-C, in the range of 650 to 1000 mg/dL[4], cutaneous and tendinous xanthomata, corneal arcus and premature coronary artery disease.

Lipid-lowering drugs such as statins, which act mainly by up-regulating hepatic LDL receptors, are not particularly effective in reducing LDL-C levels in these individuals because their LDL receptors are dysfunctional. For example, in a study of HoFH individuals (n=40, 8-63 years) treated with rosuvastatin 20 to 40 mg[5] for 12 weeks, the mean LDL-C reduction from baseline (514 mg/dL) was 22%. About one-third of the patients benefited from increasing their dose from 20 mg to 40 mg with further LDL lowering of greater than 6%. In the 27 patients with at least a 15% reduction in LDL-C, the mean LDL-C reduction was 30% (median 28% reduction). Among 13 patients with an LDL-C reduction of <15%, 3 had no change or an increase in LDL-C. Reductions in LDL-C of 15% or greater were observed in 3 of 5 patients with known receptor negative status. In a study with atorvastatin (20 to 80 mg) without a concurrent control group[6], 29 patients (ages 6 to 37 years) achieved a mean LDL-C reduction of 18%. Twenty-five patients with a reduction in LDL-C had a mean response of 20% (range of 7% to 53%, median of 24%); the remaining 4 patients had 7% to 24% increases in LDL-C.

Other therapies used to treat HoFH include LDL apheresis, portocaval shunting, partial ileal bypass surgery, and liver transplantation. Portacaval shunt and partial ileal bypass lower LDL-C, but the effect is variable and often transient. Partial ileal bypass may be complicated by malabsorptive gastrointestinal side effects, whereas portacaval shunting

2 Beigel R, Beigel Y. Homozygous familial hypercholesterolemia: Long term clinical course and plasma exchange therapy for two individual patients and review of the literature. Journal of Clinical Apheresis. 2009;24(6):219-24.
3 Vella A, Pineda AA, O'Brien T. Low-density lipoprotein apheresis for the treatment of refractory hyperlipidemia. Mayo Clinic Proceedings. 2001;76(10):1039-46.
4 Goldstein, AL, Brown MS. Molecular Medicine. The cholesterol quartet. Science. 2001;292(5520):1310-2.
5 NDA 21366 Crestor PI, 2/28/2012
6 NDA 20702 Lipitor PI, 2/28/2012

may lead to hepatic encephalopathy.[7] Liver transplantation is restricted by a lack of donor organs and the need for continuous postoperative immunosuppression.[8]

LDL-apheresis is an extracorporeal treatment that selectively removes LDL particles from plasma and achieves significant reductions of LDL-C during several weekly or biweekly sessions[9]. LDL apheresis is FDA approved and covered by most insurance companies if the LDL-C is: >500 mg/dl in patients with homozygous FH, >300 mg/dl in patients without CAD, or >200 mg/dl in patients with CAD despite 6 months of treatment with maximal drug and dietary therapy.[9]

LDL apheresis is generally well-tolerated but can be difficult in patients with vascular access problems and may require an arteriovenous shunt. LDL apheresis is commonly performed by three techniques: plasma exchange (plasmapheresis), dextran sulfate adsorption, and heparin mediated extracorporeal LDL precipitation (HELP). Side effects can include hypotension, angina, hemolysis and allergic or anaphylactic reactions. The duration of a session with different LDL apheresis systems varies between 1.5 and 3.5 hours.[10] Typically, LDL-C concentration is acutely reduced 70–80% and then begins to rise, requiring repeat procedures at approximately 2-week intervals in patients with severe heterozygous FH and at 7–10-day intervals in patients with homozygous FH. Serum triglycerides, HDL-cholesterol, and lipoprotein(a) are also acutely reduced. With regular apheresis treatments, long-term decreases are produced in both the pre-treatment and post-treatment LDL-C levels. The mean LDL-C for HeFH patients on LDL-apheresis is approximately 30% to 38% lower compared to the status before initiation of regular apheresis.[11] Available LDL apheresis methods differ with respect to their impact on the coagulation system, on C-reactive protein and on leukocyte count. With some LDL apheresis methods a bradykinin syndrome (hypotension, flush, bradycardia and dyspnea) may develop, especially when the patient is being treated with an angiotensin-converting enzyme inhibitor. Usually this syndrome can be avoided by administering an angiotensin II receptor blocker or holding ACE inhibitors for 24 hours before the procedure.

7 Deckelbaum RJ, Lees RS, Small DM, Hedberg Se, Grundy SM. Failure of complete bile diversion and oral bile acid therapy in the treatment of homozygous hypercholesterolemia. N Engl J Med. 1977;296:465– 470.
8 Lopez-Santamaria M, Migliazza L, Gamez M, Murcia J, Diaz-Gonsalez M, Camarena C, Hierro L, De la Vega A, Frauca E, Diaz M, Jara P, Tovar J. Liver transplantation in patients with homozygotic hypercholesterolemia previously treated by end-to-side portacaval shunt and ileal bypass. J Pediatr Surg. 2000;35:630–633.
9 Thompsen J, Thompson PD. A systematic review of LDL apheresis in the treatment of cardiovascular disease. Atherosclerosis. 2006: 189,31–38.
10 Julius U, Frind A, Tselmin S, Kopprasch S, Poberschin I, Siegert G. Comparison of different LDL apheresis methods. Expert Rev Cardiovasc Ther. 2008 Jun;6(5):629-39.
11 Thompson GR, Catapano A, Saheb S, Atassi-Dumont M, Barbir M, Eriksson M, et al. Severe hypercholesterolaemia: therapeutic goals and eligibility criteria for LDL apheresis in Europe. Curr Opin Lipidol. 2010;21(6):492-8.

Three studies in a total of 95 children and adults with HoFH[12] evaluated lipid changes and the occurrence of cardiovascular disease before and after therapy. As shown in the following table, 64 of the 95 patients were undergoing long-term plasma exchange or LDL apheresis, usually combined with a high dose of statin plus ezetimibe. Apheresis was typically started between the ages of 7 and 9 and maintained for periods of 6–12 years. Baseline levels of total cholesterol or LDL-C off all treatment exceeded 700 mg/dL and were reduced by 45–50% using apheresis plus additional lipid-lowering therapy. The frequency of aortic root and coronary involvement with atherosclerosis varied according to age in the three studies but was present in roughly half of the patients prior to apheresis. Approximately 20–40% of patients developed coronary or aortic valvular disease or showed progression of pre-existing ones while on apheresis, despite the marked reductions in LDL cholesterol.

Table 1. LDL Apheresis in Homozygous Familial Hypercholesterolemia

	Ref [13]	**Ref [14]**	**Ref [15]**
Homozygotes, *n*	39 (22[a])	27[b]	29[c]
On apheresis, *n*	17	27	20
Age started (years)	7	8.5	9
Duration (years)	6.6	12.6	6
Baseline cholesterol (mg/dL)	792 (TC)	886 (TC) 704 (LDL)	812 (LDL-C) at dx (n=9) 521 (LDL-C, range 243-713) baseline, n=20
Δ in baseline cholesterol with apheresis/drugs	−45%	-72% acutely −50 % chronically	-75% acutely -48% chronically w/ biweekly sessions

12 Thompson GR, Barbir M, Davies D, Dobral P, Gesinde M, Livingston M, mandry P, Marais AD, Matthews S, Neuwirth C, Pottle A, le Roux C, Scullard D, Tyler C, Watkins S. Efficacy criteria and cholesterol targets for LDL apheresis. Atherosclerosis (2010) 208: 317-321.
13 Kolansky DM, Cuchel M, Clark BJ et al. Longitudinal evaluation and assessment of cardiovascular disease in patients with homozygous familial hypercholesterolemia Am J Cardiol, 102 (2008), 1438–1443
14 Palcoux JB, Atassi-Dumont M, Lefevre P et al. Low-density lipoprotein apheresis in children with familial hypercholesterolemia: follow-up to 21 years Ther Apher Dial, 12 (2008), pp. 195–201
15 Hudgins L, Kleimann B, Scheuer A, White S, Gordon BR. Long-term safety and efficacy of low-density lipoprotein apheresis in childhood for homozygous familial hypercholesterolemia. Am J Cardiol, 102 (2008), 1199–1204

	Ref [13]	Ref [14]	Ref [15]
CVD present pre-Rx	9% ≤16 yrs 88% > 16 yrs	48%	60%
CVD developed during Rx	44%[a] (7/16) over 4-8 yrs dev'l progression of coronary and aortic valvular disease	22%	33%

n, number; TC, total cholesterol; LDLC, LDL cholesterol.
a: Aged ≤16 yrs.
b: All aged <15.
c: All aged <18

Results from different observational studies suggest that cardiovascular events can be significantly reduced by LDL apheresis therapy but not totally prevented[9]. In a non-randomized controlled trial, 87 patients with heterozygous FH who received medical therapy alone were compared to 43 heterozygous patients treated with LDL apheresis for 6 years. Both groups received a statin (pravastatin 10–20 mg/day or simvastatin 5–10 mg/day) as primary therapy. Probucol, cholestyramine, and benzafibrate were also added to maximized lipid reduction. LDL apheresis was associated with a 72% long-term reduction in total coronary events including death from CAD, non-fatal myocardial infarction, and revascularization (PTCA/CABG) compared to the pharmacologic therapy group (10% versus 36%, $p < .01$)[16]. The apheresis patients had a nearly two-fold greater reduction (approximately 50% versus 25%) in LDL-C, triglycerides, and total cholesterol.

In a prospective study, 189 hypercholesterolemic patients with documented CAD were followed in the first 5 years without LDL apheresis and in the next 5 years with regular apheresis[17]. The rate of myocardial infarction dropped by 85% under LDL apheresis. Quantitative coronary angiographic analyses confirmed significant effects of apheresis on the morphology of atherosclerosis.

Another group reported that the rate of cardiovascular events during therapy with LDL apheresis and lipid-lowering drugs was 3.5 events per 1000 patient-months of treatment compared with 6.3 events per 1000 patient-months for the 5 years before LDL apheresis therapy[18].

16 Mabuchi H, Koizumi J, Shimizu M et al. Long-term efficacy of low-density lipoprotein apheresis on coronary heart disease in familial hypercholesterolemia. Hokuriku-FH-LDL-Apheresis Study Group. Am. J. Cardiol.1998.82,1489–1495.
17 Jaeger BR. The HELP system for the treatment of atherothrombotic disorders: a review. Therap. Apher. Dial.2003: 7,391–396.
18 Gordon BR, Kelsey SF, Dau PC et al. Long-term effects of low-density lipoprotein apheresis using an automated dextran sulfate cellulose adsorption system. Liposorber Study Group. Am. J. Cardiol. 1998:81,407–411.

While LDL apheresis significantly lowers LDL-C and is considered the standard of care for patients with HoFH, the limitations include limited availability, high cost, procedure duration, and the need to maintain adequate vascular access.[19]

2.1 Product Information

Mipomersen is a second-generation 2′- MOE phosphorothioate antisense inhibitor targeted to apoB-100, the principal apolipoprotein of LDL-C and its metabolic precursor, VLDL. Mipomersen is complementary to a 20-nucleotide segment of the coding region of the mRNA for apoB-100 and binds to the mRNA by Watson and Crick base-pairing. The binding of mipomersen to the cognate mRNA results in RNase H-mediated degradation of the cognate mRNA thus inhibiting translation of the apoB-100 protein. This leads to a reduction in synthesis and transport of apo-B containing lipoprotein and a reduction in circulating LDL-C. Unlike statins, mipomersen is not dependent on LDL receptor upregulation for its beneficial effects. The targeted treatment population for this application is individuals with HoFH, an orphan-sized population with the most extreme form of familial hypercholesterolemia (FH). Orphan Drug Designation was granted to mipomersen for the treatment of HoFH.

Mipomersen's proposed indication is as an adjunct to maximally tolerated lipid-lowering medications and diet to reduce low-density lipoprotein (LDL-C), apoB, total cholesterol, non-high-density-lipoprotein-cholesterol (non-HDL) and lipoprotein (a) in individuals with homozygous familial hypercholesterolemia (HoFH). Mipomersen has been developed as an additional line of therapy for HoFH individuals without adequate control of LDL-C. Mipomersen has not been studied in individuals that have had LDL-apheresis in the last three months nor has it been studied in conjunction with LDL-apheresis.The proposed mipomersen dose for marketing is 200 mg once weekly as a subcutaneous injection.

Mipomersen has been developed by Genzyme Corporation ("the applicant") with one pivotal 6-month placebo-controlled safety and efficacy trial that evaluated 51 individuals with HoFH. This pivotal trial in the indicated population is supported by three Phase 3 trials in individuals with severe heterozygous familial hypercholesterolemia (HeFH), in individuals with HeFH and coronary artery disease (CAD), and in individuals with hypercholesterolemia who were at high risk for coronary heart disease (CHD) events as defined by the NCEP ATP III Guidelines. All individuals in these Phase 3 trials were stable on a low-fat diet and on maximally tolerated lipid-lowering medications (primarily statins).

19 Thompson GR. Lipoprotein apheresis. Curr Opin Lipidol. 2010;21: 487–491.

2.2 Tables of Currently Available Treatments for Proposed Indications

Rosuvastatin (Crestor), atorvastatin (Lipitor), simvastatin/ezetimibe (Vytorin), simvastatin (Zocor), ezetimibe (Zetia) and LDL apheresis have indications for lipid-lowering in patients with HoFH. Additional information on these treatments is described in Section 2.

2.3 Availability of Proposed Active Ingredient in the United States

Mipomersen sodium is not currently available in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

Antisense drugs bind to target RNA, resulting in inhibition or degradation of the messenger RNA (mRNA) and inhibition of synthesis of a specific protein. Unmodified phosphodiester ASOs, like natural DNA and RNA, are subject to rapid degradation by nucleases. To avoid rapid degradation, antisense subunits have been modified to improve the stability and alter the various physicochemical properties of the molecule. Phosphorothioate oligodeoxynucleotides, where sulfur has been substituted at the non-bridging oxygen in the phosphate backbone, are referred to as the first-generation of antisense therapeutics. Vitravene® (fomivirsen sodium), approved August 1998, is a first-generation antisense drug developed for the treatment of AIDS-related cytomegalovirus retinitis. The most frequently observed adverse events with this drug have been ocular inflammation (uveitis) including iritis and vitritis. Systemic adverse events reported in ~ 5 to 20% of individuals have included abdominal pain, anemia, asthenia, diarrhea, fever, headache, infection, nausea, pneumonia, rash, sepsis, sinusitis, systemic CMV, and vomiting.[20] While some of these first-generation antisense therapeutics have been approved for marketing or are in clinical development, there are a number of limitations, including lack of oral bioavailability, loss of affinity for target mRNA and nonspecific interactions with proteins.[21] Newer chemical analogues have been developed of which one is the second-generation 2′- methoxyethyl (MOE) gapmer antisense inhibitor targeted to human apoB-100. These second-generation compounds are more nuclease resistant, resulting in greater stability and longer tissue half-lives, and exhibit decreased toxicities when compared with first-generation phosphorothioate oligodeoxynucleotides.[22]

20 NDA 20961 Vitravene PI, 8/26/1998
21 Crooke ST. Progress in antisense technology. Annu. Rev. Med. (2004) 55:61-95.
22 Crooke RM. Antisense oligonucleotides as therapeutics for hyperlipidaemias Expert Opin. Biol. Ther. (2005) 5(7):907-917

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Date	Event/Notes
01 Sep 2005	Pre-IND responses to firm's questions • Firm proposed single 12-week Phase 3 study with single dose (200 mg/wk SQ) for NDA with Fast Track designation • Firm was told that there was insufficient information to proceed to a pivotal Phase 3 study. No safety margin from animal data to support 200 mg human dose. A more thorough dose-exploration was needed to establish a minimally effective dose prior to initiating the pivotal study. More rigorous renal monitoring and an assessment of immunotoxicity was required. Firm was told to submit the IND and request an End-of-Phase 2 meeting 30 days following FDA receipt.
18 Nov 2005	IND 70969 submitted by ISIS Pharmaceuticals • Preclinical toxicity concerns included an increase in aPTT, renal effects (nephrotic syndrome, glomerulonephritis, declines in renal function), liver effects (increase in liver transaminases, hepatic steatosis), and proinflammatory changes. • Potential safety concerns from clinical studies included systemic symptoms (fever, chills, arthralgias, nausea, vomiting, and flu-like symptoms), inhibition of the intrinsic coagulation pathway (prolongations of aPTT), thrombocytopenia, renal effects, liver effects (increase in liver transaminases, hepatic steatosis), proinflammatory effects (lymphadenpoathy), and injection site reactions. Recommended additional tests for Study CS9 were spot or 24-hour urine collection for total protein, microalbumin, β2-microglobulin and creatinine to determine urinary protein and glomerular filtration rate. To obtain information on the effect on complement and coagulation pathways, measurement of aPTT/PT and complement (factor Bb) was recommended.
12 Apr 2006	Fast-track designation request submitted
23 May 2006	Orphan Drug Designation (No. 06-2214) for treatment of HoFH was granted.
30 May 2006	Fast Track denied as the development program was not designed to address whether treatment with mipomersen in HoFH patients (or lower risk populations) reduces cardiovascular morbidity and mortality.
4 Jan 2007	The firm submitted a draft 6-month interim report of a one-year cynomolgus monkey toxicity study (Study ISIS301012-AS15).
8 Jun 2007	The final interim report (through Week 52) of the one year toxicity study was submitted. The new finding after one year of dosing was that animals treated with drug (3, 10 and 30 mg/kg/week) developed arterial (peri)vasculitis and intimal hyperplasia (N=5 total affected). The vasculitis was observed in the GI tract in 3 monkeys (3, 10 or 30 mg/kg) and in multiple organs in another 2 monkeys (30 mg/kg). Coronary artery vasculitis and intimal thickening was present in 1 out of 4 monkeys treated with 10 mg/kg and euthanized on Day 185 of the study. Additional

Date	Event/Notes
	new findings in the 30 mg/kg group included renal tubule epithelial cell degeneration, thrombocytopenia and decreases in complement protein C3.
11 Sep 2007	The firm requested an EOP2 meeting on May 4, 2007, which was granted. An internal meeting was held on September 5, 2007. It was determined that the clinical questions could not be addressed until some preclinical findings were resolved. The focus of the meeting was changed to a discussion of the preclinical findings in the chronic monkey study (Study ISIS 301012-AS15) and the implications for future clinical development.
29 Jan 2008	IND placed on partial clinical hold. It was the firm's position that the vasculitis in the monkeys was due to complement activation and this activation does not occur in humans at the proposed dose levels. Complement and inflammatory markers will be monitored in the proposed Phase 3 studies. However, the division was not convinced that the firm's explanations are valid and remains concerned because, among other things, monitoring for vasculitis in clinical trials is not feasible. Because of the preclinical safety concerns and the lack of a validated biomarker for vasculitis, it was determined that, at this time, studies should be limited to patients at high risk for cardiovascular disease. Risk-benefit profile only supports treatment of patients at high risk for cardiovascular events defined as 10-year risk for CVD > 20%, on maximum statin dose and not at LDL goal.
15 Feb 2008	FDA Regulatory Briefing: Preclinical toxicity concerns included an increase in aPTT, complement activation and proinflammatory changes/vasculitis, liver effects (increase in liver transaminases, hepatic steatosis) and renal effects (glomerulonephritis, declines in renal function). In clinical studies, the four most relevant safety signals observed to date were: (1) transient prolongations of aPTT following intravenous dosing; (2) constitutional symptoms such fever and chills following initial administrations; (3) dermatological responses such as erythema at subcutaneous injection sites; and (4) serum transaminase elevations. Panel discussion included the following issues: (1) whether the available preclinical data on the immunostimulatory effects (pro-inflammatory tissue changes, complement activation, vasculitis) of this compound are concerning; (2) would additional preclinical studies clarify the potential clinical significance of ISIS 301012's immunostimulatory effects; (3) can the immunostimulatory effects of ISIS 301012 and the potential for vasculitis be adequately monitored (e.g., measurement of proinflammatory biomarkers) in clinical studies; and (4) if the currently available preclinical data support the use of ISIS 301012 in: a) patients at high-risk for cardiovascular disease; and b) in patients at low-to-moderate risk for cardiovascular.
23 Jul 2008	Change of IND sponsorship from ISIS Pharmaceuticals to Genzyme Corporation
27 Feb 2009	FDA provided feedback on statistical analysis plan (SAP) for protocol ISIS 301012-CS5 entitled *A Randomized, Double-Blind, Placebo-Controlled*

Date	Event/Notes
	Study to Assess the Safety and Efficacy of ISIS 301012 as Add-On Therapy in Homozygous Familial Hypercholesterolemia Subjects.
14 Jul 2009	FDA responded to the applicant's questions on CMC issues.
31 Aug 2009	FDA provided comments on applicant's proposed QT/QTc study entitled "*A Randomized Double-Blind Crossover Trial to Define the ECG Effects of Mipomersen (ISIS 301012) using a Therapeutic and a Supra-Therapeutic Dose compared to Placebo and Maxifloxacin (a Positive Control) in Healthy Men and Women: A Thorough ECG Trial"* (MIP02800209).
25 Jan 2010	FDA provided comments on applicant's revised QT/QTc study
27 Jan 2010	FDA provided comments on applicant's proposed carcinogenicity study statistical analysis plan (SAP).
02 Feb 2010	FDA provided comments on applicant's protocol entitled *A Drug-Drug Interaction Study to Assess the Effects of a Single Dose of Mipomersen (200 mg SC) on Single-Dose Warfarin Pharmacodynamics and Pharmacokinetics in Healthy Adult Subjects* (MIPO2900509). • Mipomersen has an elimination half-life of 31 days following a 200 mg subcutaneous dose. The effect of multiple doses of mipomersen on the pharmacodynamics of warfarin may be different compared to that seen following single-dose administration. We recommend that you use a multiple-dose regimen of mipomersen when evaluating the effect on warfarin pharmacodynamics and pharmacokinetics.
23 Feb 2010	FDA responded to the applicant's questions on CMC issues.
30 Mar 2010	FDA responded to the applicant's revisions to Protocol ISIS 301012-CS6, entitled, *An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 301012 in Subjects with Familial Hypercholesterolemia*. The primary purpose of this amendment is to include MRI assessments of liver fat fraction at approximately 6-month intervals during the study.
12 Apr 2010	FDA provided comments on applicant's revised protocol MIPO2900509 and confirmed that Protocol MIPO2900509 could proceed under the partial clinical hold, since it is a multiple-dose study to be conducted in healthy volunteers.
13 Dec 2010	Pre-NDA face-to-face meeting: Non-clinical: (1) There remains uncertainty about the clinical significance, monitorability and mechanism of action by which mipomersen induced vascular lesions in monkeys (characterized as multi-focal intimal hyperplasia with mixed inflammatory infiltrates). (2) Please provide the validation report for detection of anti-mipomersen antibodies in human serum/plasma. This should be submitted and found acceptable by the Agency prior to submission of the NDA. Clin-Pharm: Clinical pharmacology program appears to be sufficient for an NDA submission.

Date	Event/Notes
	Clinical: Whether the Phase 3 study ISIS 301012-CS5, along with the open-label extension study CS6, supports an indication for the treatment of patients with HoFH will be determined after a full review of the relevant data and, most likely, input from an FDA advisory committee. (b) (4) [redacted]
16 Dec 2010	Email sent to applicant stating that after additional internal discussions, FDA has concluded that (b) (4) [redacted] Examinations of the study sample sizes used to support NDAs for orphan conditions with prevalence rates similar to severe HeFH support a request for one-year placebo-controlled data in a minimum of 300 severe HeFH patients (e.g., 200 on active drug vs. 100 on placebo). Additional safety concerns which will require further investigation include differentiating "benign" vs. clinically significant transaminase elevations during mipomersen treatment and the nature of the relationship between the transaminase elevations and steatotic changes in the liver after mipomersen administration. Since hepatic steatosis may progress to steatohepatitis and cirrhosis, additional information is needed on the long-term use of mipomersen on intrahepatic triglyceride content and hepatic lipid changes particularly in patients with varying degrees of hepatic steatosis at baseline (e.g., patients with diabetes, obesity, hypertriglyceridemia, heavy alcohol use). Careful monitoring of antibodies, renal function (quantitative urine protein measurement, measurement of glomerular filtration rates etc), blood pressure changes and adverse events will also be necessary in ongoing and future studies of mipomersen.
04 Apr 2011	The proposed proprietary name for mipomersen sodium is Kynamro which was designated conditionally acceptable in correspondence from the Division of Medication Error Prevention.
13 June 2011	Special Protocol Assessment (SPA) request for Protocol MIPO3801011: *A Phase 3, Randomized, Double-Blind, Placebo- Controlled, Parallel-Group Study to Assess the Safety and Efficacy of Two Different Regimens of Mipomersen in Patients with Familial Hypercholesterolemia and Uncontrolled Low-Density Lipoprotein Cholesterol*
22 Jul 2011	No agreement to SPA for Protocol MIPO3801011. FDA requested the firm to extend the duration of the trial in order to provide 52 weeks at the fully titrated dose. Provide which hepatic biomarkers will be utilized and the supporting evidence for choosing these biomarkers. The hepatic biomarkers should be determined prior to starting the protocol.
29 Jul 2011	Modification of the partial clinical hold to permit studies of less than six months' duration in patients who are not at high risk for CVD. Over the clinical development of mipomersen, several studies have been conducted, with FDA approval, in patients who are not at high risk for CVD. These studies include MIP02800209, a TQT study involving 60 healthy subjects each receiving a single injection of mipomersen; MIP02900509, a drug interaction study involving 18 healthy subjects each receiving four doses of mipomersen every other day; MIP03200309, a

Date	Event/Notes
	dose comparison study involving 84 healthy subjects each receiving one to three weekly doses of mipomersen for three weeks; and ISIS 301012-CS3, a Phase 2 study in 50 hypercholesterolemic subjects not on lipid-lowering therapy each receiving weekly doses of mipomersen for thirteen weeks. This accumulated clinical data have lessened our original concerns such that we are now allowing studies in low to moderate risk subjects for less than 6 months.
29 Aug 2011	Submission of SPA request for revised Protocol MIPO3801011
7 Sep 2011	The firm submitted a validation report for detection of anti-mipomersen antibodies in human serum/plasma, Study ISIS 301012-MV12 entitled Validation of an ELISA for the Detection of Anti-ISIS 301012 Antibodies in Human Serum.
27 Sep 2011	Agreement to SPA request for revised Protocol MIPO3801011 The revised protocol provides for a prospective, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 study with 60 weeks of blinded treatment which includes an 8-week adjusted dosing regimen phase and a 52-week full dose regimen phase.
1 Dec 2011	The deficiencies determined by the Office of Biotechnology Products (OBP), Division of Therapeutic Proteins (DTP) in the binding immune assay for detection of anti-mipomersen antibodies in human serum/plasma was emailed to firm.
13 Dec 2011	Tcon: Initial first generation antibody assay is inadequate. Preferably, the NDA should not be submitted until the appropriate immunological data are generated using the new assay. The firm ultimately agreed that the NDA would include the validation report for the newly developed, second-generation assays for the detection of anti-mipomersen antibodies in the human serum as well as clinical data for patients with HoFH (Study ISIS 301012-CS5) and corresponding samples for these patients in the open-label extension study, ISIS 301012-CS6. The antibody data from the remaining Phase 3 studies and ISIS 301012-CS6 would be provided in the Day 120 safety update report.

2.6 Other Relevant Background Information

Hypercholesterolemia, specifically an increase in LDL-C levels, is a major risk factor for the development of atherosclerosis and coronary heart disease (CHD). Many large-scale, randomized trials have shown that reducing LDL-C levels with statins reduces the risk of CHD, with a direct relationship between LDL-C levels and CHD events. One meta-analysis concluded that lowering LDL-C by 1 mmol/L (~40 mg/dL) for 4 to 5 years reduces the risk of coronary events and strokes by 22%[23]. Several recent trials have

23 Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170000 participants in 26 randomised trials. Lancet 2010;376:1670-1681.

shown that statin regimens using higher doses or more-potent agents, which both yield greater reductions in LDL-C, reduce the risk of vascular events more than less-intensive statin regimens in patients at very high cardiovascular risk.[24,25,26,27] The Third Report of the National Cholesterol Education Program (NCEP) Adult Treatment Panel in 2001[28] recommended an LDL-C goal of less than 100 mg/dL for patients at high risk for CHD. In 2004, based on accumulating trial data, the NCEP, the American Heart Association, and the American College of Cardiology recommended an optional more-aggressive LDL-C goal of less than 70 mg/dL for patients at very high risk for CHD, even if baseline LDL-C levels were below 100 mg/dL[29].

The goal of lipid-lowering therapy is to reduce the risk for cardiovascular disease. In the past, reduction of LDL-C alone has been viewed favorably as a surrogate outcome if the reduction was sufficiently robust and if the investigational product did not have safety signals raising concern that risk exceeded benefit. Within the last few years, however, several controlled clinical trials have demonstrated that favorable changes in lipid parameters do not always translate into the expected cardiovascular benefit. One example is the ILLUMINATE trial[30], which showed that treatment with torcetrapib decreased LDL-C and increased HDL-C levels but also increased the risk for death and CVD. Although the hypothesized reasons for these "failures" are varied, this experience challenges previous assumptions about lipid-related surrogate endpoints. Future data from Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT)[31] is expected to provide important information regarding the association between

24 Cannon CP, Braunwald E, McCabe CH, Rader D J, Rouleau JL, Belder R et al., for the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 Investigators*. Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes. N Engl J Med 2004; 350(15): 1495-504.
25 LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC et al; Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005; 352:1425–35.
26 Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I et al., on behalf of the Incremental Decrease in End Points through Aggressive Lipid Lowering Study Group. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction. The IDEAL study: a randomized controlled trial. JAMA 2005; 294:2437– 45. Erratum in: JAMA. 2005 Dec 28;294(24):3092.
27 Cannon CP, Steinberg BA, Murphy SA, Mega JL, Braunwald E. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. J Am Coll Cardiol. 2006;48(3):438-45.
28 Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001; 285: 2486-97.
29 Grundy SM, Cleeman JI, Merz CNB, et al. Implications of recent clinical trials for National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation. 2004;227- 39.
30 Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ et al; ILLUMINATE Investigators. Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med 2007; 357:2109-2122.
31 Cannon CP, Giugliano RP, Blazing MA, Harrington RA, Peterson JL, Sisk CM, Strony J, Musliner TA, McCabe CH, Veltri E, Braunwald E, Califf RM; IMPROVE-IT Investigators. Rationale and design of

non-statin based LDL-C reduction and cardiovascular outcomes.[32] Thus, in the absence of cardiovascular outcomes data, contemporary decisions to approve novel LDL-lowering therapies are not only influenced by the direction and magnitude of drug-induced changes in LDL-C, but also by the effects of the drug on other lipid parameters and markers of cardiometabolic risk, as well as evidence for off-target toxicity.

Given the rarity of HoFH, it is not feasible to require the demonstration of benefit on cardiovascular outcomes for investigational products in this population specifically. Ideally, the cardiovascular outcome efficacy and safety of a novel investigational lipid-altering product would be evaluated in a broader hyperlipidemic population before, or in parallel with, the HoFH population. However, for mipomersen, significant concern of potential harm from hepatic steatosis has limited its use to narrow populations of patients at very high risk for CAD.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The eCTD format of the submission was navigable and very well organized. The overall quality of the submission was very good. The applicant was asked to provide additional information throughout the course of the review and did so in a timely fashion.

3.2 Compliance with Good Clinical Practices

The applicant provides a statement of Good Clinical Practice. All clinical studies were conducted under the supervision of an IRB with adequate informed consent procedures.

3.3 Financial Disclosures

Genzyme submitted a completed Form FDA 3454 attesting to the absence of financial interests and arrangements for all investigators that submitted financial information.

IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial): comparison of ezetimbe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes in patients with acute coronary syndromes. Am Heart J. 2008 Nov;156(5):826-32. Epub 2008 Sep 2.

32 IMPROVE-IT is evaluating ezetimibe/simvastatin combination 10/40mg compared to simvastatin 40 mg monotherapy in subjects with stabilized high-risk acute coronary syndrome with a composite primary outcome of cardiovascular death, myocardial infarction, nonfatal stroke, rehospitalization for acute coronary syndrome, or revascularization. The trial started in October 2005 and the estimated completion date is June 2013.

Genzyme Corporation certifies that it has acted with due diligence to obtain the financial information described in 21 CFR 54.4(a)(3), but was unable to do so for five (5) principal investigators and thirty-one (31) sub-investigators involved in Study MIPO3500108.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please see Dr. Joseph Leginus' review for a full discussion of mipomersen CMC issues. The drug substance (mipomersen sodium) will be manufactured for commercial use by Isis Pharmaceuticals located in Carlsbad, CA. The drug product, mipomersen sodium injection 200 mg/mL, will be manufactured as a sterile, aqueous solution intended for delivery of 1 mL by subcutaneous injection. Other than Water for Injection, there are no excipients in the formulation. The drug product will be available in two presentations: 2 mL vials (manufactured by Hospira Inc., McPherson, KS) and 1 mL prefilled syringes (manufactured by Genzyme Biosurgery, Ridgefield, NJ).

The recommendation from a CMC perspective is pending a) satisfactory responses to the deficiencies identified in a previous review, b) acceptability of microbiology information regarding sterility assurance of the drug product, c) an Acceptable recommendation from the Office of Compliance for manufacturing facilities associated with this application, and d) confirmation from Pharmacology/Toxicology that drug substance impurities have been adequately qualified at or above the proposed limits found in the drug substance specifications.

4.2 Clinical Microbiology

Please see Dr. Robert Mello's review for a full discussion of mipomersen clinical microbiology issues.

4.3 Preclinical Pharmacology/Toxicology

Please see Dr. Ron Wange's review for a full discussion of mipomersen pharmacology/toxicology.

Pharmacologic characterization of apo B inhibition was based on the use of a mouse-specific inhibitor (ISIS 147764) since the sequence of mipomersen is not homologous

with the apo B mRNA in mice. The surrogate molecule has the same nucleotide modifications as mipomersen. In the toxicity studies, the monkey was used as the non-rodent species. Although mipomersen is partially homologous with the monkey apo B sequence, it exhibits only minimal pharmacological activity, so a monkey-specific apo B inhibitor (ISIS 326358) was used in a hypercholesterolemic monkey model to assess the effects of apoB inhibition and cholesterol reduction.

As the applicant describes in their submission, ASOs exhibit dose-dependent toxicities that can be classified as hybridization (binding)-dependent or hybridization-independent.33 Hybridization-dependent toxicity can occur through on-target exaggerated pharmacological effects or off-target RNA interactions. Hybridization-independent toxicity can occur through interactions of the negatively charged mipomersen molecule with proteins. Toxicities related to the hybridization-independent mechanism may be related to the nucleotide sequence or the chemistry of the oligonucleotide which results in a common set of toxicities from plasma protein interactions (e.g., increased activated partial thromboplastin time (APTT), complement activation) or tissue/cell interactions (e.g., inflammatory effects, injection site reactions, decreased platelets, increases in liver enzymes, renal proximal tubule effects).

While apo B-100 is produced in the liver, apo B-48, which corresponds to the N-terminal segment (48%) of apo B-100, is produced primarily in intestinal cells and is essential for the formation of chylomicrons and the uptake of dietary fat. In preclinical studies in high fat fed mice, apo B-48 protein levels and chylomicron particle numbers were unaffected by apo B ASO treatment. Dietary fat and cholesterol absorption were also unchanged after administration of the murine apo B ASO. The applicant comments that this lack of effect of apo B ASOs on chylomicron synthesis may be due to the limited distribution of antisense drugs to the gastrointestinal tract and the rapid turnover of the intestinal brush border.

Summary of Positive Findings in Nonclinical Studies

- Mipomersen produced inflammatory changes in numerous organs, including lymphohistiocytic cell infiltrates and increases in lymphoid organ weights, associated with increases in plasma cytokines and chemokines such as MCP-1 in mice.
- Increases in spleen weight and total serum IgG occurred in the chronic monkey study.
- Dose-related local injection site reactions were evident in all species treated with mipomersen by subcutaneous injection.

33 Koller, E., W. A. Gaarde, et al. (2000). Elucidating cell signaling mechanisms using antisense technology. Trends Pharmacol Sci 21(4): 142-148.

- In the chronic monkey study, multi-focal intimal hyperplasia with mixed inflammatory infiltrates was seen in vascular beds in 2 of 6 monkeys treated for 12 months with 30 mg/kg/week.
- In monkeys at the 30 mg/kg/wk dose level, repeated weekly complement activation produced a progressive decrease in plasma C3 concentrations. The degree of C3 depletion was profound in some individual monkeys with values reduced up to 75% below baseline or normal values.
- Group mean decreases of up to 30% in platelet count were observed in monkeys treated with 30 mg/kg/week starting at the 6-month time point and in rats treated with 75 mg/kg/week for 3 months.

Regulatory Implications of Findings in Nonclinical Studies:
June 2007: The final interim report (through Week 52) of the one-year monkey toxicity study (Study ISIS 301012-AS15) was submitted. The new finding after one year of dosing was that animals treated with drug (3, 10 and 30 mg/kg/week) developed arterial (peri)vasculitis and intimal hyperplasia (N=5 total affected). The vasculitis was observed in the gastrointestinal tract in 3 monkeys (3, 10 or 30 mg/kg) and in multiple organs in another 2 monkeys (30 mg/kg). Coronary artery vasculitis and intimal thickening were present in 1 out of 4 monkeys treated with 10 mg/kg and euthanized on Day 185 of the study. Additional new findings in the 30 mg/kg group included renal tubule epithelial cell degeneration, thrombocytopenia and decreases in complement protein C3.

September 2007: The findings in the chronic monkey study (Study ISIS 301012-AS15) and the implications for future clinical development was discussed at a meeting with the applicant.

January 2008: Due to the preclinical safety concerns and the lack of a validated biomarker for vasculitis, it was determined that studies should be limited to individuals at high risk for cardiovascular disease. The risk-benefit profile would only support treatment of individuals at high risk for cardiovascular events defined as 10-year risk for CVD > 20%, on maximum statin dose and not at LDL goal. On 29 January 2008, FDA issued a Partial Clinical Hold letter to Isis Pharmaceuticals to limit the clinical study to those individuals at high risk for CVD.

February 2008: FDA held a Regulatory Briefing to discuss the preclinical toxicity concerns which included an increase in aPTT, complement activation and proinflammatory changes/vasculitis, liver effects (increase in liver transaminases, hepatic steatosis) and renal effects (glomerulonephritis, declines in renal function). In clinical trials, the four most relevant safety signals observed to date were: (1) transient prolongations of aPTT following intravenous dosing; (2) constitutional symptoms such fever and chills following initial administrations; (3) dermatological responses such as erythema at subcutaneous injection sites; and (4) serum transaminase elevations.

October 2010: Study ISIS 301012-AS15 was amended to include two peer reviews of the vascular lesions by two experts outside of ISIS/Genzyme and the CRO. (b) (4) reviewed a subset of the histopathology slides, including slides from control animals and from the animals previously identified as having (peri)vasculitis. Both external experts concluded that the vascular lesions seen should not be characterized as vasculitis/perivasculitis, citing minimal medial changes (*e.g.*, no medial fibrinoid necrosis or fibrin leakage). The absence of perivascular hemorrhages was also noted. Both reviewers agreed that the vascular changes seen in the two monkeys treated at 30 mg/kg/week with the more disseminated vascular findings were drug-related. (b) (4) thought that the observed changes may indicate a chronic intimal injury with ongoing insult, suggested by infiltration of mixed inflammatory cells and cellular debris. (b) (4) further suggested that the basophilic appearance of the intima could result from influx and proliferation of smooth muscle cells. Regardless of precise nomenclature, the vascular findings in these two high dose animals were judged to be adverse by the Pharm/Tox reviewer. The vascular findings in the other animals were considered likely to be incidental.

July 2011: Over the course of clinical development for mipomersen, several trials had been conducted, with FDA approval, in individuals who were not at high risk for CVD. This accumulated clinical data from the clinic pharmacology studies had lessened FDA's original concerns such that trials in low to moderate risk subjects for less than 6 months would be allowed. FDA informed the applicant that modification of the Partial Clinical Hold would be allowed to permit trials of less than six months' duration in individuals who are not at high risk for CVD.

Dr Wange's summary of mipomersen toxicity is shown in the following table:

Table 2. Selected Mipomersen-associated Toxicities and Estimated Safety Margins

System Affected	Species	NOAEL (mg/kg/week)	Safety Margin*	Lowest Adverse Effect Level and Nature of Effects Observed
Complement	Mouse	n/a	n/a	Not assessed in the mouse. Primates are reportedly more sensitive.
	Rat	n/a	n/a	Not assessed in the rat. Primates are reportedly more sensitive.
	Monkey	10	3x	In the 1-year study at 30 mkw, Bb levels rise throughout the study, while C3 levels decline.
Cardiovascular	Mouse	5	<1x	In the 2-year study at doses ≥ 20 mkw, ↑ incidence of cardiac thrombus in ♂ & ♀ and ventricular/atrial dilatation and ↑ incidence & severity of cardiomyopathy in ♀s. Similar findings with 60 mkw ISIS 147764

System Affected	Species	NOAEL (mg/kg/week)	Safety Margin*	Lowest Adverse Effect Level and Nature of Effects Observed
				(mouse surrogate) in both sexes. May not be clinically relevant, since exacerbation of underlying pathology.
	Rat	3/10 (♂/♀)	<1x	Polyarteritis in 2-year study at 10/20 mkw (m/f). May be secondary to exacerbation of chronic progressive nephropathy.
	Monkey	10	3x	Multifocal disseminated intimal (rarely medial) hyperplasia with lymphocytic or mixed cell infiltration, with reactive endothelium, focally damaged endothelium with sporadic indication of fibrin accumulation in the lumen in 2/6 monkeys at 30 mkw. Possibly secondary to complement activation.
Renal	Mouse	>75	>2x	No kidney findings in mice in the 6-month or 2-year studies at doses up to 75 mkw; however, tissue levels saturate at relatively low doses, so the mouse may not be a good model for kidney toxicity.
	Rat	3	<1x	Worsening (minimal to severe) of chronic progressive nephropathy (CPN) in ♂s and ↑ incidence in ♀s in the 2-year study at doses ≥ 10 mkw. May not be clinically relevant, since exacerbation of underlying pathology.
	Monkey	3	<1x	In the 1-year study doses ≥ 10 mkw are associated with minimal-moderate tubular vacuolation and minimal-mild tubular epithelial cell degeneration; 30 mkw is associated with proteinuria, β2-microglobulinuria and minimal multifocal tubular hemorrhage.
Hepatic	Mouse	<5	<1x	↑ liver weights at doses ≥ 25 mkw; ↑ incidence of individual hepatocyte necrosis (minimal to slight) at doses ≥ 5 mkw; ↑ incidence/severity (minimal to moderate) of basophilic foci of cellular alteration in ♂s at doses ≥ 5 mkw; ↑ incidence/severity (minimal to moderate) of eosinophilic foci of cellular alteration in ♂s and ♀s at 60 mkw. These findings were markedly more pronounced with the mouse surrogate.
	Rat	3	<1x	↑ liver weights at doses ≥ 10 mkw; ↑ AST/ALT in ♀s following 5 months at doses ≥ 30 mkw; ↑ incidence and severity of minimal to severe centrilobular vacuolation and necrosis in both sexes at doses ≥ 10

System Affected	Species	NOAEL (mg/kg/week)	Safety Margin*	Lowest Adverse Effect Level and Nature of Effects Observed
				mkw in the 2-year study.
	Monkey	>30	>3x	Kupffer cell hypertrophy/hyperplasia at doses ≥ 10 mkw in the 1 year study; however, it is not clear that this is adverse.

* Comparison of weekly clinical dose (200 mg ~ 3 mg/kg ~ 110 mg/m^2) to the NOAEL dose using body surface area allometric scaling (mg/m^2). The exception are toxicities related to complement activation, which are compared using body mass (mg/kg) scaling.
mkw = mg/kg/week

Carcinogenicity

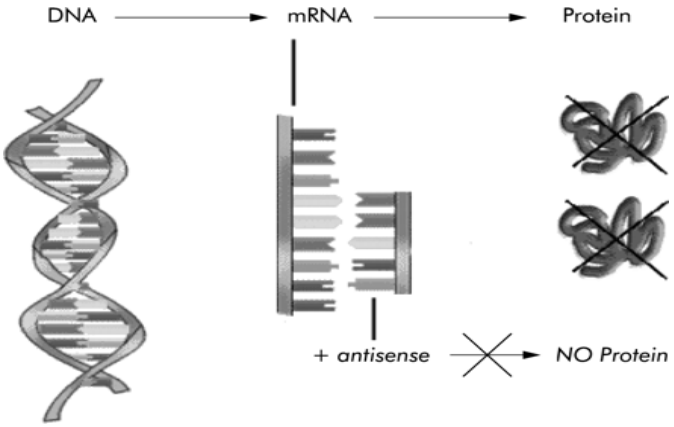
2-year carcinogenicity studies were conducted in both the mouse and the rat with mipomersen and the relevant species-specific surrogate. After review of the studies, the Executive Carcinogenicity Assessment Committee (ECAC) concluded that mipomersen was associated with multiple tumors in both species: 1) Hepatocellular adenomas and combined hepatocellular adenomas or carcinomas in female mice administered 60 mg/kg/week mipomersen; 2) Hepatocellular adenomas or carcinomas, combined, in both sexes of mice administered 60 mg/kg/week ISIS 147764 (mouse surrogate); 3) Fibrosarcoma of the skin/subcutis in male mice administered 60 mg/kg/week mipomersen; 4) Hemangiosarcomas in female mice given 60 mg/kg/week mipomersen; 5) Fibrous histiocytoma (malignant) of the skin/subcutis in male and female rats at ≥ 10 mg/kg/week; 6) Fibrosarcoma of the skin/subcutis in female rats at ≥ 10 mg/kg/week; Combined fibroma/fibrosarcoma/fibrous histiocytoma of the skin/subcutis in female rats at ≥ 10 mg/kg/week.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Mipomersen is a first-in-class antisense oligonucleotide (ASO) inhibitor targeted to apolipoprotein B-100 (apoB-100). Mipomersen is complementary to a 20-nucleotide segment of the coding region of the mRNA for apoB-100 and binds to the mRNA by Watson and Crick base-pairing. The binding of mipomersen to the cognate mRNA results in RNase H-mediated degradation of the cognate mRNA thus inhibiting translation of the apoB-100 protein (see figure below). This leads to a reduction in synthesis and transport of apo-B containing lipoprotein and a reduction in circulating LDL-C.

Figure 1. Mipomersen Mechanism of Action



4.4.2 Pharmacodynamics

Trial MIPO3200309 was a Phase 1, randomized, double-blind, placebo-controlled, parallel-group, single-center (Canada) trial investigating the relative bioavailability, PK, and PD of different SC dosing regimens of mipomersen in healthy volunteers. A total of 84 subjects (28 per cohort) were randomized into this trial to achieve 24 evaluable subjects per cohort who completed at least 1 week of treatment. Subjects were randomized equally to 1 of the 3 treatment regimens and then further randomized 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).

All 3 mipomersen regimens resulted in decreases in lipoprotein measures at Day 28/Early Termination in this healthy population. Mean baseline LDL-C was 123 mg/dL for the mipomersen 30 mg QD group (Cohort A), 122 mg/dL for the mipomersen 70 mg thrice-weekly group (Cohort B), 124 mg/dL for the 200 mg/dL every week group (Cohort C), and 109 mg/dL for the placebo group. The mean percent change in LDL-C was -9.5% for the mipomersen 30 mg QD group, -21.0% for the mipomersen 70 mg thrice weekly group, -18.3% for the mipomersen 200 mg QW group, and -1.5% for the placebo group.

Trial ISIS 301012-CS4 was a Phase 2, placebo-controlled, dose-ranging study to assess the PD of mipomersen in hypercholesterolemic individuals on stable statin therapy. A total of 74 individuals were allocated in a 4:1 (active:placebo) ratio to each of

6 dose cohorts: A, B, C, D, E, and F (30, 100, 200, 300, 400 mg, and 200 mg extended, respectively). Each cohort contained 8 individuals treated with mipomersen and 2 individuals treated with placebo, with the following exceptions: Cohort C enrolled 16 individuals treated with mipomersen and 4 individuals treated with placebo. Cohort E enrolled 9 individuals treated with mipomersen and 2 individuals treated with placebo. In Cohorts A through E, study drug was administered SC as a single dose on Day 1, followed by loading doses on Days 8, 10, and 12, and then once weekly maintenance doses on Days 15, 22, and 29. In Cohort F, study drug was administered SC as loading doses on Day 1, 3, and 5, followed by once weekly maintenance doses for 12 weeks on Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, and 85. For the 5-week cohorts, the median percent change in LDL-C from baseline to endpoint was -6.1% in the placebo group, 0.9% in the mipomersen 30 mg group, -8.3% in the 100 mg group, -22.2% in the 200 mg group, -53.6% in the 300 mg group, and -49.0% in the 400 mg group. For the 13-week cohort, the median percent change in LDL-C from baseline to endpoint was -6.1% in the placebo group and -33.6% in the mipomersen 200 mg extended group. The dosing regimen of 200 mg by SC injection once weekly was selected by the applicant for further development in Phase 3 based on the Phase 2 dose-ranging studies. This dose was selected based on the >30% LDL-C reduction in the 13-week study weighed against a higher and dose-dependent incidence of tolerability and safety findings (such as injection site reactions, flu-like symptoms, and elevations in hepatic transaminases) observed with the higher 300 mg and 400 mg once weekly doses.

Trial ISIS 301012-CS8 was a Phase 2, open-label, dose-escalation trial to assess the safety and efficacy of mipomersen add-on therapy trial in HoFH individuals. A total of 9 individuals were enrolled in this trial in three cohorts (n = 3 in each): Cohort A (50 mg), Cohort B (100 mg), and Cohort C (200 mg). The 50 mg, 100 mg, and 200 mg/wk cohorts were dosed for 6 weeks. A 13-week cohort (Cohort D, 300 mg) was subsequently added to better assess the LDL-C reduction potential in this population. All individuals in the 300 mg/wk (n=4), 13-week treatment cohort had participated earlier in either the 50 mg (n=2) or 100 mg (n=2) cohort and had undergone a washout period ≥ 5 half-lives prior to enrolling in the 300 mg/wk cohort. Three individuals received apheresis (3 individuals in the 6-week cohorts and 1 patient in the 13-week cohort). Treatment with mipomersen 50 mg, 100 mg, and 200 mg in the 6-week cohorts was associated with variable reductions in LDL-C, with no dose response evident. Eight of the 9 individuals had a reduction in LDL-C from baseline to endpoint, ranging from -0.5% to -18.2%. One patient in the mipomersen 200 mg group had an increase in LDL-C from baseline to endpoint (36.0%). In the 13-week cohort, all 4 individuals had a reduction in LDL-C from baseline to endpoint, ranging from -9.0% to -51.1%.

Trial ISIS 301012-CS9 was a Phase 2, placebo controlled, dose-escalation trial to assess the safety, efficacy, and PK of mipomersen as add-on therapy in HeFH individuals. A total of 44 individuals on stable concomitant lipid-lowering therapy with LDL-C ranging from 110 to 352 mg/dL were enrolled into the trial to receive mipomersen (at either 50, 100, 200, or 300 mg) or placebo (4 active:1 control). The 50, 100, and 200

mg cohorts (Cohorts A, B, and C, respectively) were treated for 6 weeks and the 300 mg cohort (Cohort D) was treated for 13 weeks. For the 6-week cohorts, the median percent change in LDL-C from baseline was -6.3% for the placebo group, -9.5% for the mipomersen 50 mg group, -8.6% for the mipomersen 100 mg group, and -15.1% for the mipomersen 200 mg group (none were statistically significantly different from placebo). For the 13-week cohort, the median percent change in LDL-C from baseline was -0.6% for the placebo group and -37.2% for the mipomersen 300 mg group (p=0.004).

In Trial ISIS 301012-CS19, a total of 34 high-CVD risk, statin-intolerant individuals were randomized in a 2:1 ratio to receive mipomersen 200 mg (N = 22 individuals) or a matching volume of placebo (N = 12 individuals) in SC injections weekly, for 26 weeks of treatment, followed by a 24-week post-treatment follow-up period. Mean baseline LDL-C was 242 mg/dL for the mipomersen group and 244 mg/dL for the placebo group. The mean percent reduction in LDL-C from baseline was -47.3% for the mipomersen group and -2.0% for the placebo group (p<0.001). In the mipomersen group, 47.6% of individuals had a >50% decrease in LDL-C from baseline to the PET.

PD results for the Phase 3 trials are discussed in Section 6: Efficacy.

4.4.3 Pharmacokinetics

4.4.3.1 Absorption, Distribution, Metabolism, and Elimination

Mipomersen reaches peak plasma concentrations approximately 3 to 4 hours after SC administration. Across clinical trials, most individuals appeared to approach steady state within approximately 6 months. The observed range for mean half-life in Phase 3 trials was 22 to 51 days. In the open-label extension (OLE) trial ISIS 301012-CS6, the mean calculated half-life was 43.8±24.3 days (N=45 individuals).

The applicant notes that the distribution profile of mipomersen in humans is thought to be similar to those of nonclinical species (rodents and monkeys). In preclinical studies with SC injection, mipomersen was rapidly distributed to tissues, with the kidney and liver containing the highest concentrations. Little to no drug was distributed to cardiac muscle, skeletal muscle, or brain.

Mipomersen is highly and nonspecifically bound (> 90%) to human plasma proteins. Mipomersen is not metabolized by liver microsomes or hepatocytes, but is metabolized in tissues by endonucleases to form shorter oligonucleotides that are then substrates for additional metabolism by exonucleases. The abundance of shorter chain metabolites are low, and the parent drug, mipomersen, is the predominant drug-related moiety in tissues in animal studies.

Elimination of mipomersen occurs primarily through metabolism in tissues and excretion in urine. Based on nonclinical and clinical data, intact mipomersen and metabolites are excreted slowly in the urine. In healthy human subjects, urine was collected for 24 hours following a single SC administration of 200 mg mipomersen; < 2% of the administered dose was recovered, consistent with extensive tissue distribution and a prolonged elimination half-life of mipomersen.

4.4.3.2 Specific Populations

The effects of hepatic impairment on mipomersen PK have not been studied. A clinical study examining the effects of renal impairment on mipomersen PK has not been conducted.

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. Of the covariates studied, creatinine clearance was predictive of variability for mipomersen PK. Mipomersen clearance is lower by approximately 31% at lower creatinine clearances in the range of 42.2 mL/min compared with 150 mL/min.

The applicant is not recommending a dose adjustment for individuals with renal or hepatic impairment. The applicant is recommending a contraindication of use in individuals with significant hepatic dysfunction, which may include persistent elevations of serum transaminases.

4.4.3.3 Drug-Drug Interactions

In vitro studies have demonstrated that mipomersen is not a substrate for CYP450 metabolism, does not inhibit the major drug-metabolizing CYP450 enzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4) and does not induce CYP1A2, CYP2B6, or CYP3A4. *In vitro* studies have demonstrated that mipomersen is not a substrate or an inhibitor of the P-gp transporter. Two drug-drug interactions studies conducted in healthy volunteers evaluated the potential for drug interactions between mipomersen and two hypolipidemic agents (simvastatin and ezetimibe), and between mipomersen and warfarin. Modest changes in PK parameters were observed for simvastatin, its metabolite (simvastatin acid), and ezetimibe upon co-administration of mipomersen. The ratio (% reference) of geometric least squares (GLS) means and 90% CIs for the mipomersen AUC0-24hr were 100% (93.6 to 107%) when dosed with simvastatin and 101% (92.4 to 111%) when dosed with ezetimibe. The ratio (% reference) of GLS means and 90% CIs for Cmax were 97.8% (92.8 to 103%) when dosed with simvastatin and 105% (86.4 to 128%) when dosed with ezetimibe. These changes were not felt to be clinically relevant. There was no change in the PK of mipomersen when these hypolipidemic agents were co-administered. Co-administration of mipomersen with

warfarin did not result in either PK or pharmacodynamic (PD) interactions as determined by international normalized ratio (INR), prothrombin time (PT), and activated partial thromboplastin time (aPTT).

In the population PK analysis, coadministration of mipomersen with statins, ezetimibe, nicotinic acid, 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.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 3. Summary of Clinical Studies with Mipomersen

Study Type and Number	Description	PK, PD, or Immunogenicity Assessments
Phase 1 Studies		
ISIS 301012-CS1	Phase 1 single and multiple ascending dose ranging study in healthy subjects with hypercholesterolemia	PK and PD
MIPO3200309	Phase 1 relative bioavailability study for different dosing regimens in healthy subjects	PK
MIPO3700710	Phase 1 dose escalation study in healthy Japanese subjects	PK
Phase 2 Studies		
ISIS 301012-CS3	Phase 2 dose loading and maintenance regimen study in healthy subjects with mild hypercholesterolemia	PK, PD, and IMG
ISIS 301012-CS4	Phase 2 dose ranging study in patients with hypercholesterolemia	PK, PD
ISIS 301012-CS8	Phase 2 dose-escalation add-on therapy study in HoFH	PK and IMG
ISIS 301012-CS9	Phase 2 dose-escalation add-on therapy study in HeFH	PK and IMG
ISIS 301012-CS10	Phase 2 study to determine the effect of apo B reduction on liver TG content	PK and PD
ISIS 301012-CS19	Phase 2 study in high-risk statin-intolerant subjects	PK
Phase 3 Trials		
ISIS 301012-CS5	Phase 3 placebo-controlled study in HoFH	Safety, PK and IMG
MIPO3500108	Phase 3 placebo-controlled study in severe hypercholesterolemia (not on apheresis)	Safety, PK and IMG
ISIS 301012-CS7	Phase 3 placebo-controlled study in HeFH	Safety, PK and IMG
ISIS 301012-CS12	Phase 3 placebo-controlled study in high-risk hypercholesterolemia	Safety, PK and IMG
Open-label Extension Studies		

ISIS 301012-CS17	Phase 2 OLE for CS8 and CS9 rollover patients	Safety, PK and IMG
ISIS 301012-CS6	Phase 3 OLE for CS5, CS7, and MIPO3500108 rollover patients	Safety, PK and IMG
Other Studies		
ISIS 301012-CS101	Phase 1 proof of concept study to evaluate oral formulation in healthy subjects with	PK and PD
ISIS 301012-CS2	Phase 1 DDI study with ezetimibe and simvastatin in healthy subjects	PK and PD
MIPO2900509	Phase 1 DDI study with warfarin in healthy subjects	PK and PD
MIPO2800209	Phase 1 thorough ECG study (QT/QTc) in healthy subjects	PK and PD
ISIS 301012-CS301	Phase 1 ascending dose study to investigate injection site reactions in healthy subjects	Characterize ISRs

PK = pharmacokinetics; PD = pharmacodynamics; IMG = immunogenicity; HoFH = homozygous familial hypercholesterolemia; HeFH = heterozygous familial hypercholesterolemia; DDI = drug-drug interaction; OLE = open-label extension; ISR= injection site reactions

5.2 Review Strategy

The efficacy and safety of mipomersen in the HoFH population were evaluated in the pivotal placebo-controlled Phase 3 trial ISIS 301012-CS5 (N=51). Supportive data from individuals with Severe HeFH, HeFH and CAD, and individuals with hypercholesterolemia at high risk of cardiovascular events are provided from the Phase 3 trials MIPO3500108 (N=58), ISIS 301012-CS7 (N=124), and ISIS 301012-CS12 (N=158), respectively. These Phase 3, randomized, double-blind, placebo-controlled trials evaluated the safety and efficacy of mipomersen, 200 mg SC once weekly, added on to stable, maximally tolerated lipid-lowering therapy and low-fat diet for 26 weeks. The trials used a 2:1 (mipomersen:placebo) randomization. Mipomersen was granted an Orphan Drug Designation for treatment of HoFH in May 2006. Examinations of the trial sample sizes used to support NDAs for orphan conditions with prevalence rates similar to HoFH are consistent with the database in this application; however, one-year placebo-controlled data are encouraged.

The efficacy review focused on the efficacy results from the one pivotal Phase 3 trial (ISIS 301012-CS5) and three supportive Phase 3 trials (MIPO3500108, ISIS 301012-CS7, and ISIS 301012-CS12). The long-term efficacy of mipomersen is also supported by data from the OLE trials ISIS 301012-CS6.

The safety review focused on the adverse events, adverse events of special interest and laboratory data from the following trials:

1. the four controlled, double-blind Phase 3 trials (Trials ISIS 301012-CS5, MIPO3500108, ISIS 301012-CS7, and ISIS 301012-CS12), which provided up to 26 weeks of treatment

2. the open-label extension (OLE) trial (ISIS 301012-CS6), with continued mipomersen treatment for up to 24 months.

5.3 Discussion of Individual Studies/Clinical Trials

Phase 1, 2 and 3 trials are summarized in this section. The four Phase 3 trials are discussed in more detail in Sections 6 and 7.

Dose-ranging Phase 1 and Phase 2 clinical trials tested 4 to 6 weeks or 13 weeks of treatment with mipomersen at doses ranging from 30 mg to 400 mg weekly.

5.3.1 Phase 1

The Phase 1 trials include the following:

- ISIS 301012-CS1: Double-blind, placebo-controlled, dose-escalation, single dose ranging (50 to 400 mg) trial in 36 healthy volunteers with mild hypercholesterolemia.
- ISIS 301012-CS2: Drug-drug pharmacokinetic (PK) interaction trial (simvastatin 40 mg or ezetimibe 10 mg) in 20 healthy volunteers.
- ISIS 301012-CS101: Proof-of-concept trial to evaluate oral formulation in 42 healthy volunteers with mild hypercholesterolemia.
- ISIS 301012-CS301: Trial to investigate mechanism of injection site reactions (ISRs) in 60 healthy volunteers (one dose of mipomersen 200 to 400 mg SC in 2 to 6 injections).
- MIPO2800209: A randomized, double-blind crossover trial to define the ECG effects of mipomersen in 60 healthy men and women.
- MIPO2900509: A drug-drug interaction trial to assess the effects of mipomersen on warfarin pharmacodynamics (PD) and PK in 18 healthy adult subjects.
- MIPO3200309: Randomized, double-blind, placebo-controlled, 3-week trial to assess relative bioavailability, PK and tolerability of mipomersen with different SC regimens (30 mg daily; 70 mg thrice weekly; or 200 mg SC once weekly) in 84 healthy volunteers.
- MIPO3700710: Randomized, double-blind, placebo-controlled, single dose-escalation trial to evaluate the PK and tolerability of single doses (50, 100, or 200 mg) of mipomersen administered SC to 20 Japanese healthy subjects.

5.3.2 Phase 2

Phase 2 dose-ranging trials included ISIS 301012-CS3, which enrolled individuals with mild hypercholesterolemia not on lipid-lowering therapy, and ISIS 301012-CS4, which enrolled individuals with primary hypercholesterolemia on stable statin therapy. These placebo-controlled trials included doses ranging from 50 mg in CS3, or 30 mg in CS4, to

400 mg in both trials, with treatment durations of 5 to 13 weeks. Results from these trials led to selection of a 200 mg weekly dose for the Phase 3 trials based on acceptable tolerability and >30% reduction in LDL-C after 13 weeks of treatment. The Phase 2 trials include the following:

- ISIS 301012-CS3: Double-blind, placebo-controlled dose-ranging 13 week trial in 50 individuals with mild hypercholesterolemia not on lipid-lowering therapy.
- ISIS 301012-CS4: Double-blind, placebo-controlled dose-escalation 5 or 13 week trial in 74 individuals with primary hypercholesterolemia on stable statin therapy.
- ISIS 301012-CS8: Open label dose-escalation add-on therapy, 6 or 13 weeks duration trial in 13 individuals with HoFH.
- ISIS 301012-CS9: Double-blind, placebo-controlled, dose-escalation, add-on therapy, 6 or 13 weeks duration trial in 44 individuals with HeFH.
- ISIS 301012-CS10: Double-blind, placebo-controlled trial in 38 individuals with varying degrees of hyperlipidemia and varying risk for hepatic steatosis (healthy; impaired fasting glucose and mixed dyslipidemia; HeFH; familial hypobetalipoproteinemia; or well-controlled type 2 diabetes) to assess changes in liver triglycerides (4, 13 or 52 weeks).
- ISIS 301012-CS19: Randomized, double-blind, placebo-controlled 26 week trial in 33 high CV risk (NCEP-ATP III) individuals intolerant to statins.

5.3.3 Phase 3

The mipomersen development program included one pivotal Phase 3 trial (ISIS 301012-CS5) and three supportive Phase 3 trials (MIPO3500108, ISIS 301012-CS7, and ISIS 301012-CS12). The long-term efficacy of mipomersen is also supported by data from the OLE trials ISIS 301012-CS6.

All four Phase 3 trials were randomized (2:1 ratio), double-blind, placebo-controlled, parallel-group trials evaluating 26 weeks of mipomersen therapy on LDL-C levels in individuals not reaching target lipid goals on current lipid-lowering therapy (including maximally tolerated statins). The trials had a ≤4-week screening period, 26 weeks of treatment, and a 24-week post-treatment follow-up period (unless individuals enrolled into an OLE trial). Following the Week 28 evaluations (2 weeks following the last dose of study drug), eligible individuals from all Phase 3 trials except ISIS 301012-CS12 could elect to enroll in the OLE trial (ISIS 301012-CS6) with continued mipomersen treatment for up to 24 months.

According to the applicant, the sample size calculations for all four Phase 3 trials were based on the assumption that the standard deviation of the percent change in LDL-C was approximately 22%, and were powered for the detection of a 20% difference in the percent change in LDL-C between the treatment groups. With a 2:1 randomization ratio, a total of 45 individuals (30 mipomersen: 15 placebo) would yield 80% power.

Lipid data analyses were done at a central laboratory and results were not available to the individuals, investigators, study staff, or the applicant until the study was unblinded after database lock. The applicant correctly notes that because mipomersen treatment resulted in more injection-site reactions (ISRs) than placebo, investigators, study staff, or patients may have surmised which individuals were treated with mipomersen or placebo. As the efficacy results were blinded, there was no potential for direct bias in the efficacy results. However, this assumption of treatment category may have provided bias on such factors as patient compliance, dietary compliance, withdrawal rate, and adverse event assessment.

For all four trials, the primary analysis of efficacy was the percent change from baseline to the primary efficacy time point (PET, defined by the applicant as the post-baseline visit closest to 14 days after the last dose of study treatment for which LDL-C was assessed) compared between treatment groups. Secondary efficacy endpoints include the percent change in apo B, TC and non-HDL-C from Baseline at Week 28.

A brief synopsis of the four Phase 3 trials is provided below.

ISIS 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) was a double-blind, placebo-controlled 26-week trial to assess the effect of mipomersen on lipid parameters in individuals with HoFH. A total of 51 male and female individuals ≥ 12 years of age, who were Tanner Stage >2 with a body weight ≥40 kg, a diagnosis of HoFH, fasting LDL-C ≥130 mg/dL and TG <350 mg/dL at screening, on a stable low-fat diet and a stable (≥12 weeks) lipid-lowering regimen prior to screening, were randomized 2:1 to mipomersen 200 mg SC injections weekly or placebo. Pediatric and adult subjects < 50 kg at screening received a lower dose of 160 mg or matching volume of placebo. Diagnosis of HoFH was determined by (1) history of genetic testing confirming two mutated alleles at the LDL receptor gene locus, or (2) documented history of untreated LDL-C > 500 mg/dL, and at least one of the following criteria (a) tendinous and/or cutaneous xanthoma prior to age 10 years (b) documentation of elevated LDL-C > 190 mg/dL prior to lipid-lowering therapy consistent with heterozygous familial hypercholesterolemia (HeFH) in both parents. In case a parent is not available, a history of coronary artery disease in a first degree male relative of the parent younger than 55 years old or first degree female relative of the parent younger than 60 years old was acceptable. Forty-four of the 51 individuals (86%) in the trial had genetic confirmation of HoFH: 29 were true homozygotes and 13 were compound heterozygoes.

MIPO3500108 (A Prospective Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of Mipomersen in Patients with Severe Hypercholesterolemia on a Maximally Tolerated Lipid-Lowering Regimen and who are not on Apheresis) was a double-blind, placebo-controlled 26-week trial to assess the effect of mipomersen on lipid parameters in individuals with severe

hypercholesterolemia. A total of 58 male and female individuals ≥ 18 years of age with severe hypercholesterolemia and on a stable maximally tolerated lipid-lowering regimen were randomized 2:1 to mipomersen 200 mg SC injections weekly or placebo. At screening, individuals were required to have a fasting LDL-C ≥300 mg/dL or an LDL-C ≥200 mg/dL if the patient had a history of myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft, coronary artery disease, positive exercise test, or other clinical atherosclerotic diseases. This represents a patient population that is considered to have the same or higher risk for cardiovascular events as patients in whom LDL-C apheresis is indicated in the US. Individuals on apheresis were excluded. Individuals must have had a body mass index (BMI) ≤40 kg/m^2 with stable weight (±4 kg) for at least 6 weeks prior to screening.

ISIS 301012-CS7 (RADICHOL II: A RAndomized, Double-Blind, Placebo-Controlled Study to Assess Efficacy and Safety of ISIS 301012 as Add-on Therapy in Heterozygous Familial HyperCHOLesterolemia Subjects With Coronary Artery Disease) was a double-blind, placebo-controlled 26-week trial to assess the effect of mipomersen on lipid parameters in individuals with HeFH and CAD. A total of 124 male and female individuals ≥ 18 years of age with HeFH and CAD who had a fasting LDL-C ≥100 mg/dL and TG <200 mg at screening and were on a stable low-fat diet ≥8 weeks prior to the first dose of study drug were randomized 2:1 to mipomersen 200 mg SC injections weekly or placebo. Individuals were required to be on a maximally tolerated dose of statin.

ISIS 301012-CS12 (A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of ISIS 301012 (Mipomersen) as Add-on Therapy in High Risk Hypercholesterolemic Patients) was a double-blind, placebo-controlled 26-week trial to assess the effect of mipomersen on lipid parameters in individuals with hypercholesterolemia on a maximally tolerated dose of statin and who had a diagnosis that put them at least at high risk of coronary heart disease (CHD) events as defined by the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III Guidelines. This included individuals with CHD or a CHD risk equivalent, including diabetes mellitus, or multiple risk factors that placed them at >20% risk for CHD over 10 years. Patient randomization was stratified based on type 2 diabetes mellitus status at screening, such that at least 40% enrolled would have type 2 diabetes mellitus and to ensure an even distribution of individuals with diabetes in each treatment group. A total of 158 male and female individuals ≥ 18 years of age who had a fasting LDL-C ≥100 mg/dL and TG <200 mg at screening were randomized 2:1 to mipomersen 200 mg SC injections weekly or placebo. Magnetic resonance imaging assessments of liver fat content (measured as fat fraction) were analyzed at baseline and Week 28. Among individuals with nominal increases in liver fat content from baseline of ≥5%, the number and percentage of individuals with at least 1 alanine aminotransferase (ALT) ≥3 × the upper limit of normal (ULN) was tabulated.

The following table summarizes the patient populations in the Phase 3 trials.

Table 4. Patient Populations in Phase 3 Trials

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

6 Review of Efficacy

Efficacy Summary

See *Section 1.2.1 Efficacy*

6.1 Indication

The applicant provided draft labeling text in the NDA submission. The proposed indication is as follows:

- TRADENAME (mipomersen sodium) is an apolipoprotein B (apo B) synthesis inhibitor indicated as an adjunct to maximally tolerated lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol (LDL-C), apo B, total cholesterol (TC), non-high density lipoprotein-cholesterol (non-HDL-C) and lipoprotein (a) [Lp(a)] in individuals with homozygous familial hypercholesterolemia (HoFH).

The recommended dose of TRADENAME is 200 milligrams (mg) once weekly as a subcutaneous (SC) injection.

6.1.1 Methods

This efficacy review focuses on the one pivotal Phase 3 trial, ISIS 301012-CS5 (in individuals with HoFH) and supportive data from the Phase 3 trials MIPO3500108, ISIS 301012-CS7, and ISIS 301012-CS12. The Phase 1 and Phase 2 trials were primarily proof-of-concept trials and were used to establish the appropriate dose for the pivotal and supportive Phase 3 trials. Refer to Section 4.4.2 Pharmacodynamics for a discussion of the efficacy in some of these trials. Please see Dr. Japobrata Choudhury's statistical review for a comprehensive analysis of the efficacy data.

The primary efficacy parameter for the Phase 3 trials was the percent change in LDL-C from baseline to PET at 26 weeks (the post-baseline visit closest to 14 days after the last dose of study treatment for which LDL-C is assessed). The primary analysis of efficacy parameters was assessment of the percent change from baseline to PET compared between treatment groups. If the Kolmogorov-Smirnov test of normality was statistically significant ($p \leq 0.05$; indicating non-normal distribution) then the Wilcoxon rank-sum test results were utilized. Otherwise, the 2-sample t-test was used.

For efficacy assessment of lipid parameters, baseline was defined as the average of the screening and Study Day 1 (pre-treatment) assessments. If the Study Day 1 and

screening LDL-C values were more than 12% different (relative to the maximum value), then only Study Day 1 was used.

Samples for serum lipid panels were taken after an overnight fast. Lipoprotein testing was performed in a central clinical laboratory. For individuals with TG <400 mg/dL, LDL-C was calculated using Friedewald's calculation; for individuals with TG ≥400 mg/dL, LDL-C was directly measured by the central laboratory using ultracentrifugation. Total cholesterol, TG, and HDL-C were measured by enzymatic colorimetry. Apolipoprotein B and apo A-I measures were obtained by nephelometry. The assay used to detect apo B detects both apo B-100 and apo B-48. The applicant states that as apo B-100 is approximately 99% of plasma apo B (when fasted), and since mipomersen is specific for apo B-100, changes in apo B noted in these trials were assumed to be due to changes in apo B-100.

All efficacy parameters were assessed on the Per-Protocol Set (PPS) and Full Analysis Set (FAS), with the latter being the basis for the primary efficacy analysis. The FAS, consisted of the subset of the Safety Set with a valid baseline and at least one post-baseline LDL-C measure. The PPS consisted of the subset of the FAS with no significant protocol deviations that would be expected to bias the patient's efficacy assessments.

Additional information on inclusion and exclusion criteria for the four trials is included in the tables below.

Table 5. Phase 3 Trials Inclusion Criteria

Inclusion Criterion	Clinical Trial Number			
	CS5	CS7	0108	CS12
HoFH defined by at least 1 of the following criteria: 1. History of genetic testing confirming 2 mutated alleles at the LDL-r gene locus 2. Documented history of untreated LDL-C >500 mg/dL AND at least 1 of the criteria below: i. Tendinous and/or cutaneous xanthoma prior to age 10 years ii. Documentation of elevated LDL-C >190 mg/dL prior to lipid-lowering therapy consistent with HeFH in both parents. In case a parent was not available, a history of coronary artery disease in a first degree male relative of the parent younger than 55 years or first degree female relative of the parent younger than 60 years was acceptable.	X			
Fasting LDL-C ≥ 200 mg/dL at Screening and the presence of at least 1 of the following criteria: a) MI, PCI or CABG(patient excluded if event within 24 weeks of screening); b) CAD documented by angiography or any other accepted imaging technique; c) Positive exercise test (≥ 1 mm ST-depression at maximal exercise or test terminated because of angina) or a perfusion defect, e.g., thallium or single photon; d) Other clinical atherosclerotic diseases: PAD, symptomatic carotid artery disease, AAA; e) Or, if a) through d) are not met, fasting LDL-C ≥ 300 mg/dL			X	
Diagnosis of HeFH determined by Simon Broome Register Criteria: a. History of genetic testing confirming mutation in one allele at the LDL receptor gene locus, OR b. Documented history of untreated LDL-C > 190 mg/dL and/or TC > 290 mg/dL, and at least one of the following criteria: Tendon xanthomas in the subject or in a first- or second-degree relative*; Familial hypercholesterolemia in a first- or second-degree relative*; LDL-C > 190 mg/dL or TC > 290 mg/dL in a first- or second-degree relative*; Family history of MI at < 55 years of age in a first- or second-degree relative* * First-degree relative = parent, offspring or sibling; second-degree relative = grandparent, grandchild, nephew, niece, aunt, uncle or half-sibling		X		

Presence of at least one of the following criteria for coronary artery disease: a. MI at least 24 weeks prior to Screening; b. PTCI or CABG at least 24 weeks prior to Screening; c. CAD documented by angiography or any other accepted imaging technique; d. if one or more of criteria a through c are not met: a positive exercise test (≥ 1 mm ST-depression at maximal exercise or test terminated because of angina) or a perfusion defect, e.g., thallium or SPECT		X		
Have 1 or more of the following diagnoses that categorizes the patient as at least "High- Risk" in accordance with the NCEP-ATP III Guidelines: a. CHD; b. CHD risk equivalents such as DM, other clinical atherosclerotic diseases (i.e., PAD, carotid artery disease, AAA); c. Multiple (2+) risk factors and 10-year risk for major coronary events (MI and CHD death) of >20% with Framingham risk scoring. Note: MI, PTCI, CABG, CVA, unstable angina or acute coronary syndrome that occurred *within 24 weeks of screening* were exclusion criteria for this trial				X
On maximally tolerated statin therapy		X	X	X
Fasting LDL-C criterion in mg/dL at Screening	≥ 130	≥ 100	≥ 200	≥ 100

Table 6. Phase 3 Trials Exclusion Criteria

	Clinical Trial Number			
Exclusion Criterion	**CS5**	**CS7**	**0108**	**CS12**
Myocardial infarction (MI), percutaneous transluminal coronary intervention, or coronary artery bypass graft surgery within 12 weeks prior to Screening, or cerebrovascular accident within 24 weeks prior to Screening. Subjects with adequately treated stable angina, per Investigator assessment, may be included	X			
MI, PCI, CABG, cerebrovascular accident (CVA), unstable angina or acute coronary syndrome within 24 weeks of Screening		X	X	X
Congestive heart failure defined by New York Heart Association (NYHA) Classes III or IV	X	X	X	X

Exclusion Criterion	Clinical Trial Number			
	CS5	**CS7**	**0108**	**CS12**
Presence of a clinically significant arrhythmia deemed to be uncontrolled at any time < 12 months from screening or if medication for an arrhythmia has been started or dose has changed < 12 months from screening. Individuals with implantable pacemakers or automatic implantable cardioverter defibrillators (AICDs) may be considered if deemed to be stable for the previous 12 months by the Investigator		X	X	X
Diabetes mellitus or fasting serum glucose ≥126 mg/dL (≥7.0 mmol/L) at Screening		X		
Type 1 diabetes mellitus			X	X
Hypertension, systolic blood pressure (BP) ≥ 160 mmHg, or diastolic BP ≥ 95 mmHg at Screening (despite antihypertensive medication/therapy)			X	X
Uncontrolled hypertension with SBP/DBP > 180/105 mmHg		X		
Orthostatic hypotension or supine systolic blood pressure < 90 mm Hg		X		
Uncontrolled hypothyroidism, other uncontrolled endocrine disease or any uncontrolled condition that may predispose to secondary hyperlipidemia	X	X	X	X
History of significant hepatic disease (e.g., cirrhosis or documented steatosis) prior to Screening	X	X		
History of significant renal disease, or abnormal creatinine or proteinuria at Screening (unless pre-approved by key sponsor contact)	X			
Clinically significant hepatic or renal disease or Gilbert's syndrome			X	X
Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin that had been adequately treated	X	X	X	X
Positive test for human immunodeficiency virus or hepatitis B or C at Screening		X	X	X
Active infection requiring systemic antimicrobial therapy or antiviral therapy for systemic use unless treatment was expected to be completed prior to Day 1	X	X	X	X

Exclusion Criterion	Clinical Trial Number			
	CS5	**CS7**	**0108**	**CS12**
Currently receiving apheresis treatments or last apheresis treatment within (8 weeks to 3 months, varied with trial) of Screening	X	X	X	
Any of the following laboratory values at Screening:				
Fasting TG >350 mg/dL	X		X	
Fasting TG >200 mg/dL		X		X
Serum creatine phosphokinase (CPK) ≥3 x upper limit of normal (ULN)	X	X	X	X
Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels >1.5 x ULN	X	X		
Alanine aminotransferase (ALT) levels >1.5 x ULN			X	X
Serum creatinine >0.1 mg/dL above ULN for women, or >0.2 mg/dL above ULN for men		X	X	X
Proteinuria (>1+ on dipstick, confirmed on retest, with further confirmation by quantitative total urine protein >1.0 g/24 hour)		X	X	X
Total bilirubin >1.0 x ULN		X	X	X
Glycosylated hemoglobin A1c >8.0%	X		X	X
Treatment with fibrates within 8 weeks prior to Screening	X			
Medications that could have effected lipids except those allowed per protocol, including but not limited to Cholestin (red yeast rice or monascus pupureus extract) within 8 weeks prior to Screening	X		X	X
Systemic steroids or anabolic steroids within 6 weeks of Screening. Concomitant therapy of oral corticosteroids used as replacement therapy for pituitary/adrenal disease as well as inhaled steroid therapy (e.g., Pulmicor) or intra-articular or topical may have been acceptable	X	X		
Chronic systemic corticosteroids or anabolic agents, except for replacement therapy			X	X

Exclusion Criterion	Clinical Trial Number			
	CS5	**CS7**	**0108**	**CS12**
Central and peripherally acting antiobesity products	X	X		
Hormonal contraceptives for systemic use, contraceptives for topical use			X	X
Use of the following medications unless a stable regimen ≥12 weeks prior to Screening expected to be stable until Week 28:				
Cardiovascular medications (e.g., beta blockers, calcium-channel blockers, ACE inhibitors, nitrates, α-adrenergetic blockers, thiazide diuretics or angiotensin-2 receptor antagonists), Platelet Aggregation Inhibitors Excluding Heparin	X			
Medications that could have effected lipids, including but not limited to Cholestin (red yeast rice or monascus pupureus extract), and other lipid modifying agents	X	X		
Oral anticoagulants (e.g., warfarin)			X	X
Oral anticoagulants unless dose stable for 4 weeks prior to Screening and regular clinical laboratory monitoring was performed	X	X		
Current use of hormone replacement therapy unless the dose was stable for > 12 weeks prior to Screening and was expected to be stable for the duration of the treatment period	X	X		
Hormone replacement therapy			X	X
Blood glucose lowering drugs excluding insulin, with the exception of changes of ± 10 units of insulin			X	X
Antivirals for systemic use	X		X	X
Central and peripherally acting antiobesity products or had discontinued treatment < 12 weeks prior to treatment	X			
Central and peripherally acting antiobesity products			X	X

Exclusion Criterion	Clinical Trial Number			
	CS5	CS7	0108	CS12
Other				
Age <12 years, Tanner stage < 2	X			
Age <18 years		X	X	X
Not on a stable lipid lowering regimen	X	X	X	X
BMI >40 kg/m2 and unstable weight for >6 weeks prior to Screening			X	X
Weight <40 kg,	X			
Recent history of, or current drug or alcohol abuse, or unwilling to limit alcohol consumption for the entire duration of the trial, including follow-up	X	X	X	X
Pregnant subjects and women who are not surgically sterile, postmenopausal, abstinent, or patient or partner compliant with an acceptable contraceptive regimen for 4 weeks prior to, during, and 6 months after the last study drug dose	X	X	X	X
Males who are not Surgically sterile, abstinent, or patient or partner unwilling to utilize an acceptable contraceptive method during and 6 months after the last study drug dose	X	X	X	X

A summary of the Phase 3 trial designs are provided below.

Table 7. Summary of the Phase 3 Placebo-Controlled Trials

Trial Name	Primary Endpoint	Design, Dose, Route, Regimen Duration	Diagnosis, # planned, # analyzed for Safety	Trial Population: Gender, Median age (range)	Trial Dates, # of Sites, Location
ISIS 301012 -CS5	% change in LDL-C from baseline to PET, placebo vs. mipomersen	Randomized, double-blind, placebo-controlled 200 mg mipomersen (160 mg for individuals weighing <50 kg) or placebo SC weekly for 26 weeks	HoFH Planned: 50 Analyzed: 51 (17 placebo, 34 mipomersen)	41.2%/58.8% placebo; 44.1%/55.9% mipomersen 38 years (12-53) placebo; 27 years (14–53) mipomersen	06 September 2007 – 25 March 2009; 9 study sites in 7 countries (Brazil, Canada, Singapore, South Africa, Taiwan, United Kingdom, and United States)
MIPO3 500108	% change in LDL-C from baseline to PET, placebo vs. mipomersen	Randomized, double-blind, placebo-controlled 200 mg mipomersen or placebo SC weekly for 26 weeks	Severe HC Planned: 51 to 75 Analyzed: 58 (19 placebo, 39 mipomersen)	36.8%/63.2% placebo; 46.2%/53.8% mipomersen 52 years (18-66) placebo; 51 years (21-77) mipomersen	27 January 2009 - 14 October 2010 26 study sites in 6 countries (Canada, Czech Republic, Germany, South Africa, United Kingdom, and United States)
ISIS 301012 -CS7	% change in LDL-C from baseline to PET, placebo vs. mipomersen	Randomized, double-blind, placebo-controlled 200 mg mipomersen or placebo SC weekly for 26 weeks	HeFH Planned: 100 to 125 Analyzed: 124 (41 placebo; 83 mipomersen)	68.3%/31.7% placebo; 60.2%/39.8% mipomersen 56 years (40-74) placebo; 55 years (26-76) mipomersen	14 July 2008 -18 May 2010 26 study sites (19 in the US and 7 in Canada)
ISIS 301012 -CS12	% change in LDL-C from baseline to PET, placebo vs. mipomersen	Randomized, double-blind, placebo-controlled 200 mg mipomersen or placebo SC weekly for 26 weeks	High-risk HC Planned: 180 Analyzed: 157 (52 placebo; 105 mipomersen)	55.8%/44.2% placebo; 49.5%/50.5% mipomersen 59 years (37-79) placebo; 60 years (36-81) mipomersen	24 November 2008 - 20 October 2010 43 study sites in the US

6.1.2 Demographics

Of the 390 individuals treated in the pooled Phase 3 trials, 52.8% (206/390) were male. The majority of individuals were white (84.4%; 325/390); 10.0% (39/360) were black and 3.1% (12/390) were Asian. A total of 76.2% (297/390) of individuals were between 18 and 64 years of age; 22.1% (86/390) of individuals were at least 65 years of age; and 1.8% (7/390) of individuals (all HoFH individuals from Trial ISIS 301012-CS5) were

pediatric patients less than 18 years of age. The mean age was 53.4 years for individuals in the mipomersen group and 53.0 years for individuals in the placebo group.

In the pooled Phase 3 population, the mean body mass index (BMI) was 29.1 kg/m^2 in the mipomersen group and 29.6 kg/m^2 in the placebo group. Current tobacco use was reported in 16.1% of individuals in the mipomersen group compared to 17.8% individuals in the placebo group. Current alcohol use was reported in 59.4% (155/261) of individuals in the mipomersen group compared to 49.6% (64/129) individuals in the placebo group.

In ISIS 301012-CS5, of the 51 patients, 29 (57%) were female, 38 (75%) were white, and 11 (22%) were Asian. The median age was 27 years for patients in the mipomersen group and 38 years for patients in the placebo group. The mean BMI was 26 kg/m^2 for both groups and 7 (20.6%) patients in the mipomersen group and 1 (5.9%) patient in the placebo group had metabolic syndrome at baseline. Mean baseline fasting serum insulin levels were 11.5 and 9.7 µIU/mL and fasting HbA1c levels were 5.3 and 5.5% for patients in the mipomersen group and the placebo group, respectively.

Individuals with HoFH in ISIS 301012-CS5 were younger compared to those in the other Phase 3 trials. Current tobacco and alcohol use was reported in all Phase 3 trials. The highest proportion of individuals who have never used tobacco or alcohol was reported in ISIS 301012-CS5. The table below enumerates the demographics and baseline characteristics for the Phase 3 patient population.

Table 8. Demographics and Baseline Characteristics Across Phase 3 Trials

Characteristic	ISIS 301012-CS5		MIPO3500108		ISIS 301012-CS7		ISIS 301012-CS12	
	Placebo (N=17)	Mipomersen (N=34)	Placebo (N=19)	Mipomersen (N=39)	Placebo (N=41)	Mipomersen (N=83)	Placebo (N=52)	Mipomersen (N=105)
Age (years)								
Mean (SD)	33.0 (14.1)	30.4 (11.5)	47.9 (13.5)	51.8 (14.3)	55.9 (9.3)	56.2 (9.7)	59.3 (9.5)	59.3 (10.0)
Min, Max	12, 53	14, 53	18, 66	21, 77	40, 74	26, 76	37, 79	36, 81
Age, n (%)								
<18	4 (23.5)	3 (8.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
18 to <65	13 (76.5)	31 (91.2)	17 (89.5)	31 (79.5)	34 (82.9)	66 (79.5)	34 (65.4)	71 (67.6)
≥65	0 (0.0)	0 (0.0)	2 (10.5)	8 (20.5)	7 (17.1)	17 (20.5)	18 (34.6)	34 (32.4)
Gender, n (%)								
Male	7 (41.2)	15 (44.1)	7 (36.8)	18 (46.2)	28 (68.3)	50 (60.2)	29 (55.8)	52 (49.5)
Female	10 (58.8)	19 (55.9)	12 (63.2)	21 (53.8)	13 (31.7)	33 (39.8)	23 (44.2)	53 (50.5)
Race, n (%)								
White	13 (76.5)	25 (73.5)	16 (84.2)	33 (84.6)	38 (92.7)	81 (97.6)	40 (76.9)	83 (79.0)
Black	1 (5.9)	1 (2.9)	1 (5.3)	2 (5.1)	1 (2.4)	2 (2.4)	11 (21.2)	20 (19.0)
Asian	3 (17.6)	8 (23.5)	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	2 (10.5)	3 (7.0)	2 (4.7)	0 (0.0)	1 (1.9)	2 (1.9)
Ethnicity, n (%)								
Hispanic or Latino	1 (5.9)	5 (14.7)	0 (0.0)	0 (0.0)	2 (4.9)	2 (2.4)	9 (17.3)	16 (15.29)
Mean LDL-C mg/dL (range)	400 (172, 639)	439 (190, 704)	249 (93, 427)	276 (35, 429)	143 (87, 392)	153 (36, 377)	123 (69, 265)	123 (65, 270)
BMI (kg/m2)								

Characteristic	ISIS 301012-CS5		MIPO3500108		ISIS 301012-CS7		ISIS 301012-CS12	
	Placebo (N=17)	Mipomersen (N=34)	Placebo (N=19)	Mipomersen (N=39)	Placebo (N=41)	Mipomersen (N=83)	Placebo (N=52)	Mipomersen (N=105)
Mean (SD)	26.3 (4.4)	26.0 (5.8)	30.0 (4.1)	28.4 (5.4)	30.3 (3.8)	28.7 (4.2)	30.0 (4.4)	30.7 (4.6)
Fasting hemoglobin A1c (%)								
Mean (SD)	5.5 (0.2)	5.3 (0.4)						
Tobacco, n (%)								
Current	3 (17.6)	7 (20.6)	5 (26.3)	4 (10.3)	4 (9.8)	13 (15.7)	11 (21.2)	18 (17.1)
Non-Current	3 (17.6)	4 (11.8)	7 (36.8)	11 (28.2)	17 (41.5)	32 (38.6)	19 (36.5)	31 (29.5)
Never	11 (64.7)	23 (67.6)	7 (36.8)	24 (61.5)	20 (48.8)	38 (45.8)	22 (42.3)	56 (53.3)
Alcohol, n (%)								
Current	6 (35.3)	14 (41.2)	7 (36.8)	27 (69.2)	31 (75.6)	64 (77.1)	20 (38.5)	50 (47.6)
Non-Current	3 (17.6)	3 (8.8)	4 (21.1)	5 (12.8)	7 (17.1)	10 (12.0)	12 (23.1)	24 (22.9)
Never	8 (47.1)	17 (50.0)	8 (42.1)	7 (17.9)	3 (7.3)	9 (10.8)	20 (38.5)	31 (29.5)
CV History,* n (%)								
Hypertension	2 (12)	3 (9)						
Revascularization	4 (24)	10 (29)						
Atherosclerotic disease (clinical dx)	11 (65)	19 (56)						
Aortic valve stenosis	10 (59)	16 (47)						
Aortic valve replacement	1 (6)	3 (9)						
CV History, n (%)								
Angina			5 (26.3)	11 (28.2)			5 (9.6)	9 (8.6)
CHD			14 (73.7)	28 (71.8)			21 (40.4)	52 (49.5)
MI			4 (21.1)	8 (20.5)			11 (21.2)	17 (16.2)

Characteristic	ISIS 301012-CS5		MIPO3500108		ISIS 301012-CS7		ISIS 301012-CS12	
	Placebo (N=17)	Mipomersen (N=34)	Placebo (N=19)	Mipomersen (N=39)	Placebo (N=41)	Mipomersen (N=83)	Placebo (N=52)	Mipomersen (N=105)
CABG			6 (31.6)	12 (30.8)			4 (7.7)	14 (13.3)
PCI			2 (10.5)	4 (10.3)			4 (7.7)	18 (17.1)
CAD w/out event			5 (26.3)	11 (28.2)			6 (11.5)	14 (13.3)
PAD			2 (10.5)	1 (2.6)			1 (1.9)	5 (4.8)
AAA			0	1 (2.6)			1 (1.9)	0
Carotid			5 (26.3)	6 (15.4)			1 (1.9)	8 (7.6)
Genetic confirmation of HoFH,* n (%)	14 (82)	30 (88)						
True homozygote	8 (47)	21 (62)						
Compound heterozygote	4 (24)	9 (26)						
D206E allele (at least one)	7 (41)	17 (50)						
D206E homozygote	4 (24)	10 (29)						

Source: NDA 203568, ISS Statistical Table 1.1.1S. and Reviewer created from datasets

*Source: Raal FJ, Santos RD, Blom DJ, Marais AD, Charng MJ, Cromwell WC, Lachmann RH, Gaudet D, Tan JL, Chasan-Taber S, Tribble DL, Flaim JD, Crooke ST. Mipomersen, an apolipoprotein B synthesis inhibitor, for lowering of LDL cholesterol concentrations in individuals with homozygous familial hypercholesterolaemia: a randomised, double-blind, placebo-controlled trial. Lancet. 2010 Mar 20;375(9719):998-1006. PMID: 20227758

Concomitant Medications

In the pooled Phase 3 trials, the most commonly used concomitant medications were HMG-CoA reductase inhibitors (95.6%; 373/390 of individuals overall; 95.0% [248/261] mipomersen-treated individuals; 96.9% [125/129] placebo-treated individuals). Other common concomitant medications included platelet aggregation inhibitors, excluding heparin and other lipid modifying agents (69.3% [181/261] mipomersen, 64.3% [83/129] placebo), and other lipid modifying agents (57.5% mipomersen [150/261], 55.0% placebo [71/129]).

As shown in the table below, in Trial ISIS 301012-CS5 (individuals with HoFH), the most common types of prior medications were HMG-CoA reductase inhibitors, reported by 97.1% (33/34) of individuals in the mipomersen group and 100.0% (17/17) of individuals in the placebo group, and other lipid modifying agents, reported by 79.4% (27/34) individuals in the mipomersen group and 64.7% (11/17) individuals in the placebo group. One (2.9%) patient in the mipomersen group was not on lipid-lowering medication during the trial. In total, 44 (86.3%) individuals were on maximal statin therapy with or without other lipid-lowering medications. Of these 44 individuals, 8 were on maximal statin therapy alone and 36 were on maximal statin therapy plus other lipid-lowering medications.

Table 9. Concomitant Lipid-Lowering Medications in ISIS 301012-CS5

Medication (daily dosage during treatment period)	Treatment Arm	
	Placebo (N=17) n	Mipomersen (N=34) n
Patient with any lipid-lowering medication	17	33
Individuals on any statin	17	33
Patient on maximal allowed dose of statin	15	29
Rosuvastatin (40 mg)	1	4
Atorvastatin (100 mg)	0	2
Atorvastatin (80 mg)	14	23
Simvastatin (80 mg)	0	0
Pravastatin (40 mg)	0	0
Lovastatin (80 mg)	0	0
Fluvastatin (80 mg)	0	0
Statin+ezetimibe	11	26
Statin+ezetimibe+other	5	3
Statin+niacin	2	3
Statin+bile acid sequestrants	1	1
Statin alone	6	6

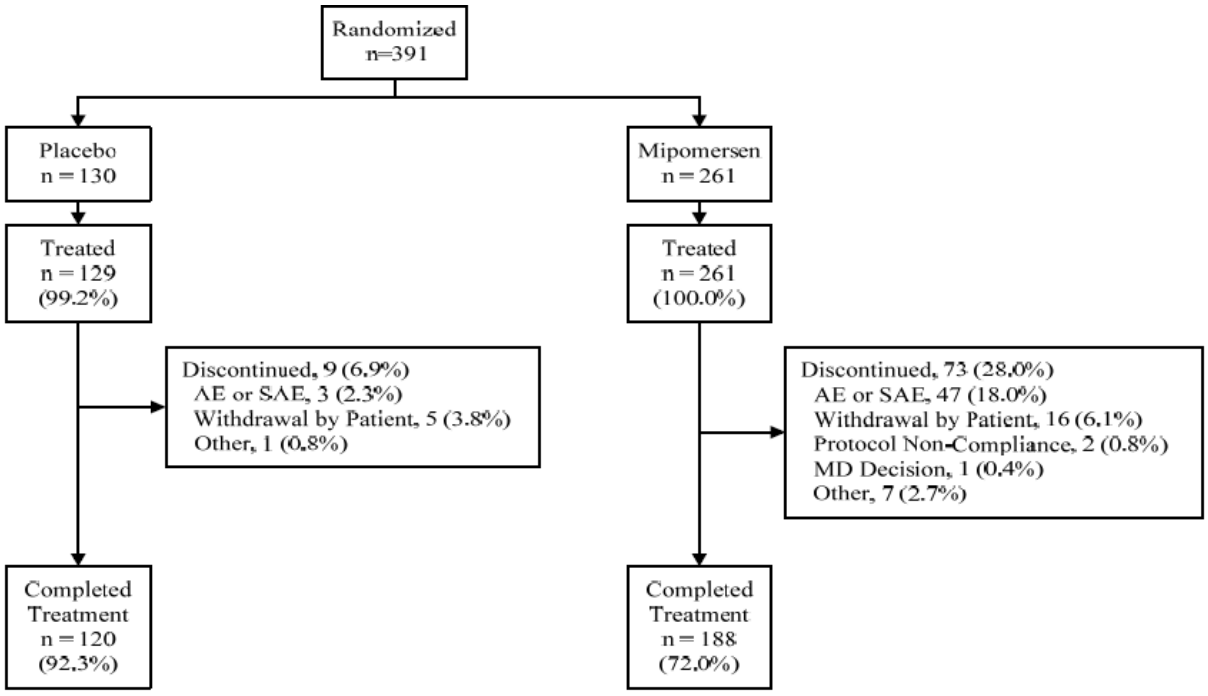
Maximal allowed dose=maximal dose allowed per region-specific drug labelling.
Source: NDA 203568, ISIS301012-CS5 Table 14.1.4.7

6.1.3 Subject Disposition

6.1.3.1 Pooled Phase 3 Trials

In the pooled Phase 3 trials, a total of 391 individuals were randomized to double-blind treatment (261 mipomersen, 130 placebo). Discontinuations were higher in mipomersen-treated individuals (28.0%; 73/261) as compared with placebo-treated individuals (6.9%; 9/130). The most common reason for discontinuation was due to AEs: 18.0% (47/261) of mipomersen-treated individuals and 2.3% (3/130) of placebo-treated individuals discontinued due to an AE or serious adverse event (SAE).

Figure 2. Pooled Phase 3 Patient Disposition



One patient, randomized to the placebo group, did not receive study treatment.
Source: NDA 203568, ISS Figure 7-1

As shown in the following table, in Trial ISIS 301012-CS5 (individuals with HoFH), 82% of individuals completed treatment and discontinuation rates due to AEs or SAEs were 11.8% (4/34) in mipomersen-treated individuals and 0.0% in

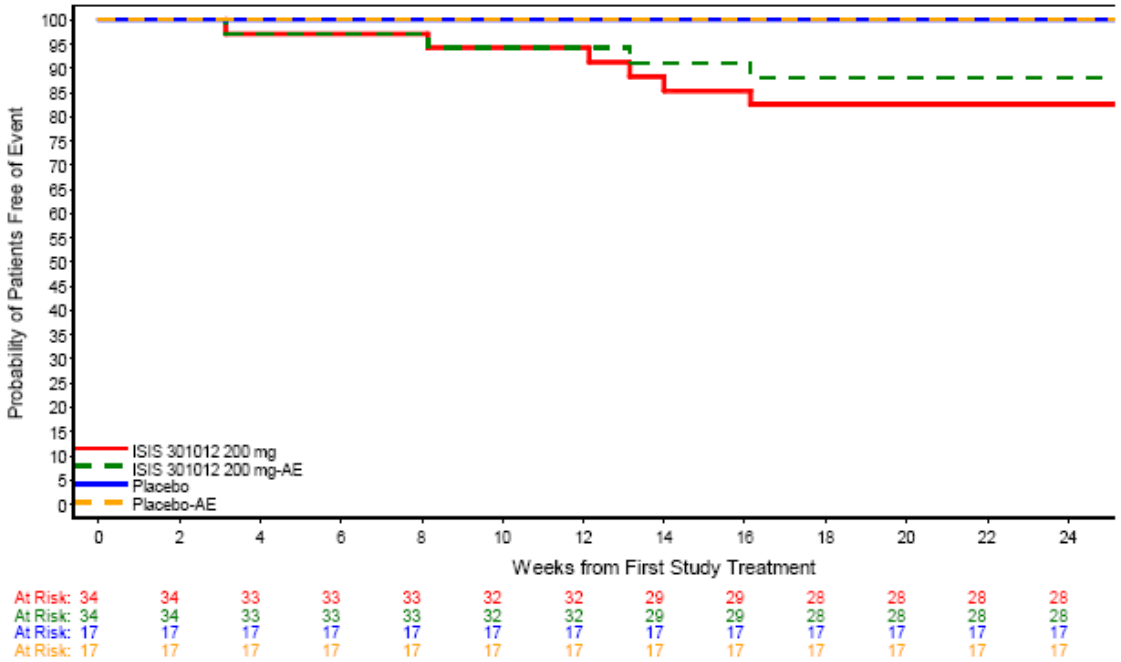
placebo-treated individuals. Trial ISIS 301012-CS12, where one-third of subjects were 65 years of age or older, had the highest discontinuation rate, both for any reason and due to adverse events. Across the three supportive trials, the percentage of mipomersen-treated individuals that discontinued treatment ranged from 12 to 43% compared to placebo, which ranged from 0 to 15%. Thus, in all four trials, more individuals administered mipomersen discontinued treatment than individuals administered placebo and adverse events comprised the majority reason for treatment discontinuation.

Table 10. Patient Disposition Across Phase 3 Trials

	ISIS 301012-CS5		MIPO3500108		ISIS 301012-CS7		ISIS 301012-CS12	
Status	**Placebo**	**Mipo**	**Placebo**	**Mipo**	**Placebo**	**Mipo**	**Placebo**	**Mipo**
Discontinuation Reason	**(N=17)**	**(N=34)**	**(N=19)**	**(N=39)**	**(N=41)**	**(N=83)**	**(N=53)**	**(N=105)**
Randomized, n	17	34	19	39	41	83	53	105
Treated, n (% of randomized)	17 (100.0)	34 (100.0)	19 (100.0)	39 (100.0)	41 (100.0)	83 (100.0)	52 (98.1)	105 (100.0)
Completed treatment, n (% of randomized)	17 (100.0)	28 (82.4)	18 (94.7)	27 (69.2)	41 (100.0)	73 (88.0)	44 (83.0)	60 (57.1)
Discontinued treatment, n (% of randomized)	0 (0.0)	6 (17.6)	1 (5.3)	12 (30.8)	0 (0.0)	10 (12.0)	8 (15.1)	45 (42.9)
Adverse Event or SAE	0 (0.0)	4 (11.8)	1 (5.3)	8 (20.5)	0 (0.0)	9 (10.8)	2 (3.8)	26 (24.8)
Withdrawal By Subject	0 (0.0)	1 (2.9)	0 (0.0)	2 (5.1)	0 (0.0)	0 (0.0)	5 (9.4)	13 (12.4)
Protocol Non-Compliance	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Physician Decision	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)	0 (0.0)	1 (1.2)	1 (1.9)	5 (4.8)

A Kaplan-Meier plot showing the percent of individuals discontinuing over time overall and due to adverse events in ISIS 301012-CS5 is presented below.

Figure 3. Time to Treatment Discontinuation, Overall and Due to Adverse Events, in ISIS 301012-CS5



Source: NDA 203568, Applicant response to information request on 25 May 2012, FS-KM-TRTDISC-ALL-AE-CS5.RTF

6.1.3.2 Open Label Extension Trial: ISIS 301012-CS6

In OLE trial ISIS 301012-CS6, 141 individuals received mipomersen treatment. Thirty-eight individuals were from ISIS 301012-CS5 (76% [38/51]), 94 were from ISIS 301012-CS7 (75.8% [94/124]) and 9 were from MIPO3500108. Of the 141 patients who received at least 1 dose of study drug as of the database cutoff date of 30 March 2012, 60 (42.6%) completed up to an initial 2 years of treatment in the current study (11 completed 1 year; 49 completed 2 years), 79 (56.0%) discontinued prior to completing the initial 2 years of treatment (29 discontinued prior to completing 1 year; 50 discontinued prior to completing 2 years), and 2 (1.4%) were continuing to receive the up to 2 years of initial treatment.

In OLE trial ISIS 301012-CS6, 79 of 141 (56.0%) of the treated individuals discontinued treatment prior to completing 2 years of treatment: 44.0% (62/141) due to an AE or SAE, 12 (8.5%) withdrew consent, 2 (1.4%) due to lack of efficacy, 2 (1.4%) due to physician's decision, and 1 (0.7%) due to pregnancy. In individuals with HoFH, 60.5% (23/38) of individuals discontinued treatment, 47.4% (18/38) due to an AE or SAE, 4 (10.5%) withdrew consent, and 1 (2.6%) due to pregnancy. As of the data cut-off date of 30 November 2011, one patient (Patient 1523-6120) was continuing in Year 2 of dosing, and 2 individuals

(Patient 1523-6051 and Patient 1523-6054) were continuing in Year 3 of dosing. Another patient (Patient 1500-6028) started Year 3 of dosing, but discontinued treatment due to the occurrence of an AE (Depression).

Reviewer comment: The discontinuation rates in the HoFH extension trial are high with 23 of the 38 (61%) HoFH individuals discontinuing, of which 78% of the discontinuations (18/23) are from AEs or SAEs. The overall incidence of discontinuation in the pooled Phase 3 population is also high with 77 of the 141 (55%) individuals discontinuing, of which 79% of the discontinuations (61/77) is from AEs or SAEs.

6.1.4 Analysis of Primary Endpoint(s)

6.1.4.1 Primary Efficacy Endpoint: Percent Change in LDL-C at 6 Months

Table 11 presents the results for percent change in LDL-C from baseline to the PET for the Full Analysis Set in all four Phase 3 trials.

CS5: The mean percent change in LDL-C was -24.7% for individuals in the mipomersen group and -3.3% for individuals in the placebo group ($p<0.001$). The treatment difference from placebo was -21.4%. For the mipomersen group, the mean LDL-C level was 439 mg/dL at baseline and 326 mg/dL at the PET; the mean absolute change in LDL-C was -113 mg/dL. For the placebo group, the mean LDL-C level was 400 mg/dL at baseline and 388 mg/dL at the PET; the mean absolute change in LDL-C was -12 mg/dL.

Site 1501, a site that recruited > 50% of individuals into the trial (Placebo 10: Mipo 16), had somewhat lower efficacy results compared to the results of the overall trial. The mean percent change in LDL-C was -16.7% for individuals in the mipomersen group and -2.3% for individuals in the placebo group. The treatment difference from placebo was -14.4%.

For the Per-Protocol Set (Placebo:16; Mipo:29), the mean percent change in LDL-C was -23.0% for the mipomersen group and 2.8% for the placebo group ($p<0.001$).

MIPO108: The mean percent change in LDL-C was -35.9% for the mipomersen group and 12.5% for the placebo group ($p<0.001$). The treatment difference from placebo was -48.4%. For the mipomersen group, the mean LDL-C level was 276 mg/dL at baseline and 175 mg/dL at the PET; the mean absolute change in LDL-C was -101 mg/dL. For the placebo group, the mean LDL-C level was 249 mg/dL

at baseline and 264 at the PET; the mean absolute change in LDL-C was 15 mg/dL.

There were seven individuals with baseline LDL-C below 200 mg/dL as required by the entry criterion for baseline LDL-C (fasting LDL-C ≥300 mg/dL, or fasting LDL-C ≥200 mg/dL in the presence of CAD). For 6 of the 7 individuals (Patients 1010-1005, 1030-1006, 3002-1031, 4000-1010, 4000-1053, and 5003-1037) the Study Day 1 and screening LDL-C values were >12% different (relative to the maximum value), and the application of the statistical convention for definition of the baseline LDL-C levels in such a case resulted in a baseline value for efficacy assessment of <200 mg/dL. The seventh patient (Patient 3000-1058) had a pretreatment LDL-C of 199 mg/dL and a Day 1 LDL-C of 205 mg/dL. An additional patient, Patient 3000-1023, had a baseline LDL-C of 199 mg/dL and 8.7% difference between screening and Day 1 LDL-C assessments.

For the Per-Protocol Set, the mean percent change in LDL-C was -37.8% for the mipomersen group and 3.7% for the placebo group (p<0.001).

CS7: The mean percent change in LDL-C was -28.0% for individuals in the mipomersen group and 5.2% for individuals in the placebo group (p<0.001). The treatment difference from placebo was -33.2%. For the mipomersen group, the mean LDL-C level was 153 mg/dL at baseline and 104 mg/dL at the PET; the mean absolute change in LDL-C was -49 mg/dL. For the placebo group, the mean LDL-C level was 143 mg/dL at baseline and 146 mg/dL at the PET; the mean absolute change in LDL-C was 3.5 mg/dL.

Ten individuals had pre-treatment LDL-C levels below 100 mg/dL. For 7 of these individuals, the LDL-C was <100 mg/dL only at the Day 1 visit but was ≥ 100 mg/dL at screening. Three individuals had an initial screening lab < 100 mg/dL which was found to be ≥100 mg/dL upon re-test of the screening lab. Using the baseline average used for the efficacy analyses[34], there were a total of 6 individuals with LDL-C <100 mg/dL.

For the Per-Protocol Set, the mean percent change in LDL-C was -28.5% for the mipomersen group and 7.3% for the placebo group (p<0.001).

34 Determination of Baseline of Lipid Parameters for Efficacy PET: For efficacy assessment of lipid parameters, baseline was defined as the average of the screening and Study Day 1 (pre-treatment) assessments. An assessment was not included in this calculation if it was associated with a non-fasting blood draw or was drawn more than 4 weeks prior to Study Day 1. If the Study Day 1 and screening LDL-C values were more than 12% different (relative to the maximum value), then only Study Day 1 was used because the Study Day 1 value represented the best estimate of the patient's condition at the beginning of study medication.

CS12: The mean percent change in LDL-C was -36.9% for individuals in the mipomersen group and -4.5% for individuals in the placebo group ($p<0.001$). The treatment difference from placebo was -32.4%. For the mipomersen group, the mean LDL-C level was 123 mg/dL at baseline and 75 mg/dL at the PET; the mean absolute change in LDL-C was -47.3 mg/dL. For the placebo group, the mean LDL-C level was 123 mg/dL at baseline and 113 mg/dL at the PET; the mean absolute change in LDL-C was -9.4 mg/dL.

Thirty-three individuals had pre-treatment LDL-C levels <100 mg/dL. For 29 of these individuals, the LDL-C was <100 mg/dL only at the Day 1 visit but was ≥ 100 mg/dL at screening. Four individuals had an initial screening lab <100 mg/dL which was found to be ≥100 mg/dL upon re-test of the screening lab. Using the baseline average, there were a total of 30 individuals with LDL-C <100 mg/dL.

For the Per-Protocol Set, the mean percent change in LDL-C was -43.3% for the mipomersen group and -6.9% for the placebo group ($p<0.001$).

Table 11. Primary Endpoint: Percent Change in LDL-C from Baseline to the PET (Full Analysis Set)

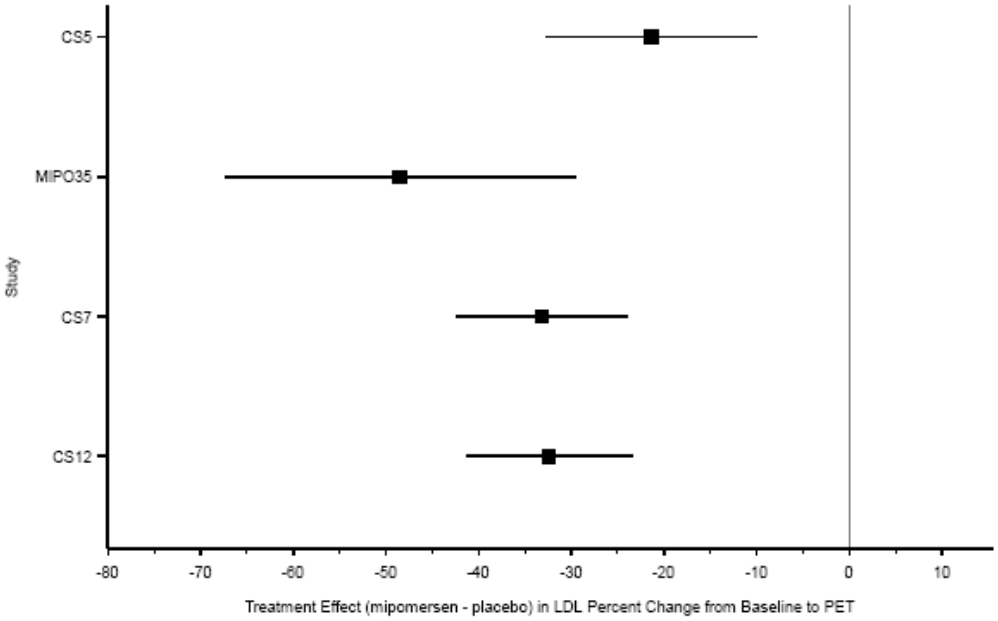
	ISIS 301012-CS5		MIPO3500108		ISIS 301012-CS7		ISIS 301012-CS12	
LDL-C (mg/dL)	**Placebo (N=17)**	**Mipo (N=34)**	**Placebo (N=18)**	**Mipo N=39)**	**Placebo (N=41)**	**Mipo (N=83)**	**Placebo (N=52)**	**Mipo (N=105)**
Baseline - Mean (SD)	400.2 (141.5)	438.9 (138.6)	249.4 (84.3)	276.1 (72.1)	142.9 (51.6)	152.9 (48.7)	122.7 (38.6)	122.6 (31.7)
Min, Max	172, 639	190, 704	93 , 427	112 , 470	87 , 392	36 , 377	69 , 265	65 , 270
PET - Mean (SD)	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)
Min, Max	129, 606	62, 587	128 , 595	35 , 429	96 , 344	19 , 200	41 , 227	14 , 174
Percent change from baseline- Mean (SD)	-3.3 (17.1)	-24.7 (19.9)	12.5 (46.9)	-35.9 (24.7)	5.2 (18.0)	-28.0 (27.0)	-4.5 (24.2)	-36.9 (26.9)
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
95% CI	(-12.1, 5.5)	(-31.6, -17.7)	(-10.8 , 35.9)	(-43.9 , -27.9)	(-0.52 , 10.9)	(-34.0 , -22.1)	(-11.4 , 2.4)	(-42.2 , -31.6)
Treatment Difference from Placebo (%)		-21.4 (95% CI: -32.9 to -9.8)		-48.4%		-33.2%		-32.4%
Wilcoxon signed rank test (p-value)	0.323	<0.001	0.417	<0.001	0.063	<0.001	0.300	<0.001
t-test (p-value)		<0.001		<0.001		<0.001		<0.001
Kolmogorov-Smirnov (p-value)		0.120		0.075		>0.150		<0.010

If the Kolmogorov-Smirnov test of normality was statistically significant ($p \leq 0.05$) then the Wilcoxon rank-sum test results were utilized. Otherwise, the 2-sample t-test was used. Changes within treatment groups were assessed using the Wilcoxon signed-rank test.
For individuals with <TG 400 mg/dL, LDL-C was obtained using Friedewald's calculation; and for individuals with TG ≥400 mg/dL, LDL-C was directly measured by the central laboratory using ultracentrifugation.
CI = confidence interval; Max = maximum; Min = minimum; PET = primary efficacy time point; SD = standard deviation.
Source: NDA 203568, CSR CS5, MIPO108, CS7, CS12:Tables 11-1 and 14.2.1.1a

6.1.4.2 Treatment Difference from Placebo

The treatment effect of mipomersen (the effect in mipomersen-treated individuals minus the effect in placebo-treated individuals) is shown in the figure below. The LDL-C reduction effect with mipomersen was highly variable among individuals in CS5 ranging from a 2% increase to an 82% reduction. The mipomersen treatment difference from placebo was also variable and the mean effect ranged from 21% LDL-C reduction in CS5 to a 48% reduction in MIPO108.

Figure 4. LDL-C 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 Trials (Full Analysis Set)



Source: NDA 203568, 2.7.3 Summary of Clinical Efficacy, Figure 3

6.1.4.3 Sensitivity Analyses of Primary Endpoint

Several sensitivity analyses were done to explore the primary endpoint results. Consistent results were seen when the lipid assessment closest to 14 days after the last protocol-prescribed dosing day was used instead of data from the PET; when the Per-Protocol group was used instead of the Full Analysis Set; and

when the alternative baseline definition was used (baseline determined by a single assessment for all individuals).

Sensitivity analyses of the primary efficacy parameter consisted of the following:

1. Percent change at the lipid assessment closest to 14 days after the last protocol-prescribed dosing day (i.e., in a 26-week treatment trial, this corresponded to the Week 28 assessment). For individuals completing 26 weeks of study treatment, these data were identical to that in the PET analysis. For individuals who discontinued study treatment early, these assessments are after their last dose of study medication.
    a. CS5: The mean percent change in LDL-C from baseline to Week 28 or the early termination visit (LOCF) for the Full Analysis Set was -24.0% for the individuals in mipomersen group and -3.3% for individuals in the placebo group. The treatment difference was statistically significant (p=0.001).
    b. MIPO108: Mipo: -26.9%; Placebo: 5.2% (treatment diff, p=0.002)
    c. CS7: Mipo: -29.4%; Placebo: 12.5% (treatment diff, p<0.001)
    d. CS12: Mipo: -28.0%; Placebo: -5.2% (treatment diff, p<0.001)
2. Linear regression analyses and corresponding subgroup tabulations for the following factors: baseline LDL-C, age, sex, and race (e.g., white vs. non-white if supported by adequate distribution of individuals).
    a. CS5: Analyses showed homogeneity across the factors measured (baseline LDL-C value, age, sex, and race), with no appreciable confounding relationships. It is unclear why there was no effect by gender in this trial when it was observed in the other 3 trials. In addition, CS5 and MIPO108 had a similar number and percentage of female subjects in the trials.
    b. MIPO108: the effect of treatment on LDL-C was influenced by gender (p=0.001). There was a more pronounced effect in females than in males. For females, the mean percent change in LDL-C from baseline to the PET was -43.6% for the mipomersen group and 29.9% for the placebo group (p<0.001). For males, the mean percent change in LDL-C from baseline to the PET was -27.0% for the mipomersen group and -14.7% for the placebo group (p<0.001).
    c. CS7: the effect of treatment on LDL-C was influenced by gender. The mean percent change in LDL-C was -20.0% for males receiving mipomersen and -40.6% for females receiving mipomersen. The mean percent change in LDL-C was 5.9% for males receiving placebo and 3.7% for females receiving placebo.
    d. CS12: the effect of treatment on LDL-C was influenced by gender and age. There was a more pronounced effect in females and in individuals with age above the median. The mean percent change in LDL-C was -32.7% for male individuals receiving mipomersen and -41.2% for female individuals receiving mipomersen. The mean

percent change in LDL-C was -8.6% for male individuals receiving placebo and 1.1% for female individuals receiving placebo. The mean percent change in LDL-C was -29.8% for individuals with age below the median receiving mipomersen and -41.8% for individuals with age above the median receiving mipomersen. The mean percent change in LDL-C was -7.4% for individuals with age below median receiving placebo and -1.9% for individuals with age above median receiving placebo.

The table below shows the p-values for the affect of age, gender, race and baseline LDL on mipomersen efficacy for the Phase 3 trials.

Table 12. Treatment-by-Factor p-Values in Phase 3 Studies

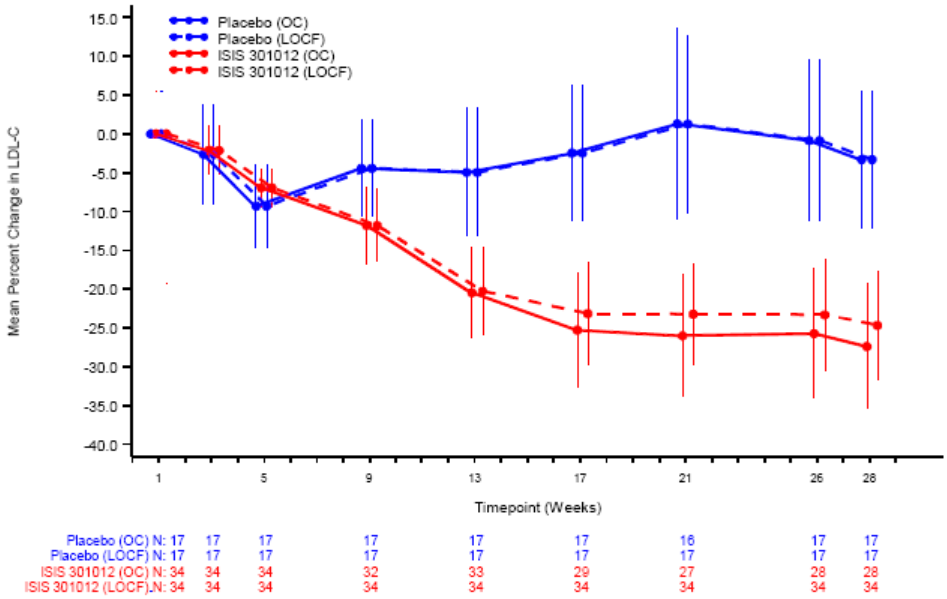
	Phase 3 Trial			
Factor	**ISIS 301012-CS5**	**MIPO3500108**	**ISIS 301012-CS7**	**ISIS 301012-CS12**
Age	0.099	0.249	0.959	0.027
Gender	0.664	0.001	0.051	0.045
Race	0.380	0.889	0.066	0.074
Baseline LDL-C	0.463	0.074	0.168	0.651

Source: NDA 203568: ISIS 301012-CS5 CSR Table 14.2.2.1; MIPO3500108 CSR Table 14.2.2.1; ISIS 301012-CS7 CSR Table 14.2.2.1; and ISIS 301012-CS12 CSR Table 14.2.2.1

3. Robustness of overall findings was assessed by a qualitative comparison to LDL-C percent change from Day 1 to PET (i.e., only a single assessment was used in the baseline determination).
    a. CS5: The mean percent change in LDL-C from baseline to Week 28 or the early termination visit (LOCF) for the Full Analysis Set was -24.3% for the individuals in mipomersen group and -2.7% for individuals in the placebo group. The treatment difference was statistically significant ($p<0.001$).
    b. MIPO108: Mipo: -36.3%; Placebo: 13.2% (treatment diff, $p<0.001$)
    c. CS7: Mipo: -27.7%; Placebo: 5.3% (treatment diff, $p<0.001$)
    d. CS12: Mipo: -36.7%; Placebo: -4.6% (treatment diff, $p<0.001$)

The figure below shows the effect of dropouts on the primary efficacy endpoint in CS5. The mean (and 95% confidence interval) percent change in LDL-C over time is presented and the figure contains 4 lines: the observed cases (OC) for mipomersen and placebo groups and the last observation carried forward (LOCF) approach for mipomersen and placebo groups. This figure for CS5 as well as the figures for the 3 supportive trials (not shown) show that a progressive decrease in LDL-C levels occurred in the mipomersen group compared with placebo using both OC and LOCF.

Figure 5. Mean (95% CI) Percent Change in LDL-C over Time in ISIS 301012-CS5

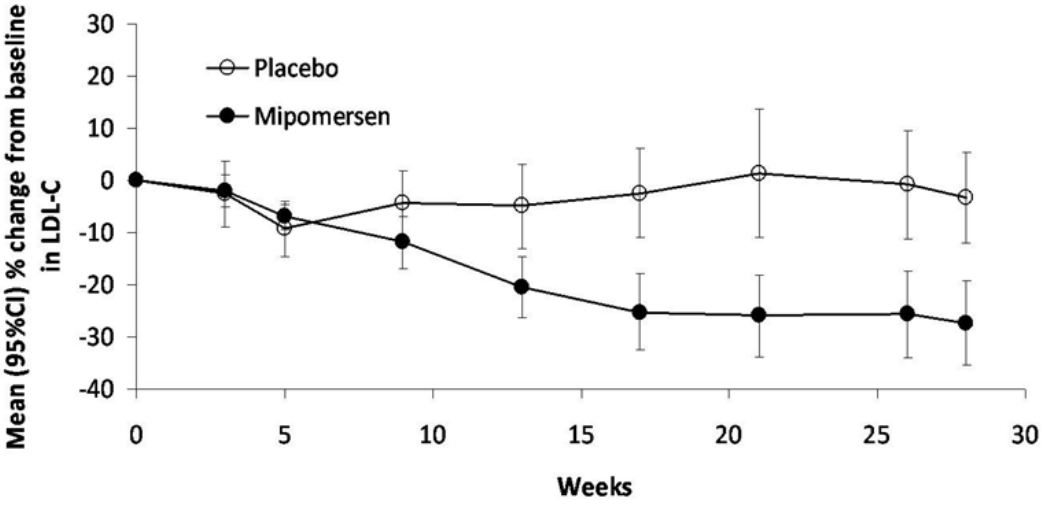


Source: NDA 203568, Applicant response to information request on 25 May 2012, FE-MEANCHGPLOT-LDL-CS5.RTF

6.1.4.4 Change in LDL-C Over Time in ISIS 301012-CS5

The next figure shows the mean percent change in LDL-C over time in ISIS 301012-CS5 for the Full Analysis Set. A progressive decrease in LDL-C levels occurred in the mipomersen group over the first 16 weeks of treatment. From Week 17 to Week 28, the LDL-C levels remained generally stable. A similar pattern was seen in the other three Phase 3 trials although in MIPO108 and CS7 the decrease continued until Week 26.

Figure 6. Mean Percent Change in LDL-C in Trial ISIS 301012-CS5 (Full Analysis Set)



CI, confidence interval; LDL-C, low-density lipoprotein cholesterol
Vertical bars indicate 95% confidence intervals
Source: NDA 203568, ISIS 301012-CS5 CSR Figure 11-1

6.1.4.5 Individual Percent Change in LDL-C from Baseline in ISIS 301012-CS5

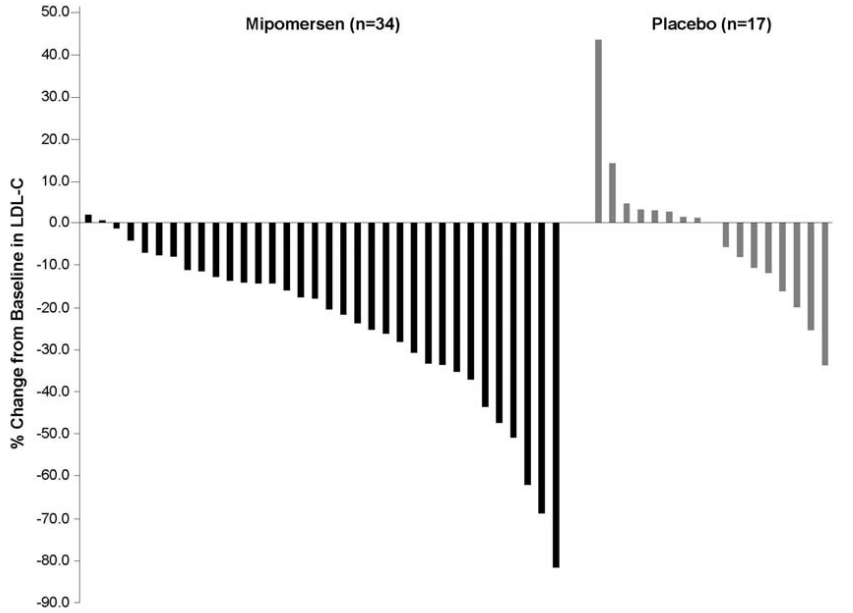
The figure below shows the percent change in LDL-C from baseline to the PET for each individual in ISIS 301012-CS5. There was notable variability in the individual results for the mipomersen group, which ranged from a 2% increase in LDL-C to an 82% decrease in LDL-C. The authors of the Lancet article on ISIS 301012-CS535 did not find a correlation between the LDL-receptor mutation and response to mipomersen. However, they note that four individuals in the mipomersen group with an LDL-receptor negative mutation (V408M) paired with D206E (the most frequent allele in this trial) had a smaller reduction in LDL-C (median reduction 14%, range -31 to -8) than the other individuals. The authors caution that the small number of individuals and presence of many different mutations makes it difficult to detect a correlation with genotype.

Reviewer Comment: A varied response in the placebo-treated HoFH population is also noted in Figure 6 and some subjects with HoFH in the statin trials have likewise shown a variable response to treatment. Nevertheless, this variability in response will be important to detail in labeling, if mipomersen is approved. The benefit:risk profile is quite different for an individual who achieves a large

35 Raal FJ, Santos RD, Blom DJ, Marais AD, Charng MJ, Cromwell WC, Lachmann RH, Gaudet D, Tan JL, Chasan-Taber S, Tribble DL, Flaim JD, Crooke ST. Mipomersen, an apolipoprotein B synthesis inhibitor, for lowering of LDL cholesterol concentrations in patients with homozygous familial hypercholesterolaemia: a randomised, double-blind, placebo-controlled trial. Lancet. 2010 Mar 20;375(9719):998-1006. PMID: 20227758

reduction in LDL-C as compared to one who receives little or no LDL-C reduction from mipomersen. This is of particular concern for mipomersen because the safety database is much smaller than what is typically required for an LDL-C lowering agent intended for the general hyperlipidemic population. As significant reductions in baseline LDL-C levels were near maximum by Week 17, one consideration is to recommend that physicians assess the patient's LDL-C level after 4 months of mipomersen treatment and discontinue therapy if the patient has not achieved a robust LDL-C reduction (>15%).

Figure 7. Patient Response for Percent Change in LDL-C From Baseline



Source: NDA 203568: CSR CS5 Figure 11-3, Data listing 16.2.6.1-1b

6.1.4.6. LDL-C Response Categories in the Four Phase 3 Trials

The table below presents the numbers and percentages of individuals in different lipid response categories.

CS5: Fifty percent of individuals in the mipomersen group of ISIS 301012-CS5 had at least a 20% decrease in LDL-C levels from baseline to PET, compared with 12% of individuals in the placebo group. Four (11.8%) individuals in the mipomersen group had a >50% decrease in LDL-C levels from baseline to PET, compared with no individuals in the placebo group. Approximately 47% of individuals in the placebo group had an increase in LDL-C compared with 6% of mipomersen-treated individuals.

MIPO108: Approximately 69% of individuals in the mipomersen group had at least a 20% decrease in LDL-C levels from baseline to PET, compared with 17% of individuals in the placebo group. Ten (25.6%) individuals in the mipomersen group had a >50% decrease in LDL-C levels from baseline to PET compared with no individuals in the placebo group.

CS7: Approximately 63% of individuals in the mipomersen group had at least a 20% decrease in LDL-C levels from baseline to PET, compared with 5% of individuals in the placebo group. Seventeen (20.7%) individuals in the mipomersen group had a >50% decrease in LDL-C levels from baseline to PET compared with no individuals in the placebo group.

CS12: Approximately 74% of individuals in the mipomersen group had at least a 20% decrease in LDL-C levels from baseline to PET, compared with 20% of individuals in the placebo group. Thirty-five (34.7%) individuals in the mipomersen group and 3 (6.0%) individuals in the placebo group had a >50% decrease in LDL-C levels from baseline to PET.

Table 13. LDL-C Response Categories in the Four Phase 3 Trials

Change from Baseline Category	ISIS 301012-CS5		MIPO3500108		ISIS 301012-CS7		ISIS 301012-CS12	
	Placebo (N=17) n (%)	Mipo (N=34) n (%)	Placebo (N=18) n (%)	Mipo (N=39) n (%)	Placebo (N=41) n (%)	Mipo (N=83) n (%)	Placebo (N=50) n (%)	Mipo (N=101) n (%)
Increase	8 (47)	2 (6)	10 (56)	3 (8)	26 (63)	8 (10)	22 (44)	11 (11)
0% to 10% decrease	3 (18)	5 (15)	5 (28)	4 (10)	8 (20)	8 (10)	8 (16)	7 (7)
>10% to 20% decrease	4 (24)	10 (29)	0	5 (13)	5 (12)	14 (17)	10 (20)	8 (8)
>20% to 30% decrease	1 (6)	6 (18)	1 (6)	2 (5)	0	14 (17)	3 (6)	6 (6)
>30% to 40% decrease	1 (6)	5 (15)	1 (6)	5 (13)	1 (2)	13 (16)	2 (4)	18 (18)
>40% to 50% decrease	0	2 (6)	1 (6)	10 (26)	1 (2)	8 (10)	2 (4)	16 (16)
>50% decrease	0	4 (12)	0	10 (26)	0	17 (20)	3 (6)	35 (35)
<100 mg/dL at the PET	0	2*(6)	0	6 (15)	2 (5)**	37 (45)**	19 (38) ††	77 (76) ††
<70 mg/dL at the PET	0	1†(3)	0	3 (8)	0	9 (11)	4 (8)	51 (51)

Source: NDA 203568: CSR ISIS 301012-CS5, MIPO108, ISIS 301012-CS7, ISIS 301012-CS12 Table 11-3 and Table 14.2.3.2.
* Subject 1523-8309: Week 28: 94 mg/dL
† Subject 1536-8317 Week 28: 62 mg/dL
**One of the 2 placebo-treated subjects and 4 of the 37 mipomersen-treated subjects had an LDL-C<100 mg/dL at Baseline
†† 8 of the 19 placebo-treated subjects and 19 of the 77 mipomersen-treated subjects had an LDL-C<100 mg/dL at Baseline

6.1.5 Analysis of Secondary Endpoints(s)

Secondary efficacy parameters included percent changes from baseline to PET in apo B, non-HDL-C, and TC levels. Corrections for multiple analyses by use of

a sequential inferential approach were performed. The table below presents the results for the secondary efficacy endpoints: percent change in apo B, TC, and non-HDL-C from baseline to the PET for the Full Analysis Set in all four Phase 3 trials. Statistically significant percent reductions with mipomersen compared to placebo were seen for apo B, TC, and non-HDL-C from baseline to PET in the four Phase 3 trials. A variable response in these secondary efficacy endpoints was seen in both treatment groups.

Table 14. Secondary Endpoints: Percent Change in ApoB, TC, and non-HDL-C from Baseline to the PET (Full Analysis Set)

	ISIS 301012-CS5		MIPO3500108		ISIS 301012-CS7		ISIS 301012-CS12	
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)**
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 (12.6)	-26.8 (17.0)*	11.4 (36.8)	-35.9 (23.0)*	7.0 (16.5)	-26.3 (22.2)*	-1.7 (-12.6, 7.5)	-40.6 (-53.0, -22.6)*
Min, max	-23.5, 29.2	-77.7, -2.2	-41.1 , 130.0	-87.1 , 12.6	-30.3 , 51.3	-73.8 , 32.7	-46.4 , 38.6	-77.1 , 25.6
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 (14.8)	-21.2 (17.7)*	11.1 (34.74)	-28.3 (20.4)*	3.9 (12.8)	-19.4 (19.3)*	-2.7 (14.6)	-26.4 (18.7)*
Min, max	-29.1, 40.4	-75.2, 3.0	-36.7 , 121.6	-80.2 , 12.0	-36.1 , 32.5	-60.7 , 32.7	-36.4 , 25.7	-62.7 , 19.6
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 (16.3)	-24.5 (19.2)*	14.2 (47.8)	-34.0 (23.8)*	3.7 (16.0)	-25.1 (25.7)*	-1.2 (-13.6, 11.5)	-38.7 (-54.0, -24.2)*
Min, max	-33.3, 42.6	-81.1, 0.8	-43.3 , 181.1	-87.7 , 13.6	-39.4 , 38.7	-71.4 , 79.2	-48.2 , 58.4	-81.3 , 28.1

Apo, B, apolipoprotein B; 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 trials.

6.1.6 Tertiary Endpoints

Tertiary efficacy parameters included percent changes from baseline to PET in TG, Lp(a), VLDL-C, LDL/HDL ratio, apo A-I, and HDL-C. Of note, corrections for multiple analyses by use of a sequential inferential approach were not performed. The table below presents the results for the tertiary efficacy endpoints from baseline to the PET for the Full Analysis Set in all four Phase 3 trials.

In ISIS 301012-CS5, nominally statistically significant reductions occurred in Lp(a), TG, VLDL-C, and LDL/HDL ratio from baseline to PET. A nominally statistically significant increase in HDL-C was noted in mipomersen-treated individuals as compared with placebo-treated individuals. Changes in apo A-I were not statistically significant.

In the 3 supportive Phase 3 trials (MIPO3500108, ISIS 301012-CS7, and ISIS 301012-CS12), nominally statistically significant reductions in Lp(a), and LDL/HDL ratio were noted in the mipomersen-treated group as compared with placebo. Reductions in TG and VLDL-C occurred but were not consistently statistically significant. HDL-C did not decrease in these trials. However, apolipoprotein A-I (apo A-I), which is the major protein component of HDL-C, decreased from baseline and as compared to the placebo group in the mipomersen group in the 3 supportive trials. It is not known why there is a discordant change in apo A-I and HDL-C in the supportive trials; apo A-II was not measured in these trials.

Table 15. Tertiary Endpoints: Percent Change in TG, Lp(a), VLDL-C, LDL/HDL ratio, apo A-I, and HDL-C Baseline to the PET (Full Analysis Set)

	ISIS 301012-CS5		MIPO3500108		ISIS 301012-CS7		ISIS 301012-CS12	
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)**
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)
Min, Max	3, 164	10, 176	3 , 102	3 , 338	3 , 220	3 , 260	3 , 154	3 , 268
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 (21.9)	-31.1 (23.0)	-1.5 (25.7)	-32.7 (33.0)	0 (-8.0, 13.0)	-21 (-37.9, 0)	2.3 (28.1)	-24.0 (24.5)
p-value		0.001		<0.001		<0.001		<0.001
TG (mg/dL)	**Median (Q1, Q3)**		**Mean (SD)**		**Median (Q1, Q3)**		**Median (Q1, Q3)**	
Baseline	92 (80, 105)	91 (73, 141)	140.3 (49.8)	142.2 (86.0)	100 (74 , 137)	107 (85 ,137)	139 (98 , 176)	143 (105 , 175)
Min, Max	45, 140	48, 365	58 , 223	48 , 472	44 , 283	50 , 210	42 , 371	43 , 516
PET	85 (65, 117)	76 (52, 116)	164.5 (61.2)	116.3 (63.3)	101 (76 , 139)	89 (70 , 127)	135 (96 , 177)	88 (67 , 128)
% change from baseline	0.9 (-25.0, 29.5)	-17.5 (-36.0, -4.8)	26.5 (60.6)	-8.7 (40.1)	0.5 (-16.2 , 17.9)	-14.3 (-32.7 , 9.7)	2.7 (-24.0 , 24.2)	-26.2 (-48.1 , -8.8)
p-value		0.013		0.034*		0.042		<0.001
VLDL-C (mg/dL)	**Median (Q1, Q3)**		**Mean (SD)**		**Median (Q1, Q3)**		**Median (Q1, Q3)**	
Baseline	18 (16, 21)	18 (15, 28)	28.1 (9.9)	29.1 (20.0)	20 (15 , 28)	21 (17 , 27)	28 (20 , 35)	29 (21 , 35)

Parameter	ISIS 301012-CS5		MIPO3500108		ISIS 301012-CS7		ISIS 301012-CS12	
	Placebo (N=17)	Mipomersen (N=34)	Placebo (N=18)	Mipomersen (N=39)	Placebo (N=41)	Mipomersen (N=83)	Placebo (N=52)	Mipomersen (N=105)
PET	17 (13, 23)	15 (10, 23)	32.8 (12.3)	23.2 (12.6)	20 (15 , 28)	18 (14 , 25)	27 (19 , 35)	18 (13 , 26)
% change from baseline	2.3 (-25.0, 28.6)	-17.3 (-37.1, -3.0)	25.1 (58.7)	-9.4 (39.6)	0.0 (-15.4 , 15.0)	-13.8 (-33.3 ,11.8)	1.9 (-23.1 , 26.3)	-26.7 (-46.8 , -9.1)
p-value		0.009		0.032*		0.023		<0.001
LDL/HDL ratio	**Mean (SD)**		**Median (Q1, Q3)**		**Median (Q1, Q3)**		**Mean (SD)**	
Baseline	12.1 (7.7)	13.0 (6.1)	5.9 (3.9 , 6.6)	5.2 (4.1 , 7.0)	2.7 (2.5 , 3.3)	2.99 (2.6 , 4.0)	2.8 (1.4)	2.5 (0.8)
PET	11.4 (7.1)	8.1 (3.9)	5.9 (3.3 , 7.8)	3.1 (2.1 , 4.3)	3.0 (2.2 , 3.5)	2.1 (1.5 , 3.0)	2.5 (1.1)	1.5 (0.8)
% change from baseline	-6.2 (18.8)	-34.3 (21.0)	1.9 (-14.3 ,18.0)	-41.8 (-57.4 , -16.4)	-2.8 (-13.1 , 13.1)	-29.2 (-46.8 , -13.7)	-5.3 (25.3)	-37.4 (27.2)
p-value		<0.001		<0.001		<0.001		<0.001
Apo A-I (mg/dL)	**Mean (SD)**		**Mean (SD)**		**Mean (SD)**		**Mean (SD)**	
Baseline	118.6 (33.0)	111.5 (27.9)	139.2 (32.6)	154.9 (31.4)	146.1 (24.9)	150.7 (28.1)	150.8 (30.5)	156.8 (25.4)
PET	124.5 (34.9)	118.8 (20.5)	140.7 (34.2)	147.9 (27.0)	151.5 (29.1)	145.4 (27.9)	147.8 (27.3)	146.8 (24.5)
% change from baseline	5.4 (10.6)	9.3 (17.6)	1.8 (14.3)	-3.0 (15.8)	3.7 (8.7)	-2.4 (14.2)	-1.0 (11.2)	-5.6 (12.6)
p-value		0.328		0.278		0.004		0.032
HDL (mg/dL)	**Median (Q1, Q3)**		**Mean (SD)**		**Median (Q1, Q3)**		**Mean (SD)**	

Parameter	ISIS 301012-CS5		MIPO3500108		ISIS 301012-CS7		ISIS 301012-CS12	
	Placebo (N=17)	Mipomersen (N=34)	Placebo (N=18)	Mipomersen (N=39)	Placebo (N=41)	Mipomersen (N=83)	Placebo (N=52)	Mipomersen (N=105)
Baseline	38 (27, 49)	35 (32, 44)	43.1 (11.6)	51.1 (15.1)	48 (41 , 53)	47 (40 , 58)	48.4 (15.9)	50.8 (12.0)
Min, Max	22, 74	20, 79	27 , 75	25 , 84	28 , 78	29 , 82	24 , 109	30 , 88
PET	43 (28, 53)	43 (37, 48)	44.8 (16.3)	53.4 (16.7)	51 (42 , 58)	48 (40 , 58)	48.9 (16.1)	51.1 (12.3)
% change from baseline	4.1 (-2.0, 13.2)	14.8 (3.3, 27.0)	3.2 (16.5)	5.8 (21.3)	5.8 (0.0 , 11.5)	2.5 (-10.3 , 11.7)	2.2 (16.4)	2.2 (18.0)
p-value		0.035		0.647		0.207		0.977

Apo A-I, apolipoprotein A-I; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; Q1, first quartile; Q3, third quartile; SD, standard deviation
Data presented as mean and SD, with p-values calculated using the 2 sample t-test, 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, with p-values calculated using the Wilcoxon rank sum test.
* The significant treatment difference can be attributed to the large mean increase from baseline in the placebo group.
Source: CS5, MIPO108, CS7, CS12: CSR Section 11.1.3, Table 14.2.1.1a

6.1.7 Subpopulations

Please refer to Section *6.1.4.3 Sensitivity Analyses of Primary Endpoint* for an analysis of the primary endpoint in terms of age, gender, race and baseline LDL-C.

6.1.7.1 Immunogenicity

The immunogenicity of mipomersen was evaluated in individuals from Phase 3 trial ISIS 301012-CS5 and individuals from trial ISIS 301012-CS5 who subsequently enrolled in OLE trial ISIS 301012-CS6. In ISIS 301012-CS5, 11 of 34 (32%) mipomersen-treated individuals tested positive for anti-mipomersen antibodies, 22 of 34 (65%) tested negative for anti-mipomersen antibodies, and 1 of 34 (3%) had no post-baseline assessment. None of placebo-treated individuals tested positive for anti-mipomersen antibodies. Individuals who tested positive for anti-mipomersen antibodies had similar LDL-C reduction (-36.4%) as individuals who remained negative for anti-mipomersen antibodies (-24.2%).

A total of 38 individuals from trial ISIS 301012-CS5 (22 mipomersen; 16 placebo) were dosed in the OLE trial. Of the 22 individuals in ISIS 301012-CS6 who were treated with mipomersen in trial ISIS 301012-CS5, seven were positive for anti-mipomersen antibodies during the index trial, and remained positive for anti-mipomersen antibodies in OLE trial ISIS 301012-CS6. Of the remaining 15 individuals who received mipomersen in the index trial and tested negative for anti-mipomersen antibodies prior to entry into the OLE trial, 9 subsequently tested positive for anti-mipomersen antibodies during the OLE trial. Of the 16 individuals in ISIS 301012-CS6 who received placebo during trial ISIS 301012-CS5, all tested negative for anti-mipomersen antibodies in the index trial, and 10 subsequently tested positive for anti-mipomersen antibodies during the OLE trial. Thus, of the 38 individuals who were dosed in the OLE trial, 12 (31.6%) remained anti-mipomersen antibody negative.

6.1.7.2 Pediatric Patients

Of the 51 individuals in CS5, seven were adolescents (12 to <18 years of age), three of whom were randomized to mipomersen and four to placebo. A dose adjustment was allowed for individuals below 50 kg (to 160 mg mipomersen once weekly); however, all of the mipomersen-treated children in ISIS 301012-CS5 were above 50 kg (range, 55 to 61 kg; between 14 and 16 years of age), so all were treated with 200 mg mipomersen once weekly. During ISIS 301012-CS5, mipomersen resulted in changes in LDL-C from -30.8% to -62.0% in the three

mipomersen-treated adolescent individuals. The percent change in LDL-C in the 4 placebo-treated individuals ranged from -7.9% to 43.1%. After Week 28, the seven adolescent individuals from ISIS 301012-CS5 enrolled in OLE trial ISIS 301012-CS6. The three individuals who were receiving mipomersen in ISIS 303012-CS5 continued to receive 200 mg mipomersen once weekly. The percent change in LDL-C as of their last dose of mipomersen ranged from -35.9% to 3.9% in these three individuals. The four placebo individuals from ISIS 301012-CS5 were assigned to receive mipomersen at 200 mg once weekly (3 individuals) or 160 mg once weekly (1 patient at 45.8 kg; 13 years of age) in ISIS 301012-CS6. Changes in LDL-C in these individuals as of their last dose of mipomersen ranged from -42.1% to 11.2%. While the number of individuals is small, the results are within the range of results seen in the adult individuals in CS5 and CS6.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

All Phase 3 trials used a 200 mg dose administered subcutaneously every week.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

CS5: Individuals with HoFH

A total of 39 individuals with HoFH have enrolled in ISIS 301012-CS6, and 38 of these individuals have received treatment under this protocol. Twelve (32%) individuals have completed treatment, 23 (60%) have discontinued treatment (18 of 23 due to AEs/SAEs) , and 3 (8%) are continuing treatment. Baseline (for measurement of lipid parameters) was defined as the last value prior to receiving mipomersen in ISIS 301012-CS6 for individuals who had received placebo in their index trial or who had last received mipomersen ≥6 months prior to receiving mipomersen in ISIS 301012-CS6. For individuals who received their last dose of mipomersen in their index trial less than 6 months prior to their first dose in ISIS 301012-CS6, baseline was defined as the last value prior to receiving the first dose of mipomersen in their index trial. Although the number of individuals is small after Week 52, the mean percent LDL-C reductions during this extension trial were basically consistent with those observed during the 26-week, double-blind treatment period of CS5.

Table 16. LDL-C Reduction in Individuals with HoFH Enrolled in ISIS 301012-CS6 (Full Analysis Set)

LDL-C (mg/dL)	Level		% Change from Baseline	
Time Point	n	Mean (SD)	n	Mean (95% CI)
Baseline	38	420.1 (145.8)	--	--
Week 26	32	336.4 (109.6)	32	-25.07 (-30.7, -19.4)
Week 52	27	341.0 (126.8)	27	-24.71 (-32.3, -17.2)
Week 76	10	322.2 (163.0)	10	-32.91 (-51.1, -14.7)
Week 104	3	254.7 (109.5)	3	-38.47 (-114.1, 37.1)
Week 130	4	404.4 (174.6)	4	-17.52 (-34.8, -0.2)

CI, confidence interval; SD, standard deviation
Data are through 25 March 2011.
Source: ISIS 301012-CS6 subset HoFH CSR, Table 14.2.1a

All Individuals Enrolled in ISIS 301012-CS6

Individuals who had successfully completed ISIS 301012-CS5, ISIS 201012-CS7, or MIPO3500108 with an acceptable safety profile could have consented to either 52, 104, or 208 weeks of treatment in OLE trial ISIS 301012-CS6. A total of 141 individuals from these three trials enrolled and were treated in CS6. Forty-eight (34%) individuals have completed treatment up to two years of initial treatment, 77 (55%) have discontinued treatment (61 of 77 due to AEs/SAEs) , and 16 (11%) are continuing treatment. Although the number of individuals is small after Week 104, the mean percent LDL-C reductions during this extension trial were basically consistent with those observed during the 26-week, double-blind treatment period of the initial trials.

Table 17. LDL-C Reduction in All Individuals Enrolled in ISIS 301012-CS6 (Safety Set)

LDL-C (mg/dL)	Level		% Change from Baseline	
Time Point	n	Mean (SD)	n	Mean (95% CI)
Baseline	141	232.7 (147.4)	--	--
Week 26	130	164.9 (117.9)	130	-28.48 (-31.9, -25.1)
Week 52	111	168.3 (121.9)	111	-27.03 (-31.2, -22.8)
Week 76	66	144.3 (105.8)	66	-27.32 (-33.0, -21.6)
Week 104	53	115.4 (54.2)	53	-28.35 (-34.7, -22.0)
Week 130	31	146.6 (94.5)	31	-18.76 (-29.6, -7.9)
Week 156	5	128.5 (27.1)	5	-19.95 (-49.6, 9.7)
Week 164	2	102.0 (26.9)	2	-38.40 (-181.9, -105.1)

CI, confidence interval; SD, standard deviation
Data are through 30 November 2011.
Source: ISIS 301012-CS6 CSR Addendum, Table 14.2.1a

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety Summary

See Section 1.2.2 Safety

7.1 Methods

This review primarily focuses on the four Phase 3 trials; these results are discussed in detail. Some discussions of safety issues include summaries of adverse events and other safety outcomes from the Phase 1 and 2 trials and the long-term safety data from the OLE trial ISIS 301012-CS6. In general, the 6 month results will be presented for the 4 trials combined (pooled analysis), as the designs were similar. As the ISIS 301012-CS5 trial data represents the indicated patient population for this submission, those data will be discussed separately as needed.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The four Phase 3 trials were randomized, double-blind, six-month, placebo-controlled parallel group trials and employed a 2:1 (active:placebo) randomization. Mipomersen was dosed at 200 mg subcutaneously (SC) once weekly for up to 26 weeks, and was added to stable, maximally-tolerated lipid-lowering therapy. The trials consisted of a ≤ 4-week screening period, 26 weeks of treatment, and a 24-week post-treatment follow-up period (unless individuals enrolled into the OLE trial ISIS 301012-CS6). The long half-life of mipomersen made it necessary to have an extended duration in the post-treatment follow-up period. Most Phase 3 trials had an option for individuals to enter OLE trial ISIS 301012-CS6 with up to 24 months of mipomersen treatment; subjects from ISIS 301012-CS12 and some sites in MIPO3500108 were not eligible.

The safety database cut off was 30 November 2011. For the ongoing OLE trial ISIS 301012-CS6, the cut-off date was 25 March 2011. As of the 25 March 2011 database cut-off date, only 3 HoFH individuals were continuing treatment in the

OLE trial. The applicant has provided a review of the safety data for these 3 HoFH individuals between the 2 database cut off dates.

7.1.2 Categorization of Adverse Events

Adverse events were classified using the standardized Medical Dictionary for Regulatory
Activities (MedDRA) (Version 13.0). The categories of AEs defined in the Mipomersen Core Statistical Analysis Plan (MCSAP) are:

- Pre-treatment Adverse Events (PTAEs)
- Treatment-emergent Adverse Events (TEAEs) – any AE occurring on or after the first dose of study treatment. TEAEs were subdivided into 2 categories:
    - On-treatment AEs (OTAEs) – the subset of TEAEs arising between first dose and the later of two weeks post-last dose and the PET date (defined as the laboratory assessment date closest to two weeks after the last dose)
    - After-treatment Adverse Events (ATAEs) – the subset of TEAEs that arose after the later of two weeks post-last dose and the PET date (defined as the laboratory assessment date closest to two weeks after the last dose)

Pooled data analyses were used to summarize OTAEs. The primary study with substantive ATAEs is ISIS 301012-CS12 in which all patients, regardless of treatment group, have post-treatment follow-up. Patients in ISIS 301012-CS12 were not eligible to enroll in the long- term OLE ISIS 301012-CS6. In ISIS 301012-CS6, TEAEs were defined as AEs with start dates / times on or after the date / time of the first dose of mipomersen.

Analyses of Flu-like Symptoms and Injection Site Reactions

1. Flu-like Symptoms: The following MedDRA preferred terms were determined to be flu-like symptoms: Influenza like illness, Pyrexia, Chills, Myalgia, Arthralgia, Malaise, and Fatigue. The number and percent of patients with OTAEs in this list, whose OTAEs were determined to have started within two days after an injection, were tabulated overall (i.e., having any one of the above events) and by preferred term for each treatment group.

2. Injection Site Reactions (ISRs): The following MedDRA terms were determined to represent ISRs to the study treatment: Injection and infusion site reactions, Injection Site Reactions, Injection site recall reaction, Injection site discoloration The number and percent of patients with OTAEs in the above high level terms and preferred terms were tabulated

overall (i.e., having any one of the above events) and by preferred term for each treatment group.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The four Phase 3 trials had a similar trial design. They were all randomized, double-blind, six-month, placebo-controlled parallel group trials which used 2:1 (active:placebo) randomization and a mipomersen dose of 200 mg subcutaneously (SC) once weekly added to stable, maximally-tolerated lipid-lowering therapy. Therefore, it is appropriate to pool these 4 trials for assessments of safety.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

7.2.1.1 Patient Population Exposure to Mipomersen

As of the cutoff date of this NDA (30 March 2012), a total of 811 subjects have been exposed to mipomersen via the SC, IV, and/or oral administration routes; 749 subjects have been exposed to mipomersen via the SC administration route.

A total of 243 individuals were exposed to mipomersen at 200 mg/week for at least 6 months, 113 individuals were exposed for at least 12 months, 75 individuals were exposed for at least 18 months, and 54 individuals were exposed for at least 24 months.

The table below summarizes mipomersen exposure for all subjects who received any SC mipomersen doses (mg/week) in the four Phase 3, six Phase 2, eight Phase 1, and two OLE trials, both overall and by treatment duration intervals.

Table 18. Exposure by Time Interval to Subcutaneous Mipomersen

Duration (Months)	Dose (mg/week)						Total (Any Dose)*
	30 or 50	100	200	300	400	800	
	(n)	(n)	(n)	(n)	(n)	(n)	(n)
0-3	39	38	274	36	46	17	435
>3-6	0	1	139	3	0	0	138
>6-12	0	1	69	0	0	0	66
>12-18	0	3	30	0	0	0	31
>18	0	0	74	0	0	0	79
Total (Any Duration)	39	43	586	39	46	17	749

Source: NDA 203568, ISS Statistical Table 2
Individuals were summarized according to the planned weekly dose. Individuals weighing <50 kg and treatment with 160 mg/week were included in the 200 mg/week group. Subjects treated with 30 mg QD or 70 mg 3 times weekly were also included in the 200 mg/week group.
*The total (any dose) column is independent of dose and represents the summary of each patient's total duration (months) exposed to mipomersen. If a patient appeared in more than 1 dose category
(mg/week) for a given duration (months), he/she was counted only once for the total duration of exposure at any dose.

Exposure in the HoFH Population:
A total of 41 individuals with HoFH were exposed to mipomersen at 200 mg/week for at least 6 months, and 25 individuals with HoFH were exposed for at least 12 months. Seven individuals (18.4%) with HoFH from ISIS 301012-CS5 received treatment for 0 to 6 months; 14 individuals (36.8%) received treatment for >6 to 12 months; 7 individuals (18.4%) received treatment for >12 to 18 months; 6 individuals (15.8%) received treatment for >18 to 24 months; and 4 individuals (10.5%) received treatment for >24 months. Three HoFH individuals (Subjects 1523-6120, 1523-6051, and 1523-6054) remained on treatment in OLE trial ISIS 301012-CS6. The overall exposure in these three individuals during the evaluable treatment period, including exposure in the index trial, was 680, 969, and 968 days, respectively.

Exposure for the Open-label Treatment Extension Trial (ISIS 301012-CS6) - All Individuals:
For the 141 individuals in ISIS 301012-CS6 (as of 30 March 2012), the mean length of study treatment, including exposure to mipomersen in the index study, was 19.8 months and the median was 18.2 months. A total of 17 individuals (12.1%) received treatment for 0 to 6 months, 27 individuals (19.1%) received treatment >6 to 12 months, 23 individuals (16.3%) received treatment for >12 to 18 months, 20 individuals (14.2%) received treatment for >18 to 24 months, 17 individuals (12.1%) received treatment for >24 to 30 months, 26 individuals

(18.4%) received treatment for >30 to 36 months, and 11 individuals (7.8%) received treatment for >36 months.

Fifty (35.5%) individuals, seven of which were individuals with HoFH, required a dose adjustment (a dose decrease or dose interruption) during the trial, most commonly due to AEs such as alanine aminotransferase (ALT) increased or aspartate aminotransferase (AST) increased.

Exposure for Pooled Phase 3 Placebo-Controlled Trials
A summary of exposure by trial for the pivotal trial (ISIS 301012-CS5) and the supportive trials (MIPO3500108, ISIS 301012-CS7, and ISIS 301012-CS12) is presented below.

Table 19. Exposure in Pivotal and Supportive Trials

	ISIS 301012-CS5		MIPO3500108		ISIS 301012-CS7		ISIS 301012-CS12	
Statistic	**Placebo (N=17)**	**Mipo (N=34)**	**Placebo (N=19)**	**Mipo (N=39)**	**Placebo (N=41)**	**Mipo (N=83)**	**Placebo (N=52)**	**Mipo (N=105)**
Length of Trial Treatment (days) [a]								
n	17	34	19	39	41	83	52	105
Mean (SD)	176.2 (0.4)	158.8 (40.2)	166.8 (36.8)	147.7 (53.2)	175.9 (0.7)	162.7 (36.8)	158.9 (43.8)	128.2 (63.0)
Median	176	176	176	176	176	176	176	174
Min, Max	176, 177	22, 178	15, 176	1, 190	174, 177	15, 181	8, 183	1, 185

Source: NDA 203568, Module 5: Table 5-5, ISS Statistical Table 3.1.1S
(a): Length of trial treatment is defined to be (date of last dose) - (date of first dose) + 1.
SD = standard deviation; Max = maximum; Min = minimum

Demographics are discussed in Section 6.1.2.

7.2.2 Explorations for Dose Response

All Phase 3 trials used a 200 mg dose administered subcutaneously every week.

7.2.3 Special Animal and/or In Vitro Testing

None.

7.2.4 Routine Clinical Testing

The following laboratory tests were analyzed depending on data collection for the individual trials:

- Chemistry: alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, bicarbonate, bilirubin (total, direct, and indirect), blood urea nitrogen (BUN), calcium, chloride, creatinine, eGFR (MDRD), glucose, lactate dehydrogenase (LDH), phosphorus, potassium, sodium, uric acid, total protein, globulin, creatinine phosphokinease (CPK), and HbA1c (only collected at baseline and over time in ISIS 301012-CS12 and MIPO3500108).
- Hematology: hematocrit, haemoglobin, MCV, MCH, MCHC, platelets, red blood cells (RBCs), white blood cells (WBCs), and WBC differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils)
- Coagulation: prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR).
- Cardiovascular risk markers: hsCRP. For the Phase 3 placebo-controlled studies, hsCRP changes were further evaluated via a shift table from baseline to Week 28/ET (≤ 3 vs. >3 mg/L) for each treatment group.
- Inflammatory markers – Complement (C3) and erythrocyte sedimentation rate data were pooled, as available; to the degree that they were available, other inflammatory markers (e.g., IL6) were addressed in particular studies
- IgG
- Urinalysis: urobilinogen, creatinine, total protein, urine protein/creatinine ratio, microalbumin, urine albumin/creatinine ratio, β2-microglobulin

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to Section 4.4 Clinical Pharmacology.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Refer to Section 2.4: Important Safety Issues With Consideration to Related Drugs

7.3 Major Safety Results

7.3.1 Deaths

Table 20. Deaths in Mipomersen Trials as of 30 November 2011

Patient ID (Study Number)	MedDRA PT resulting in Fatal Outcome	Treatment Group	Days Since First Study Drug Dose	Days Since Final Study Drug Dose
1681-2132 (ISIS 301012-CS12)	Acute hepatic failure	Mipomersen 200 mg SC weekly	325 days	148 days
3002-1027 (MIPO3500108)	Acute myocardial infarction	Mipomersen 200 mg SC weekly	205 days	29 days
1525-6001 (ISIS 301012-CS6; index trial ISIS 301012-CS5)	Myocardial infarction	Mipomersen 200 mg SC weekly	434 days after starting mipomersen in this trial and 630 days after receiving first dose of mipomersen in his index trial	77 days
1547-1420 (ISIS 301012-CS12)	Acute myocardial infarction; Cardiogenic shock	Placebo	112 days	6 days

Source: NDA 203568; CSR Section 12.3: ISIS 301012-CS6, MIPO3500108, ISIS 301012-CS12
MedDRA = Medical Dictionary for Regulatory Activities; SOC = system organ class; PT = preferred term; SC =subcutaneous

The narratives of individuals who died during the clinical development program are summarized in Section 9.4.

7.3.2 Nonfatal Serious Adverse Events

7.3.2.1 Phase 1

ISIS 301012-CS101: One subject experienced an SAE, Diverticulitis

ISIS 301012-CS301: One subject experienced an SAE during the follow-up period (multiple trauma from an accident).

ISIS 301012-CS1: One subject experienced an SAE, Gastric cancer.

7.3.2.2 Phase 2

Trial ISIS 301012-CS3: One (12.5%) subject in the mipomersen 200 mg QOW group had an SAE (Encephalitis), which led to discontinuation from the trial.

ISIS 301012-CS4: In the 5-week cohorts, 1 patient in the mipomersen 400 mg group had an SAE (hospitalized for Pyrexia). Patient 1498-5011 was a 60-year-old female who experienced pyrexia associated with nausea and influenza-like symptoms following her initial 400 mg SC dose of mipomersen. While the patient's temperature was only moderately elevated (39.0°C), she was hospitalized for precautionary monitoring by the Investigator and study drug was permanently discontinued. This event led to discontinuation from the trial.

In the 5-week cohorts during the after-treatment period, one patient in the mipomersen 200 mg group had an SAE of Lumbar spinal stenosis and one patient in the mipomersen 400 mg group had an SAE of Myocardial infarction.

ISIS 301012-CS8: This trial was an open-label, dose-escalation trial in individuals with homozygous FH on stable concomitant lipid-lowering therapy. One patient in the mipomersen 200 mg group in the 6-week cohorts had a post-treatment SAE of Acute coronary syndrome.

Trial ISIS 301012-CS9 was a randomized, double-blind, placebo-controlled, dose-escalation, multicenter trial in HeFH or severe hypercholesterolemia (defined as LDL-C >200 mg/dL) individuals on stable concomitant lipid-lowering therapy who did not meet their LDL-C treatment target. One patient in the mipomersen 300 mg group in the 13-week cohort had an SAE (Syncope).

Trial ISIS 301012-CS17 was an open-label treatment extension trial of mipomersen in individuals with FH on concomitant lipid-lowering therapy who completed dosing in trial ISIS 301012-CS8 or ISIS 301012-CS9 at a site in the US with an acceptable safety profile, per Investigator judgment. Trial ISIS 301012 CS17 consisted of a ≤2 week screening period, up to 3 years of treatment, and a 24 week post treatment follow-up period. SAEs included Angina pectoris, CADx3; inguinal hernia; non-cardiac chest pain x3 in the same individual; ALT increase; and malignant melanoma. Patient 1503-1214 in Trial ISIS 301012-CS17 was a 44-year-old male who experienced an ALT >5 x ULN 358 days after starting mipomersen study treatment. Study drug was permanently discontinued.

Trial ISIS 301012-CS19 was a randomized, double-blind, placebo-controlled trial to assess the safety and efficacy of mipomersen in high-risk statin-intolerant individuals with hypercholesterolemia. This trial consisted of a ≤3-week screening period, 26 weeks of treatment, and a 24-week post-treatment follow-up period.

One patient in the placebo group had an on-treatment SAE of Acute myocardial infarction, which led to discontinuation of study drug. One patient in the mipomersen group had an SAE of Coronary artery restenosis during the post-treatment follow-up period.

7.3.2.3 Phase 3

According to Genzyme's Global Patient Safety and Risk Management Database, as of 30 November 2011, a total 122 SAEs have been reported in 83 individuals. The most frequently reported SAEs were classified as Cardiac Disorders, with 48 events occurring in 36 individuals (30 mipomersen; 6 placebo). Thirty-one of the 36 individuals with Cardiac Disorders SAEs (37 events) had histories of CAD including 25 who had undergone prior coronary artery intervention. Five of the individuals with Cardiac Disorders SAEs (7 events) did not have histories of CAD.

Pooled 6-month Phase 3 Trials: As shown in the following table, 8% (21/261) of mipomersen-treated individuals and 5.4% (7/129) of placebo-treated individuals experienced at least one SAE. The most frequently reported SAEs were the Cardiac Disorders, occurring in 3.8% (10/261) of mipomersen-treated individuals and 3.1% (4/129) of placebo-treated individuals. The high number of cardiac events in these trials of 6 months duration likely reflects the increased underlying cardiovascular risk of the population. The percentage of CV events is similar between the mipomersen- and placebo-treated groups. The narrative of the one patient who experienced the SAEs of ALT and AST elevation and hepatic steatosis is summarized below:

- Patient 4000-1052 (MIPO3500108): 63-year-old female with HeFH who experienced an increase in ALT 3.9 x ULN (162 U/L, normal reference range 6-41 U/L), on day 57 following administration of 9 doses of mipomersen The patient's AST was elevated at 73 U/L (normal reference range 9-34 U/L) and there was a slight elevation in lactate dehydrogenase (230, reference range 113-226 U/L) other laboratory measures on that day, including alkaline phosphatase, creatine kinase, total bilirubin, albumin, and coagulation parameters (INR, PT, PTT), were normal. Study drug was permanently discontinued due to the increase in ALT. Screening ALT and AST values for this patient were normal, 30 and 25 U/L respectively. Review of lab data showed that the patient first had an increase after the second injection of mipomersen (study day 15) at which time her ALT was 49 U/L with a normal AST of 24 U/L. The highest ALT value reached was 201 U/L (4.9xULN), 100 days after her first dose and 44 days after her last dose of mipomersen study drug. In addition, 93 days after starting mipomersen study drug (23 days after last dose) MRI showed increased hepatosteatosis as compared to the examination performed prior to study randomization. An initial MRI scan showed incipient steatosis, malrotation of right kidney with cortical cyst, status post cholecystectomy, and diastasis of straight abdominal muscles. No value was assigned to the degree of steatosis seen. The liver and spleen were not enlarged, the gallbladder was missing, and no other

findings of note were made. The same local radiologist reviewed the second MRI (93 days after starting mipomersen study treatment; 23 days after last dose). Conclusions of that review were as follows: hepatomegaly and marked hepatosteatosis with changes from the previous examination and malrotation of the right kidney with cortical cyst (no change from previous MRI). The patient was started on treatment with Silymarin (a flavonoid) due to the hepatosteatosis and elevated ALT and AST and phospholipids essentialia. This patient also experienced an injection site reaction (erythema) and flu-like symptoms at the time of the first injection which lasted for one day. Other investigations, including hepatitis B surface antigen and hepatitis C antibody titers, remained non-reactive. HIV screening was also negative. Total bilirubin, albumin, alkaline phosphatase, hsCRP, and coagulation parameters (aPTT, PT, and INR) remained within normal limits. Approximately 8 months after the ALT elevation SAE, the ALT and AST values had declined to less than 1.2 times the upper limit of normal and the patient was considered recovered without sequelae from the events hepatosteatosis and elevated ALT and AST.

ISIS 301012-CS5: As shown in the table below, three individuals had SAEs during the trial. Two individuals were in the mipomersen group and the reported SAE were acute coronary syndrome and ankle fracture. One individual in the placebo group had an SAE of nephrolithiasis. In addition, one individual (Patient 1523-8309) in the mipomersen group had a severe SAE of Cervical intraepithelial neoplasia III that was not recorded in CS5 because the Investigator was not made aware of the event until after the patient had signed informed consent for the open-label extension trial (ISIS 301012-CS6). The event is captured in the ISIS 301012-CS6 database.

Table 21. On-Treatment Serious Adverse Events by System Organ Class and Preferred Term for CS5 and the Four Pooled Phase 3 Placebo-Controlled Trials

System Organ Class Preferred Term	CS5 Placebo (N=17)	CS5 Mipo (N=34)	TOTAL Placebo (N=129)	TOTAL Mipo (N=261)
Any AE, n (%)	**1 (5.9)**	**2 (5.9)**	**7 (5.4)**	**21 (8.0)**
Cardiac disorders	**0**	**1 (2.9)**	**4 (3.1)**	**10 (3.8)**
Acute myocardial infarction	0	0	1 (0.8)	2 (0.8)
Angina pectoris	0	0	0 (0.0)	3 (1.1)
Acute coronary syndrome	0	1 (2.9)	1 (0.8)	1 (0.4)
Angina unstable	0	0	0 (0.0)	2 (0.8)
Coronary artery disease	0	0	1 (0.8)	1 (0.4)
Cardiac failure	0	0	0 (0.0)	1 (0.4)
Cardiogenic shock	0	0	1 (0.8)	0 (0.0)
Prinzmetal angina	0	0	0 (0.0)	1 (0.4)

System Organ Class Preferred Term	CS5 Placebo (N=17)	CS5 Mipo (N=34)	TOTAL Placebo (N=129)	TOTAL Mipo (N=261)
Supraventricular tachycardia	0	0	1 (0.8)	0 (0.0)
General disorders and administration site conditions	**0**	**0**	**1 (0.8)**	**4 (1.5)**
Non-cardiac chest pain	0	0	1 (0.8)	2 (0.8)
Chest pain	0	0	0 (0.0)	1 (0.4)
Device malfunction	0	0	0 (0.0)	1 (0.4)
Hepatobiliary disorders	**0**	**0**	**0 (0.0)**	**1 (0.4)**
Hepatic steatosis	0	0	0 (0.0)	1 (0.4)
Injury, poisoning and procedural complications	**0**	**1 (2.9)**	**0 (0.0)**	**1 (0.4)**
Ankle fracture	0	1 (2.9)	0 (0.0)	1 (0.4)
Investigations	**0**	**0**	**1 (0.8)**	**1 (0.4)**
Alanine aminotransferase increased	0	0	0 (0.0)	1 (0.4)
Aspartate aminotransferase increased	0	0	0 (0.0)	1 (0.4)
Electrocardiogram abnormal	0	0	1 (0.8)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**0**	**0 (0.0)**	**2 (0.8)**
Basal cell carcinoma	0	0	0 (0.0)	1 (0.4)
Non-small cell lung cancer	0	0	0 (0.0)	1 (0.4)
Nervous system disorders	**0**	**0**	**0 (0.0)**	**1 (0.4)**
Hypoaesthesia	0	0	0 (0.0)	1 (0.4)
Renal and urinary disorders	**1 (5.9)**	**0**	**1 (0.8)**	**0 (0.0)**
Nephrolithiasis	1 (5.9)	0	1 (0.8)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	**0**	**0**	**1 (0.8)**	**1 (0.4)**
Dyspnoea exertional	0	0	1 (0.8)	0 (0.0)
Pulmonary embolism	0	0	0 (0.0)	1 (0.4)
Vascular disorders	**0**	**0**	**0 (0.0)**	**1 (0.4)**
Hypertension	0	0	0 (0.0)	1 (0.4)

Source: NDA 203568: ISS Statistical Table 3.3.2.1.1, CSR CS5 Data Listing 16.2.7.5.
On-Treatment adverse events are defined as adverse events that started during the treatment period. The treatment period spans the time during which the study treatment is administered until the later of the primary efficacy timepoint (PET, date of the efficacy assessment closest to 14 days beyond the last study medication date) and 14 days beyond the last study medication date.
If a patient had more than one event within a particular system organ class or preferred term, he/she is counted only once for that system organ class or preferred term.

OLE Trial CS6: 33 (23.4%) individuals (all receiving mipomersen) experienced a treatment-emergent SAE through the data cut-off of 30 March 2012. Six of these events occurring in ISIS 301012-CS6 occurred in individuals with HoFH. One of

these was the patient with Ankle Fracture, which was experienced in ISIS 301012-CS5 but was included in the ISIS 301012-CS6 analysis. SAE preferred terms in CS6 include aortic valve stenosis, syncope, atrial fibrillation, coronary artery disease, femoral artery occlusion, aortic stenosis, contrast media allergy, peripheral artery dissection, myocardial infarction, angina unstable, chest pain, angina pectoris, glomerulonephritis membranous and biliary colic.

The SAE of glomerulonephritis membranous is summarized in Appendix 9.4.7 and the SAE of biliary colic is summarized below:

- Patient 1523-6053 (previously enrolled in ISIS 301012-CS6): 52-year-old female with HoFH who was admitted to the hospital due to biliary colic 362 days after starting mipomersen treatment. She also experienced elevated ALT (>11.9xULN) and AST (>18.1xULN) during that hospitalization. She was diagnosed with cholecystolithiasis and was discharged uneventfully with no specific follow-up plans described. Study drug was permanently discontinued. Ths patient had also experienced an AE of angina pectoris earlier in her course that required coronary angioplasty and 2 stent placements.

For the ongoing trials, during the period after the data cut-off date of 30 Nov 2011 through 30 December 2011, no new SAEs were received.

7.3.3 Dropouts and/or Discontinuations

7.3.3.1 Phase 1

ISIS 301012-CS1: Three subjects discontinued the trial due to TEAEs: 1 subject each in the 200 mg and 400 mg due to mild hepatic enzyme elevations and 1 subject in the 400 mg due to mild neutrophilia accompanied by moderate vomiting.

MIPO3200309: Three subjects discontinued study drug due to a TEAE (1 subject in the mipomersen 30 mg QD group with Asthenia and Atrial flutter; 1 subject in the mipomersen 70 mg TIW group with Gastroesophageal reflux disease; and 1 subject in the mipomersen 70 mg TIW group with Muscle tightness, AST increased, LDH increased, CPK increased, and ALT increased. All of these TEAEs resolved.

7.3.3.2 Phase 2

Trial ISIS 301012-CS3: One subject in the mipomersen 200 mg QOW group had an SAE of encephalitis, which led to discontinuation from the trial. Four subjects in the mipomersen 400 mg QW group discontinued from the trial due to a TEAE (Hepatic enzyme increased).

ISIS 301012-CS4: In the 5-week cohorts, 1 patient in the mipomersen 400 mg group had an SAE of pyrexia which led to discontinuation from the trial. One patient in the mipomersen 400 mg treatment group discontinued from the trial due to an AE (Pneumonia).

Trial ISIS 301012-CS9: Three individuals in the 6-week cohorts discontinued study drug due to an AE: 1 patient in the mipomersen 50 mg group (3 events of Injection site inflammation), 1 patient in the mipomersen 200 mg group (Influenza like illness), and 1 patient in the mipomersen 200 mg group (Erythema, 2 events of Arthralgia, and Influenza). One patient in the mipomersen 300 mg group in the 13-week cohort discontinued study drug due to an AE (reoccurrence of Proteinuria).

Trial ISIS 301012-CS10 was a randomized, double-blind, placebo-controlled trial to measure the effect of treatment with mipomersen on liver TG content in individuals with varying degrees of hyperlipidemia and risk for hepatic steatosis. One patient discontinued study drug due to an AE. Patient 1497-5003, in the mipomersen group from Cohort E, discontinued study drug due to Influenza like illness.

Trial ISIS 301012-CS19 : Four (19.0%) individuals in the mipomersen group discontinued study drug due to an on-treatment AE (1 patient with Malaise, 1 patient with Influenza-like illness, 1 patient with Bone disorder and Myalgia, and 1 patient with Liver function test abnormal). Two (16.7%) individuals in the placebo group discontinued study drug due to an on-treatment AE (1 patient with Acute myocardial infarction and 1 patient with Diarrhea).

7.3.3.3 Phase 3

Adverse events that led to early treatment discontinuation by SOC and preferred term for CS5 and the pooled Phase 3 placebo-controlled, 6-month duration clinical trials are presented in the following table. In the pooled Phase 3 population, 18.0% (47/261) of mipomersen-treated individuals and 2.3% (3/129) of placebo-treated individuals withdrew due to AEs. In the mipomersen individuals who discontinued due to an AE, injection site reactions (ISRs), flu-like symptoms (FLS), and abnormal hepatic tranaminases were the major reasons.

The most common preferred terms resulting in discontinuation in the mipomersen treatment group were Injection site pain (3.1%; 8/261 individuals), Injection site erythema (2.3%; 6/261 individuals), Injection site pruritus (2.3%; 6/261 individuals), Fatigue (1.1%, 3/261 individuals) and Chills (1.1%, 3/261 individuals), which is within the General Disorders and Administration Site Conditions SOC (8.0% [21/261] of mipomersen-treated individuals versus 0.8%

[1/129] of placebo-treated individuals). The Investigations SOC also had a high number of discontinuations (6.1% [16/261] of mipomersen-treated individuals versus 0.8% [1/129] of placebo-treated individuals) primarily due to the following preferred terms in the mipomersen group: ALT increased (3.4%, 9/261), AST increased (2.3%, 6/261), and Liver function test abnormal (1.5%, 4/261). In the Hepatobiliary SOC, 3 individuals in the mipomersen group discontinued due to hepatic steatosis (1.1%) and 1 (0.4%) each for hepatic function abnormal and liver tenderness.

Discontinuations due to AEs were less common in ISIS 301012-CS5: 11.8% [4/34] of mipomersen-treated individuals and 0% of placebo-treated individuals. The AEs that most commonly leading to discontinuation in these individuals with HoFH (Rash, AST increase, Injection site pruritus, and Injection site pain) were similar to results in the pooled Phase 3 population. Early treatment discontinuations due to an AE were most frequent in the mipomersen group of ISIS 301012-CS12 (24.8%) vs placebo (3.8%).

In OLE trial ISIS 301012-CS6, 46.1% (65/141) of individuals discontinued treatment due to an AE over the up to 2 years of the trial. Four (2.8%) individuals discontinued treatment with study drug due to an SAE: Patient 1506-6130 due to Glomerulonephritis membranous, Patient 1523-6053 due to Biliary colic and Angina pectoris, Patient 1575-6073 due to Dementia Alzheimer's type, and Patient 1578-6117 due to Alcoholism. As in the pooled Phase 3 population, common AEs leading to treatment discontinuations were increases in ALT, ISRs and FLS. In the individuals with HoFH from ISIS 301012-CS6, 47.4% (18/38) individuals discontinued due to an AE. Three HoFH individuals were continuing treatment with mipomersen as of 30 November 2011 from those reported in the ISIS 301012-CS6 subset HoFH CSR. One patient (Patient 1500-6028) started Year 3 of dosing, but discontinued treatment due to the occurrence of an AE (Depression).

Reviewer comment: As mentioned previously, the high discontinuation rates from adverse events are problematic for a therapeutic agent that needs to be taken chronically.

Table 22. On-Treatment Adverse Events the Led to Discontinuation by System Organ Class and Preferred Term for ISIS 301012-CS5 and Pooled Phase 3 Placebo-Controlled Trials (6-month duration)

System Organ Class Preferred Term	CS5 Placebo (N=17) n (%)	CS5 Mipo (N=34) n (%)	TOTAL Placebo (N=129) n (%)	TOTAL Mipo (N=261) n (%)
Any AE, n (%)	**0**	**4 (11.8)**	**3 (2.3)**	**47 (18.0)**

System Organ Class Preferred Term	CS5 Placebo (N=17) n (%)	CS5 Mipo (N=34) n (%)	TOTAL Placebo (N=129) n (%)	TOTAL Mipo (N=261) n (%)
Cardiac disorders	**0**	**0**	**1 (0.8)**	**1 (0.4)**
Acute myocardial infarction	0	0	1 (0.8)	0 (0.0)
Cardiogenic shock	0	0	1 (0.8)	0 (0.0)
Palpitations	0	0	0 (0.0)	1 (0.4)
Gastrointestinal disorders	**0**	**0**	**0 (0.0)**	**6 (2.3)**
Abdominal pain upper	0	0	0 (0.0)	2 (0.8)
Constipation	0		0 (0.0)	2 (0.8)
Nausea	0	0	0 (0.0)	2 (0.8)
Vomiting	0	0	0 (0.0)	1 (0.4)
General disorders and administration site conditions	**0**	**2 (5.9)**	**1 (0.8)**	**21 (8.0)**
Injection site pain	0	1 (2.9)	0 (0.0)	8 (3.1)
Injection site erythema	0	0	0 (0.0)	6 (2.3)
Injection site pruritus	0	1 (2.9)	0 (0.0)	6 (2.3)
Fatigue	0	0	1 (0.8)	3 (1.1)
Chills	0	0	0 (0.0)	3 (1.1)
Injection site discoloration	0	0	0 (0.0)	3 (1.1)
Injection site swelling	0	0	0 (0.0)	3 (1.1)
Influenza like illness	0	0	0 (0.0)	2 (0.8)
Chest pain	0	0	0 (0.0)	1 (0.4)
Injection site hematoma	0	0	0 (0.0)	1 (0.4)
Injection site induration	0	0	0 (0.0)	1 (0.4)
Injection site rash	0	0	0 (0.0)	1 (0.4)
Injection site recall reaction	0	0	0 (0.0)	1 (0.4)
Injection site urticaria	0	0	0 (0.0)	1 (0.4)
Injection site warmth	0	0	0 (0.0)	1 (0.4)
Non-cardiac chest pain	0	0	0 (0.0)	1 (0.4)
Pain	0	0	0 (0.0)	1 (0.4)
Pyrexia	0	0	0 (0.0)	1 (0.4)
Hepatobiliary disorders	**0**	**0**	**0 (0.0)**	**5 (1.9)**
Hepatic steatosis	0	0	0 (0.0)	3 (1.1)
Hepatic function abnormal	0	0	0 (0.0)	1 (0.4)
Liver tenderness	0	0	0 (0.0)	1 (0.4)
Infections and infestations	**0**	**0**	**0 (0.0)**	**1 (0.4)**
Influenza	0	0	0 (0.0)	1 (0.4)
Investigations	**0**	**1 (2.9)**	**1 (0.8)**	**16 (6.1)**

System Organ Class Preferred Term	CS5 Placebo (N=17) n (%)	CS5 Mipo (N=34) n (%)	TOTAL Placebo (N=129) n (%)	TOTAL Mipo (N=261) n (%)
Alanine aminotransferase increased	0	0	0 (0.0)	9 (3.4)
Aspartate aminotransferase increased	0	0	0 (0.0)	6 (2.3)
Liver function test abnormal	0	0	0 (0.0)	4 (1.5)
Hepatic enzyme increased	0	0	0 (0.0)	2 (0.8)
Blood creatinine increased	0	0	1 (0.8)	0 (0.0)
Blood urea increased	0	0	1 (0.8)	0 (0.0)
Platelet count decreased	0	0	0 (0.0)	1 (0.4)
Musculoskeletal and connective tissue disorders	**0**	**0**	**0 (0.0)**	**4 (1.5)**
Myalgia	0	0	0 (0.0)	2 (0.8)
Pain in extremity	0	0	0 (0.0)	2 (0.8)
Musculoskeletal pain	0	0	0 (0.0)	1 (0.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**0**	**0 (0.0)**	**1 (0.4)**
Non-small cell lung cancer	0	0	0 (0.0)	1 (0.4)
Nervous system disorders	**0**	**0**	**1 (0.8)**	**3 (1.1)**
Lethargy	0	0	0 (0.0)	2 (0.8)
Headache	0	0	1 (0.8)	0 (0.0)
Presyncope	0	0	0 (0.0)	1 (0.4)
Restless legs syndrome	0	0	1 (0.8)	0 (0.0)
Psychiatric disorders	**0**	**0**	**0 (0.0)**	**1 (0.4)**
Depression	0	0	0 (0.0)	1 (0.4)
Renal and urinary disorders	**0**	**0**	**0 (0.0)**	**1 (0.4)**
Chromaturia	0	0	0 (0.0)	1 (0.4)
Skin and subcutaneous tissue disorders	**0**	**1 (2.9)**	**0 (0.0)**	**4 (1.5)**
Rash	0	1 (2.9)	0 (0.0)	2 (0.8)
Pruritus	0	0	0 (0.0)	1 (0.4)
Urticaria	0	0	0 (0.0)	1 (0.4)

Source: ISS Statistical Table 3.3.3.1.1 and 3.3.3.1.1S
On-treatment adverse events are defined as adverse events that started during the treatment period. The treatment period spans the time during which the study treatment is administered until the later of the primary efficacy timepoint (PET, date of the efficacy assessment closest to 14 days beyond the last study medication date) and 14 days beyond the last study medication date.
If a patient had more than 1 event within a particular system organ class or preferred term, he/she is counted only once for that system organ class or preferred term.

7.3.4 Significant Adverse Events

Refer to Section 7.3.5.

7.3.5 Submission Specific Primary Safety Concerns

7.3.5.1 Hepatic Issues

Mild hepatic toxicity (increases in liver weights and serum transaminase and lymphohistiocytic infiltrates) was noted in mice treated with ≥ 25 mg/kg/week of mipomersen. There was no liver fibrosis at any dose or duration of treatment (up to 2 years in rats and 1 year in monkeys) in either species. There were no increases in ALT and no hepatic or intestinal steatosis in the toxicology studies in rodent or monkey.

The Phase 3 trials included exclusion criteria for documented history of hepatic disease, liver cirrhosis, or liver steatosis (ISIS 301012-CS5), history of significant hepatic disease (ISIS 301012-CS7), or clinically significant hepatic disease or Gilbert's syndrome (ISIS 301012-CS12, MIPO3500108). The Phase 3 trials also included exclusions for abnormal laboratory test results at screening (ALT > 1.5xULN in all, AST > 1.5 xULN in CS5 and CS12, TBili >ULN in Mipo108, CS7 and CS12). All trials included testing at screening for hepatitis B virus and hepatitis C virus. ALT, AST, alkaline phosphatase, total bilirubin (and direct bilirubin if total bilirubin was abnormal), and gamma-glutamyl transpeptidase were evaluated approximately every 4 to 5 weeks during treatment, with intervals up to 2 months after longer duration of therapy in the OLE trials. Hepatic fat was assessed by MRI (or CT if MRI was contraindicated) at baseline and when patients met safety monitoring rules for ALT/AST. ISIS 301012-CS7 and ISIS 301012-CS12 included follow-up assessments of hepatic fat by MRI at Week 28 or Early Termination. In ISIS 301012-CS12, MRI assessment was also performed the end of follow-up (24 weeks after the last dose of study drug, Week 50). An amendment to OLE trial ISIS 301012-CS6 included assessments of hepatic fat by MRI at approximately 6 month intervals and "for-cause" in patients who met safety monitoring rules for ALT/AST.

In the Phase 3 trials and OLE trial ISIS 301012-CS6, patients who developed ALT or AST ≥ 3 x ULN should have been assessed for other potential causes of transaminase elevations, and monitored with weekly and then biweekly visits and laboratory assessments. The following evaluations were to be performed: history of symptoms and prior and concurrent diseases; history for concomitant drug use, alcohol use, recreational drug use, and special diets; history for exposure to environmental chemical agents and travel; serology for viral hepatitis; serology for autoimmune hepatitis; liver MRI, and (except for ISIS 301012-CS5)

measurement of serum albumin, PT or INR, and activated partial thromboplastin time (aPTT or PTT). Repetition of these evaluations was to be considered if ALT and/or AST were ≥ 5 x ULN. All Phase 3 trials included hepatic stopping rules, summarized in the table below.

Table 23. Stopping Rules for Liver Chemistry Elevations for Pooled Phase 3 Placebo-Controlled Trials

Trial	AST or ALT, confirmed	Consecutive AST or ALT over 7 days	AST or ALT ≥ 3 x ULN with Elevation in Total Bilirubin
ISIS 301012-CS5	≥ 5 x ULN	N/A	> ULN
MIPO3500108	≥ 8 x ULN	≥ 5 x ULN	≥ 1.5 x ULN
ISIS 301012-CS7	≥ 8 x ULN	≥ 5 x ULN	≥ 2 x ULN
ISIS 301012-CS12	≥ 8 x ULN	≥ 5 x ULN	≥ 1.5 x ULN
Source: NDA 203568: ISIS 301012-CS5 CSR; MIPO3500108 CSR; ISIS 301012-CS7 CSR; ISIS 301012-CS12 CSR			

7.3.5.1.1 Hepatic-Related Adverse Reactions

One individual in ISIS 301012-CS12 (Patient ID 1681-2132) had fulminant hepatic failure resulting in death 148 days after the patient's last dose of mipomersen. This case is discussed in Section 9.4.1.

As shown in the next table, the mipomersen group had a greater number of AEs related to elevations in serum transaminase levels and hepatic steatosis as compared to the placebo group.

For the individuals in the OLE trial CS6, AEs of ALT increased occurred in 18% of the total population and in 32% of the HoFH population. In the HoFH subgroup, 5 individuals discontinued treatment with mipomersen due to a TEAE related to liver enzyme elevations: Patients 1501-6021 (ALT increased), 1505-6002 (ALT increased and AST increased), 1501-6036 (ALT increased and AST increased), 1523-6053 (Hepatic enzyme increased), and 1536-6024 (ALT increased). One (2.6%) individual (Patient 1523-6053) had a moderate TEAE of Hepatomegaly; this individual also had elevations in ALT and AST and a TEAE of Hepatic enzyme increased.

For the entire CS6 population, 15 (10.6%) individuals had a TEAE of Hepatic steatosis. Seven of the 15 individuals (Patients 1505-6002, 1608-6131, 1578-6122, 1580-6144, 1589-6115, 1608- 6080, and 1622-6133) had corresponding elevations in ALT and/or AST. Six (4.3%) individuals had a TEAE of Hepatomegaly. Patient 1579-6088 and Patient 1608-6089 also each had a TEAE of Hepatic steatosis. Patient 1608-6089 had an average liver fat fraction >20%.

Patient 1590-6121 also had a TEAE of biliary cyst. Patient 1523-6053 also had elevations in ALT and AST, a TEAE of Hepatic enzyme increased (2 events), a TEAE of biliary colic, and a TAE of cholecystitis. Patient 1608-6080 also had elevations in ALT and a TEAE of Hepatic steatosis.

Table 24. Adverse Events Related to Liver Enzyme Elevations by System Organ Class and Preferred Term for ISIS 301012-CS5, the Pooled Phase 3 Placebo-Controlled Trials and ISIS 301012-CS6

System Organ Class Preferred Term	CS5 Placebo (N=17)	CS5 Mipo (N=34)	Pooled Phase 3 Placebo (N=129)	Pooled Phase 3 Mipo (N=261)	CS6-HoFH Mipo (N=38)	CS6-All Subjects Mipo (N=141)
Investigations, n (%)						
ALT increased	0	4 (11.8)	1 (0.8)	25 (9.6)	12 (31.6)	26 (18.4)
AST increased	1 (5.9)	4 (11.8)	3 (2.3)	16 (6.1)	11 (28.9)	22 (15.6)
Liver function test abnormal	0	0	1 (0.8)	14 (5.4)	0	3 (2.1)
Hepatic enzyme increased	1 (5.9)	0	1 (0.8)	9 (3.4)	1 (2.6)	6 (4.3)
Transaminases increased	0	0	0	0	0	1 (0.7)
Hepatobiliary disorders, n (%)						
Hyperbilirubinaemia	0	1 (2.9)	0	1 (0.4)	0	0
Hepatic steatosis	0	0	2 (1.6)	19 (7.3)	1 (2.6)	15 (10.6)
Hepatomegaly					1 (2.6)	6 (4.3)

Source: NDA 203568: ISS Statistical Tables 3.2.2.1 and 3.2.2.1S; ISIS 301012-CS6 subset HoFH CSR Table 12-9 and Addendum Table 14.3.1.8
On-Treatment adverse events are defined as adverse events that started during the treatment period. The treatment period spans the time during which the study treatment is administered until the later of the primary efficacy timepoint (PET, date of the efficacy assessment closest to 14 days beyond the last study medication date) and 14 days beyond the last study medication date.
If a patient had more than one event within a particular system organ class or preferred term, he/she is counted only once for that system organ class or preferred term.

7.3.5.1.2 Serum Transaminase Effects

Transaminase elevations occurred more frequently in the mipomersen-treated group. Across the pooled Phase 3 trials, 16.5% (43/261) of mipomersen-treated individuals as compared to one placebo-treated individual (0.8%; 1/129) had at least 1 result that was ≥ 3 x ULN during the treatment period. Thirty-six of 261 (13.8%) of mipomersen-treated individuals had increases in ALT and AST that met protocol-defined monitoring/safety rules for liver chemistry. Dosing with mipomersen was stopped for 5.4% (14/261) of these individuals.

In ISIS 301012-CS5, ALT increases 3xULN occurred in 4 of 34 (11.7%) individuals in the mipomersen group compared to none in the placebo group. For these 4 individuals (Patients 1501-8101, 1501-8417, 1523-8117, and 1536-8317), there were no significant elevations in bilirubin, INR, or PTT. For two of the individuals (Patients 1523-8117 and 1501-8417) there was either no or minimal increases in hepatic fat (2% to 6%, roughly within normal limits) as measured by MRI. Patients 1501-8417 continued mipomersen treatment in the open-label extension trial. A third individual (Patient 1536-8317) had persistent ALT increases 3xULN, with an increase in hepatic fat from an elevated baseline of 9.6% to 24.8% (Day 121), which returned to 6% by the end of follow-up (Day 345). This individual also had a notable decrease in LDL-C on mipomersen treatment (–71%; with a baseline LDL-C of ~200 mg/dL and an LDL-C of ~ 55 mg/dL by Week 13 which persisted until the end of treatment at Week 26 as detailed in Section 9.4.4). The fourth individual (Patient 1501-8101) had an increased ALT before dosing (>5x ULN) and again at Week 17. The investigator suggests this may be related to oral contraceptive use. This ALT level met the protocol-defined stopping rule, and dosing was stopped (MRI was not done). No cases of ALT levels ≥ 8 x ULN were noted and no patient met Hy's law (ALT increases ≥3 x ULN with concomitant elevations in total bilirubin ≥ 2 x ULN).
As summarized in the table below, a total of 8.4% (22/261) of mipomersen-treated individuals had ALT levels ≥ 3 x ULN on at least 2 consecutive occasions at least 7 days apart following initial dosing as compared to no placebo-treated individuals. Of note, all individuals with any elevation of ALT/AST ≥ 3 x ULN on at least 1 occasion were not always reported as AEs so the numbers of hepatic AEs related to transaminase elevations will be somewhat different than the transaminase elevation data. Section 9.4.4 contains narratives of some of the 22 mipomersen-treated patients that experienced ALT levels ≥3 x ULN on at least 2 consecutive occasions, at least 7 days apart.

In the 22 individuals with ALTs ≥ 3 x ULN on at least 2 consecutive occasions, 19 had a decrease in ALT to a value < 3 x ULN within the treatment period of the study. For these 19 individuals, the median time to a decrease in ALT < 3 x ULN was 77 days (IQR: 35, 133). The remaining three individuals had a decrease in ALT to a value < 3 x ULN in the post-treatment period. For these 22 individuals, mipomersen was discontinued because either the 26-week treatment period was over or they met a safety stopping criteria. Thus, all subjects had reductions in ALT off treatment. In general, when mipomersen therapy was stopped, ALT levels trended back to baseline values over a period of months. Of note, mipomersen has a terminal elimination half-life of approximately 1 to 2 months. Six individuals in the mipomersen group had ALTs ≥ 8 x ULN (peak ALTs ranged from 8.1 to 14.7 x ULN). The narratives and select laboratory values for these patients appear in Section 9.4.5.

Table 25. Hepatic Transaminase Levels in ISIS 301012-CS5 and the Pooled Phase 3 Placebo-Controlled Trials

Test	Incidence rate, n (%)	CS5 Placebo (N=17)	CS5 Mipo (N=34)	TOTAL Placebo (N=129)	TOTAL Mipo (N=261)
ALT maximum	> ULN and < 2 x ULN	7 (41.2)	12 (35.3)	42 (32.6)	95 (36.4)
	≥ 2 x ULN and < 3 x ULN	2 (11.8)	12 (35.3)	6 (4.7)	61 (23.4)
	≥ 3 x ULN and < 5 x ULN	0	1 (2.9)	1 (0.8)	31 (11.9)
	≥ 5 x ULN and < 10 x ULN	0	3 (8.8)	0 (0.0)	9 (3.4)
	≥ 10 x ULN and < 20 x ULN	0	0	0 (0.0)	3 (1.1)
	≥ 20 x ULN	0	0	0	0
	Total ≥ 3x ULN	**0**	**4 (12%)**	**1 (1%)**	**43 (16%)**
ALT	≥ 3 x ULN, two consecutive results (at least 7 days apart), n (%)	0	1 (2.9)	0 (0.0)	22 (8.4)
AST maximum	> ULN and < 2 x ULN	8 (47.1)	11 (32.4)	49 (38.0)	124 (47.5)
	≥ 2 x ULN and < 3 x ULN	1 (5.9)	3 (8.8)	4 (3.1)	27 (10.3)
	≥ 3 x ULN and < 5 x ULN	1 (5.9)	1 (2.9)	1 (0.8)	19 (7.3)
	≥ 5 x ULN and < 8 x ULN	0	1 (2.9)	0 (0.0)	4 (1.5)
	≥ 8 x ULN	0	0	0 (0.0)	3 (1.1)
AST	≥ 3 x ULN, two consecutive results (at least 7 days apart), n (%)	0	1 (2.9)	0 (0.0)	11 (4.2)

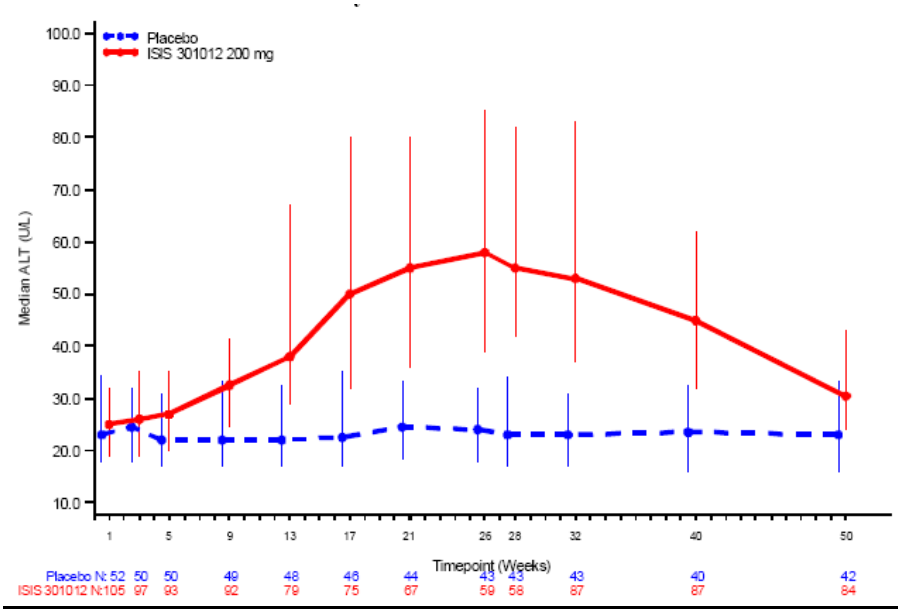
Source: ISS Statistical Table 3.4.3.1.1
ALT = alanine aminotransferase (SGPT), AST = aspartate aminotransferase (SGOT), ULN = upper limit of normal range.

No placebo-treated individuals in the Phase 3 trials had ALT levels ≥5 x ULN. No mipomersen-treated individuals in CS5 had ALT levels ≥8 x ULN. However, there were three mipomersen-treated individuals in the pooled supportive trials who had ALT levels ≥10 x ULN: one individual each in MIPO108 (peak ALT 604 U/L, 14.7 x ULN), CS7 (peak ALT 486 U/L, 11.9 x ULN) and CS12 (peak 415 U/L, 10.1 x ULN). Of note, these three individuals, as was the case with most subjects with significant ALT/AST elevations, met the liver chemistry-stopping rule (AST or ALT ≥ 8 x ULN for MIPO108, CS7 or CS12; ≥ 5 x ULN for CS5). Mipomersen was discontinued and the ALT elevations decreased off drug over a period of weeks. The narratives for these individuals and a graph plotting select laboratory values appear in Appendix 9.4.5.

In the pooled Phase 3 analysis, the mean change in ALT was 38.0 U/L in the mipomersen group and -6.0 U/L in the placebo group. In ISIS 301012-CS5 (patients with HoFH), the mean change in ALT was 14.6 U/L in mipomersen group and -6.9 U/L in the placebo group. In the pooled analysis, the median

change in ALT from baseline to Week 28/ET was 25 U/L (IQR 4, 56) in the mipomersen group and -1 U/L (IQR -6, 4) in the placebo group. The median ALT over time was examined in ISIS 301012 CS12. CS12 was the only Phase 3 trial where all individuals were followed for 24 weeks after their last dose and they did not have the option of entering the OLE trial. As shown in the figure below, a progressive increase in ALT levels was observed in the mipomersen group during the first 26 weeks of treatment. ALT decreased during the post-treatment follow-up period but was still somewhat above baseline levels at Week 50.

Figure 8. Median ALT (U/L) Over Time – ISIS 301012-CS12



Vertical bars represent the interquartile range.
Last mipomersen dose was scheduled for Week 26.
ALT = alanine aminotransferase; ISIS 301012 = mipomersen.
Source: NDA: 203568: ISIS 301012-CS12 CSR Figure 14.3.4.5-3

The FDA Guidance for evaluating premarketing drug-induced liver injury[36] considers the best predictor for severe hepatotoxicity as aminotransferase (AT) elevation accompanied by increased serum total bilirubin, not explained by any other cause and without evidence of cholestasis (i.e., “Hy’s law”), together with an increased incidence of AT elevations in the overall trial population compared to control. There were no cases of Hy’s law (ALT increases ≥3 x ULN with concomitant elevations in total bilirubin ≥ 2 x ULN) during the 6-month treatment period in the mipomersen clinical program. Of note, bilirubin (total, direct, indirect) was measured with every ALT measurement and, in general, when

36 FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf Accessed 28 July 2010.

ALT/AST levels where elevated to ≥3 x ULN. During the treatment period, chemistry laboratory tests were performed prior to study drug administration at outpatient visits at Weeks 1, 3, 5, 9, 13, 17, 21, and 26 and post-treatment at Week 32 36, 40, 44 (not for CS7 and CS12), and 50.

There were 4 individuals with elevations in total bilirubin ≥ 2 x ULN during the mipomersen treatment period.

- Patient 1501-8461 in ISIS 301012-CS5 (mipomersen treatment) had a history of probable Gilbert's disease, with an elevated total bilirubin at screening (2.1 mg/dL to 2.4 mg/dL) and an elevation in total bilirubin of 2.2 mg/dL at Week 3 not accompanied by ALT elevation. These elevations were accompanied by increases in indirect bilirubin.
- Patient 1505-8401 in ISIS 301012-CS5 (mipomersen treatment) had a medical history of Gilbert's syndrome and elevations in total bilirubin at screening (1.9 mg/dL to 2.0 mg/dL). This patient had several elevations of total bilirubin ≥2 x ULN in ISIS 301012-CS5 and the OLE (ISIS 301012-CS6), one of which was accompanied by a slight elevation in ALT (42 U/L). These elevations were accompanied by increases in indirect bilirubin.
- Two patients in the Phase 1 and Phase 2 studies had elevations of total bilirubin ≥2 x ULN unaccompanied by concomitant ALT elevations (ISIS 301012-CS301: Patient1468-0047; ISIS 301012-CS4: Patient 1493-4097).

In OLE trial ISIS 301012-CS6, dosing with mipomersen was stopped for 6.4% (9/141) of patients consistent with the protocol-defined liver stopping rules at that time. An amendment to this protocol allowed for the mipomersen dose to be held or decreased to 100 mg/week for a subset of the individual who met protocol-defined monitoring rules, which may have affected the incidence of ALT elevations and the number of patients who met the stopping rules. In CS6, as shown in the following table, increases in ALT ≥ 3 x ULN and < 5 x ULN occurred in 14.9% (21/141), increases in ALT ≥ 5 x ULN and < 10 x ULN occurred in 7.1% (10/141), and 2 consecutive elevations in ALT ≥ 3 x ULN at least 7 days apart occurred in 12.8% (18/141) of individuals. In individuals with HoFH in the OLE trial, ALT increases ≥ 3 x ULN and < 5 x ULN on at least 1 occasion occurred in 13.2% (5/38) and ALT ≥ 5 x ULN and < 10 x ULN occurred in 13.2% (5/38). Five of these (13.1% of HoFH population) had 2 consecutive elevations in ALT ≥3 x ULN at least 7 days apart.

Patients who had an ALT ≥8 × ULN and <10 include Patient 1501-6021 who was on mipomersen in the ISIS 301012-CS5 index study and Patient 1501-6024 who was on placebo in the ISIS 301012-CS5 index study.

- Patient 1501-6021 had a pre-treatment ALT of 52 U/L and AST of 34 U/L. At Week 58, ALT was 171 U/L and AST was 93 U/L. Apo B value was 212.0 mg/dL. At Week 70, ALT was 336 U/L and AST was 186 U/L. Apo B

value was 179.0 mg/dL. At the Week 70 follow-up visit, ALT was 143 U/L and AST was 98 U/L. Apo B was 191.0 mg/dL. Following this visit, the patient entered the post-treatment follow-up period. At the Week 24 post-dose visit, levels of ALT and AST were 60 U/L and 71 U/L, respectively. The patient met the liver chemistry stopping rule and study drug was discontinued. Patient 1501-6021 had a liver MRI in the ISIS 301012-CS5 index study on Day -7; the average liver fat fraction was -3.0%. The patient had a liver MRI in the ISIS 301012-CS6 extension study on Day 433; the average liver fat fraction was 18.8%.

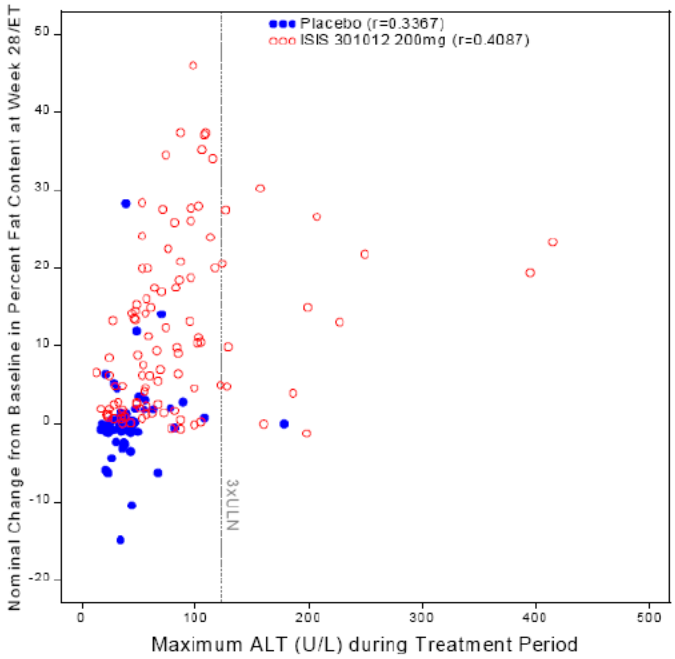
Table 26. Hepatic Transaminase Levels in ISIS 301012-CS6: Total and HoFH Subset

Test	Incidence rate	HoFH Subset (N=38) n (%)	All Subjects (N=141) n (%)
ALT maximum	> ULN and < 2 x ULN	13 (34.2)	53 (37.6)
	≥ 2 x ULN and < 3 x ULN	7 (18.4)	39 (27.7)
	≥ 3 x ULN and < 5 x ULN	5 (13.2)	21 (14.9)
	≥ 5 x ULN and < 10 x ULN	5 (13.2)	10 (7.1)
	≥ 10 x ULN	0	0
	Total ≥ 3x ULN	**10 (26%)**	**31 (22%)**
ALT	≥ 3 x ULN, two consecutive results (at least 7 days apart)	5 (13.2)	18 (12.8)
AST maximum	> ULN and < 2 x ULN	14 (36.8)	68 (48.2)
	≥ 2 x ULN and < 3 x ULN	6 (15.8)	29 (20.6)
	≥ 3 x ULN and < 5 x ULN	5 (13.2)	18 (12.8)
	≥ 5 x ULN and < 8 x ULN	2 (5.3)	2 (1.4)
	≥ 8 x ULN	0	0
AST	≥ 3 x ULN, two consecutive results (at least 7 days apart)	3 (7.9)	5 (3.5)

Source: DA 203568: ISIS 301012-CS6 subset HoFH CSR Table 12-17 and CSR Table 12-18
Note: data are presented as of database cut off of 25 March 2011.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal range.

There was some evidence of an association between increases in ALT and increases in liver fat as the pooled Phase 3 trials yielded a correlation coefficient (r) of 0.4087 (Figure 9). However, this correlation does not prove causality. For an individual subject, elevated transaminases may or may not occur in conjunction with an increase in hepatic fat, and vice versa.

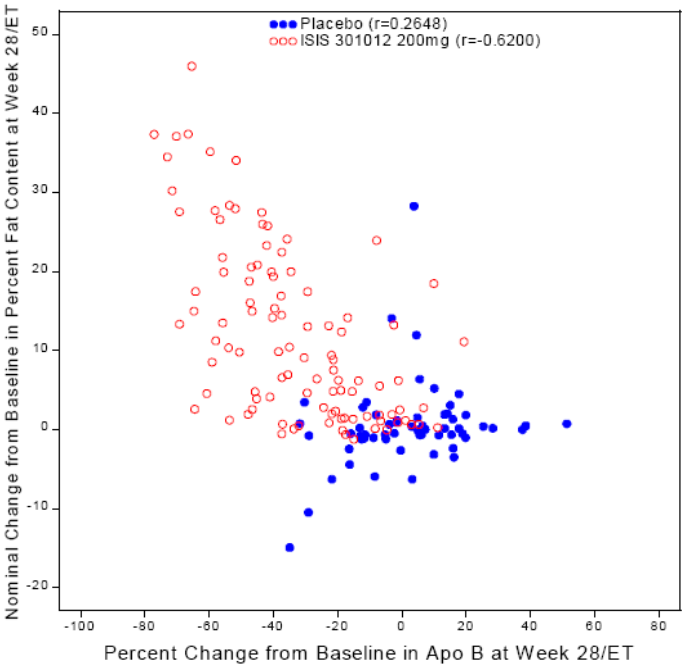
Figure 9. Scatter Plot of Maximum ALT vs. Nominal Change from Baseline in Percent Fat Content at Week 28/ET



r = Spearman Correlation Coefficient.
Note: Only patients from CS7 and CS12 were pooled for this analysis.

There was a stronger association between higher liver fat content and greater reductions in apo B (r = -0.6200) (Figure 10). This association is consistent with the proposed mechanism of action for mipomersen, which causes a reduction in apo B synthesis in the liver and thus affects the export of triglycerides from the liver.

Figure 10. Scatter Plot of Nominal Change from Baseline in Percent Fat Content at Week 28/ET vs. Percent Change from Baseline in Apo B at Week 28/ET



r = Spearman Correlation Coefficient.
Note: Only patients from CS7 and CS12 were pooled for this analysis.

7.3.5.1.3 Hepatic Steatosis

Nonalcoholic fatty liver disease (NAFLD) is characterized by hepatic steatosis, either by imaging or by histology, and no causes for secondary hepatic fat accumulation such as significant alcohol consumption, use of steatogenic medication or hereditary disorders. Drugs that can cause macrovesicular steatosis include amiodarone, methotrexate, tamoxifen, and corticosteroids. Drugs that can cause microvesicular steatosis include valproate and anti-retroviral medicines.[37] NAFLD is histologically categorized into nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). NAFL is defined by hepatic steatosis with no evidence of hepatocellular injury in the form of ballooning of the hepatocytes. NASH is defined by hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis.[37] This distinction is important because individuals with simple steatosis typically have

37 Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, Charlton M, Sanyal AJ. The Diagnosis and Management of Non-alcoholic Fatty Liver Disease: Practice Guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. Gastroenterology 2012;142:1592–1609

slow, if any, histological progression while individuals with NASH can exhibit histological progression to cirrhotic-stage disease.[37, 38, 39]

7.3.5.1.3.1 Hepatic Steatosis in Familial Hypobetalipoproteinemia

Mipomersen leads to drug-induced fatty liver in some subjects. Patients with familial hypobetalipoproteinemia (FHBL) can also develop fatty livers, presumably due to the inability of the liver to secrete triglyceride in VLDL particles. FHBL is an autosomal genetic disorder, often due to mutations in the apolipoprotein B gene resulting in truncated forms of apo B-100, that is characterized by <5th percentile plasma levels of LDL-C and/or total apoB and appears to be protective from cardiovascular disease[40,41]. One study[42] assessed hepatic steatosis as well as noninvasive surrogate markers for CVD (carotid intima-media thickness (IMT) and distal common carotid arterial wall stiffness) in subjects with FHBL and in matched controls. Whereas transaminase levels were modestly elevated (<3xULN), both prevalence (54% versus 29%; P=0.01) and severity of steatosis were significantly higher in FHBL individuals compared with controls. Despite similar IMT measurements, arterial stiffness was significantly lower in FHBL (P=0.04) compared with controls. The authors concluded that the observed decreased level of arterial wall stiffness, most pronounced in the presence of nonlipid risk factors, was indicative of cardiovascular protection in these subjects.

Abetalipoproteinemia and homozygous familial hypobetalipoproteinemia patients present with severe manifestations such as fat malabsorption, fatty liver, progressive neurologic degenerative diseases, retinitis pigmentosa and acanthocytosis. Most heterozygous FHBL patients are usually asymptomatic but the condition has been associated with fatty liver and elevated hepatic transaminases.[43] Familial heterozygous hypobetalipoproteinemia affects approximately one in 500 people.[44]

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38 Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther 2011;34:274–285.

39 G, Gambino R, Cassader M, Pagano G. Meta-analysis: Natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. Annals of Medicine 2011;43(8):617–49.

40 Feingold KR. Does inhibition of apolipoprotein B synthesis produce foie gras? J. Lipid Res. 2010, 51: 877-878.

41 Schonfeld G, Lin X, Yue P. Familial hypobetalipoproteinemia: genetics and metabolism. Cell. Mol. Life Sci. 2005. 62:1372-1378.

42 Sankatsing RR, Fouchier SW, de Haan S, Hutten BA, de Groot E, Kastelein JJ, Stroes ES. Hepatic and cardiovascular consequences of familial hypobetalipoproteinemia. Arterioscler Thromb Vasc Biol. 2005 Sep;25(9):1979-84. Epub 2005 Jul 7.

43 Sen D, Dagdelen S, Erbas T. Hepatosteatosis with hypobetalipoproteinemia. J Natl Med Assoc. 2007 March; 99(3): 284–286.

44 Wishingrad M, Paaso B, Garcia G. Fatty Liver Due to Heterozygous Hypobetalipoproteinemia.

Schonfeld et al[45] have reported that the mean liver triglyceride content in apoB-impaired FHBL subjects (n=21; liver fat % 16.7±11.5) is ~5-fold that of controls (n=14; liver fat 3.3% ±2.9), but liver fat content in FHBL subjects (as well as in the controls) varied greatly among individuals. Tanoli et al[46] found that FHBL subjects (n=33; liver fat 14.8% ±12.0) were more susceptible to developing fatty livers at any given amount of abdominal adipose tissue than the control subjects (n=32; liver fat % 5.2±5.9; matched for age, gender, and indices of obesity). Increasing insulin resistance also exerted greater liver fat-increasing effects in the FHBL subjects. Liver fat percentage was significantly correlated with serum ALT and ALT-AST ratio in FHBL subjects (r=0.558 and 0.580, respectively, both P<0.001) and less so in controls (r=0.339, P=0.057 and r=0.419, P=0.017, respectively). Liver fat percentage also tended to increase with age (liver fat vs. age r=0.366, P=0.051 in FHBL subjects and r=0.324, P=0.099 in controls). When considering FHBL and control groups together, the important factors determining liver fat were FHBL-affected status, intra-abdominal fat, and AUC insulin. The authors present a stepwise regression analysis which showed that intraperitoneal adipose tissue accounted for 55% of the variation in liver fat in FHBL subjects, and apoB accounted for 19% (R2 for the model was 0.94); homeostatic model assessment (HOMA) index (fasting plasma glucose (mmol/l) x fasting plasma insulin (μU/ml)/22.5) and AUC glucose each accounted for <10% of the variation. In controls, AUC insulin accounted for 50% of the variation, HOMA index for 13%, and intraperitoneal adipose tissue for only 8% (R2 for the model was 0.71). The authors concluded that while intra-abdominal fat was an important determinant of liver fat in both groups, it was more important in FHBL subjects than in controls. Conversely, indices of insulin action were more important in controls.

In the general population, Youssef et al showed that up to 25% of patients with fatty liver disease may progress to nonalcoholic steatohepatitis[47], which is associated with the development of progressive fibrosis and eventually cirrhosis in approximately 20% of cases.[48] In the FHBL population, long-term follow-up data with regard to liver outcome are lacking, thus the natural course of this hepatic fat accumulation in FHBL is still unknown. It is also unknown if the

Am J Gastroenterol. 1994;89:1 106-1107.
45 Schonfeld, G., B. W. Patterson, D. A. Yablonskiy, T. S. Tanoli, M. Averna, N. Elias, P. Yue, and J. Ackerman. Fatty liver in familial hypobetalipoproteinemia: triglyceride assembly into VLDL particles is affected by the extent of hepatic steatosis. J. Lipid Res. 2003. 44: 470–478.
46 Tanoli T, Yue P, Yablonskiy D, Schonfeld G. Fatty liver in familial hypobetalipoproteinemia: roles of the APOB defects, intra-abdominal adipose tissue, and insulin sensitivity. J. Lipid Res. 2004. 45: 941–947.
47 Youssef W, McCullough AJ. Diabetes mellitus, obesity, and hepatic steatosis. Semin Gastrointest Dis. 2002; 13: 17–30.
48 Yu AS, Keeffe EB. Nonalcoholic fatty liver disease. Rev Gastroenterol Disord. 2002; 2: 11–19.

mipomersen induced fatty liver will follow a similar clinical course to the fatty liver observed in FHBL patients.

7.3.5.1.3.2 NAFLD and CVD

NAFLD is associated with the typical risk factors for CVD[49]. A literature search revealed an article summarizing the available data linking NAFLD with CVD[50]. Villanova et al. [51] evaluated the flow-mediated vasodilation of the brachial artery in patients with NAFLD based on the observation that atherosclerosis is often associated with endothelial dysfunction. They found that flow-mediated vasodilation was lower in NAFLD versus controls and that the defect was more pronounced in those with steatohepatitis than in those with pure fatty liver. Lautamaki et al.[52] evaluated 55 patients with type 2 diabetes and coronary artery disease that were divided into two groups with low and high liver fat content. Coronary angiography demonstrated that the median of the degree of the main stenotic lesion was 60% (range 9-100%) with no significant differences between the groups. Westerbacka et al.[53] obtained liver biopsies from 24 subjects who had varying amounts of histologically determined fat in the liver ranging from normal to steatosis due to NAFLD, and found that the mRNA expression of inflammatory genes, such as the monocyte-attracting chemokine CCL2 [monocyte chemoattractant protein (MCP)-1], were overexpressed proportionally to the amount of the hepatic fat content. The authors suggest that chronic inflammation of the liver secondary to triglyceride infiltration could increase the production of factors that cause systemic insulin resistance. In the Diabetes Heart Study, hepatic steatosis, defined as a liver:spleen attenuation ratio of < 1.0 by computed tomography, was evaluated in 623 individuals. The study quantified visceral fat and subcutaneous fat as well as coronary, aortic and carotid artery calcium by computed tomography, and carotid atherosclerosis by ultrasound. They found no significant associations between the liver:spleen attenuation ratio and coronary, aortic or carotid calcium, or carotid intimal thickness.[54] Similarly,

49 Gastaldelli A, Kozakova M, Højlund K, et al; RISC Investigators: Fatty liver is associated with insulin resistance, risk of coronary heart disease, and early atherosclerosis in a large European population. Hepatology 2009; 49: 1537–1544.
50 Perseghin G. The Role of Non-Alcoholic Fatty Liver Disease in Cardiovascular Disease Dig Dis 2010;28:210-213
51 Villanova N, Moscatiello S, Ramilli S, et al: Endothelial dysfunction and cardiovascular risk profile in nonalcoholic fatty liver disease. Hepatology 2005; 42: 473–480.
52 Lautamaki R, Borra R, Iozzo P, et al: Liver steatosis coexists with myocardial insulin resistance and coronary dysfunction in patients with type 2 diabetes. Am J Physiol Endocrinol Metab 2006; 291:E282–E290.
53 Westerbacka J, Kolak M, Kiviluoto T, et al: Genes involved in fatty acid partitioning and binding, lipolysis, monocyte/macrophage recruitment, and inflammation are overexpressed in the human fatty liver of insulinresistant subjects. Diabetes 2007; 56: 2759– 2765.
54 McKimmie RL, Daniel KR, Carr J, et al: Hepatic steatosis and subclinical cardiovascular disease in a cohort enriched for type 2 diabetes: the diabetes heart study. Am J Gastroenterol 2008; 103: 3029–3035.

in the Dijon Study, 101 patients with type 2 diabetes mellitus were studied measuring liver fat using 1 H-MRS and carotid intima-media thickness using ultrasound, and found no significant difference between those with and those without hepatic steatosis for intima-media thickness values.[55] This result was in contrast with a report by Targher et al.[56] that compared carotid intima-media thickness (CIMT) values in subjects with and without nonalcoholic hepatic steatosis. Subjects with hepatic stenosis had significantly greater (~ 20%) CIMT measurements than those without hepatic stenosis. The hepatic stenosis subjects also had higher values for BMI, visceral abdominal fat, diastolic blood pressure, plasma insulin, and triglycerides and lower HDL cholesterol concentration. Perseghin[50] concluded that the epidemiologic studies support a causal link between fatty liver and type 2 diabetes but the causal association between NAFLD and CVD is weak.

In another study Targher et al.[57] assessed whether NAFLD, as diagnosed by ultrasound, predicts the risk of incident CVD events in a large cohort of type 2 diabetic adults. During 6.5 years of follow-up, there were 384 CVD events: 219 cases of nonfatal coronary heart disease (151 myocardial infarction and 68 revascularization procedures), 44 cases of nonfatal ischemic stroke, and 121 cardiovascular deaths. Subjects who developed CVD events during follow-up were older, had higher liver enzymes and A1C, and had greater prevalence of metabolic syndrome than those who did not develop CVD events. Gender, smoking, LDL-C, diabetes duration, and treatment did not differ between the groups. The frequency of NAFLD was markedly higher in those who developed CVD events than in those who did not. In univariate regression analysis, NAFLD (hazard ratio [HR] 2.01 [95% CI 1.4–2.9]), metabolic syndrome (1.74 [1.3–3]), age (1.11 [1.05–1.2]), male sex (1.52 [1.3–1.8]), smoking (1.48 [1.2–2.2]), A1C (1.44 [1.4–2.9]), LDL cholesterol (1.37 [1.1–1.8]), alanine aminotransferase (1.47 [1.2–1.9]), and other liver enzymes were significantly ($P < 0.01$) associated with incident CVD, whereas diabetes duration and medications were not. In multivariate regression analysis, the significant association between NAFLD and incident CVD was little affected (1.96 [1.4–2.7], $P < 0.001$) by adjustment for sex, age, smoking, diabetes duration, A1C, LDL cholesterol, and medications (hypoglycemic, antihypertensive, lipid-lowering, or antiplatelet drugs).

55 Petit JM, Guiu B, Terriat B, Loffroy R, Robin I, Petit V, et al: Nonalcoholic fatty liver is not associated with carotid intima-media thickness in type 2 diabetic patients. J Clin Endocrinol Metab 2009; 94: 4103–4106.
56 Targher G, Bertolini L, Padovani R, et al: Relations between carotid artery wall thickness and liver histology in subjects with nonalcoholic fatty liver disease. Diabetes Care 2006; 29: 1325–1330.
57 Targher G, Bertolini L, Rodella S, Tessari R, Zenari L, Lippi G, Arcaro G. Nonalcoholic fatty liver disease is independently associated with an increased incidence of cardiovascular events in type 2 diabetic patients. Diabetes Care. 2007 Aug;30(8):2119-21. Epub 2007 May 22.

Bhatia et al.[58] reviewed the multiple epidemiological studies that have reported an increased incidence of adverse CV events in NAFLD subjects compared with the general population as well as the evidence linking NAFLD with CVD. Several studies show a significantly increased coronary atherosclerotic burden in the presence of NAFLD using coronary artery calcium scoring with cardiac CT and a strong association between NAFLD and the prevalence of significant CAD determined by coronary angiography. The authors comment that the development and progression of insulin resistance (IR), appears to be the key mediator in the initiation and propagation of NAFLD, primarily through adverse changes in glucose, fatty acid, and lipoprotein metabolism. Bhatia et al. presented evidence that worsening grades of NAFLD contribute to progressive cardiometabolic risk, such that NASH represents a marker as well as a mediator of increased CV risk more than simple steatosis.

Non-drug induced NAFLD is characterized by an atherogenic lipid profile, consisting of elevated levels of TG, LDL-C, VLDL and apolipoprotein B100 and low HDL-C concentrations. This type of atherogenic dyslipidemia is linked to adverse CV outcome. Non-drug induced NAFLD is associated with insulin resistance and there are data supporting that NAFLD may be associated with increased cardiovascular risk. One of the key questions is whether mipomersen-induced fatty liver would be associated with a similar potential for increased risk for cardiovascular events as non-drug induced fatty liver.

7.3.5.1.3.3 Hepatic Steatosis in the Mipomersen Phase 3 Clinical Trials

As discussed above, one of the concerns with mipomersen is that in some individuals mipomersen increases hepatic fat and it is not known what the long-term consequences are from this drug-induced hepatic steatosis. Other questions include what is the best way to monitor for hepatic steatosis/fatty liver, whether there is an extent of fatty liver that is sufficiently dangerous to warrant drug withdrawal, and how does one distinguish between fatty liver and nonalcoholic steatohepatitis (NASH).

In the mipomersen clinical trials, hepatic fat quantification was assessed by measuring the liver fat fraction (%) derived from MRI using 3 regions of interest defined with respect to anatomical landmarks. The data are expressed as percent fat fraction, where fat fraction is a measure of the proportion of the liver mass attributable to fat. The applicant notes that the technique can result in negative liver fat fraction (%) data, particularly if liver fat fraction (%) was low, because of technical considerations related to fat-fat-water cancellation and effective transverse relaxation time. In the mipomersen clinical trials, significant

58 Bhatia LS, Curzen NP, Calder PC, Byrne CD. Non-alcoholic fatty liver disease: a new and important cardiovascular risk factor? European Heart Journal (2012) 33, 1190–1200

hepatic fat accumulation was defined by the applicant as ≥ 5 % change from baseline.

In ISIS 301012-CS7 and ISIS 301012-CS12, hepatic fat fraction was assessed with MRI at baseline and Week 28 / Early Termination. The table below shows the analyses of hepatic fat fraction between baseline to Week 28/ET in the individuals that had MRIs at both timepoints. In the analysis of ISIS 301012-CS7, 65% of individuals receiving mipomersen had 2 or more paired exams, and in ISIS 301012-CS12, 46% of individuals receiving mipomersen had 2 or more paired exams. Results from these studies, in which baseline and 6 month MRI data are available, demonstrated a median increase in hepatic fat fraction of 9.6% in mipomersen-treated patients vs. 0.02% in placebo-treated patients. In ISIS 301012-CS7 and ISIS 301012-CS12, 61.8% (63/102) of individuals in the mipomersen group had a ≥ 5 percentage point change from baseline in hepatic fat content. Of these 63 individuals, 10 (15.9%) had at least one ALT ≥ 3 x ULN. For the placebo group, 8.3% (5/60) of individuals had a ≥ 5 % change from baseline in hepatic fat content. Of these five individuals, none had at least one ALT ≥ 3 x ULN. Approximately 84% of mipomersen-treated individuals with significant hepatic fat accumulation (defined as ≥ 5 % change from baseline) did not have ALT abnormalities 3x ULN or greater. Thus, ALT monitoring alone would not be an adequate method to determine which individuals are developing hepatic fat elevations of 5% or greater on mipomersen.

Table 27. Change From Baseline to Week 28 / Early Termination in Liver Fat Content (%) in Studies ISIS 301012-CS7 and ISIS 301012-CS12 -Pooled dataset

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

Parameter	Statistic	Placebo (N=93)	Mipomersen (N=188)
At least one ALT ≥ 3 x ULN, n/N (%)		0/5 (0.0)	10/63 (15.9)
Percent fat content change from baseline <5%, n/N (%)		55/60 (91.7)	39/102 (38.2)

Source: NDA 203568: ISS Statistical Table 3.5.2.1 and ISS Statistical Table 3.5.3.1
Note: data are presented as of database cut off of 25 March 2011.

More mipomersen-treated patients ≥ 65 years of age (78.6%; 22/28 patients) had hepatic fat elevations (defined as ≥ 5% change from baseline) compared to the 18 to < 65 age group (55.4%; 41/74 patients). Of the 22 individuals in the mipomersen group that were 65 years of age or older and had ≥ 5% increase from baseline in hepatic fat content, only 14% (3/22) had at least one ALT ≥ 3xULN.

Hepatic fat and non-alcoholic fatty liver disease (NAFLD) are associated with insulin resistance. However, the nature of this relationship is debatable, as some experts believe that the insulin resistance causes the hepatic fat, while others have suggested that hepatic fat may promote insulin resistance.[59] In ISIS 301012-CS7 and ISIS 301012-CS12, in the mipomersen-treated group that had a ≥5 % change from baseline in hepatic fat content, no notable adverse changes were seen in weight, glucose, HbA1c, or triglycerides over the 6-month duration of these trials when compared to the placebo-treated group that also exhibited a ≥5 % hepatic fat change. However, HbA1c% decreased in both the mipomersen- and placebo-treated groups who exhibited hepatic fat change <5% and it increased to a similar degree in the mipomersen- and placebo-treated groups that exhibited ≥5 % hepatic fat change. Not surprisingly, the mipomersen-treated groups, regardless of hepatic fat change, had greater TG reduction than the placebo groups.

Table 28. MRI and Glucose Assessment in Individuals from CS7 and CS12

	Hepatic Percent Fat Change ≥5 %		Hepatic Percent Fat Change <5 %	
Parameter	**Placebo (N=93)**	**ISIS 301012 200 mg (N=188)**	**Placebo (N=93)**	**ISIS 301012 200 mg (N=188)**
Percent fat content change from baseline ≥ 5%, n/N (%)	5/60 (8.3)	63/102 (61.8)		

59 Lockman KA, Nyirenda MJ. Interrelationships between hepatic fat and insulin resistance in non-alcoholic fatty liver disease. Curr Diabetes Rev. 2010 Sep;6(5):341-7.

Percent fat content change from baseline <5%, n/N (%)			55/60 (91.7)	39/102 (38.2)
At least one ALT ≥ 3 x ULN, n/N (%)	0/5 (0.0)	10/63 (15.9)		
Weight (kg) change from baseline to Week 28/ET				
n	5	63	55	39
Mean (SD)	3.52 (1.9)	-0.54 (3.1)	-0.33 (3.3)	0.05 (2.5)
Median (P25, P75)	3.4 (3.2, 4.3)	-0.7 (-3.0, 1.2)	0.0 (-1.3, 1.1)	-0.2 (-1.3, 1.6)
Min, Max	(0.8, 5.9)	(-6.6, 8.5)	(-14.1, 7.0)	(-6.6, 7.5)
95% C.I.	(1.2, 5.8)	(-1.3, 0.2)	(-1.2, 0.6)	(-0.8, 0.9)
Glucose (mg/dL) change from baseline to Week 28/ET				
n	5	63	55	39
Mean (SD)	12.2 (13.7)	1.0 (14.4)	2.2 (24.4)	1.1 (13.7)
Median (P25, P75)	11 (4, 16)	2 (-6, 6)	-2 (-7, 5)	-1 (-7, 6)
Min, Max	(-3, 33)	(-57, 43)	(-57, 148)	(-25, 41)
95% C.I.	(-5, 29)	(-3, 5)	(-4, 9)	(-3, 5)
HbA1c (%) change from baseline to Week 28/ET				
n	4	37	27	11
Mean (SD)	0.13 (0.3)	0.11 (0.3)	-0.03 (0.4)	-0.01 (0.3)
Median (P25, P75)	0.1 (-0.1, 0.3)	0.1 (0.0, 0.3)	-0.1 (-0.2, 0.2)	-0.1 (-0.2, 0.1)
Min, Max	(-0.2, 0.5)	(-0.4, 0.7)	(-1.0, 0.8)	(-0.2, 0.6)
95% C.I.	(-0.3, 0.6)	(0.0, 0.2)	(-0.2, 0.1)	(-0.2, 0.2)
TG (mg/dL) change from baseline to Wk 28/ET				
n	5	63	55	39
Mean (SD)	48.50 (50.0)	-18.75 (75.4)	-4.02 (51.7)	-17.36 (32.7)
Median (P25, P75)	21.0 (14.0, 92.5)	-25.0 (-64.3, -7.0)	-3.0 (-29.5, 18.0)	-15.0 (-34.0, 4.0)
Min, Max	(3.0, 112.0)	(-156.0, 295.0)	(-105.0, 232.0)	(-129.0, 36.0)
95% C.I.	(-13.5, 110.5)	(-37.7, 0.2)	(-18.0, 10.0)	(-28.0, -6.8)

Source: NDA 203568, ISS Statistical Table 3.5.3.1

In the subgroup of individuals with Type 2 diabetes in ISIS 301012-CS12, the median change in average hepatic fat fraction from baseline to Week 28/ET was 15.2% for the mipomersen group (n=24) and 0.2% for the placebo group (n=18). The change in average liver fat fraction ranged from 0.1% to 46.0% for patients in the mipomersen group and -14.7% to 28.3% for patients in the placebo group. The median change in average liver fat fraction for patients without diabetes was 16.2% for patients in the mipomersen group (n=24) and -0.6% for patients in the placebo group (n=15). The change in average liver fat fraction ranged from -0.1% to 30.2% for patients in the mipomersen group and -6.3% to 13.8% for patients in

the placebo group (see Table 29). In this subgroup, the individuals with diabetes on mipomersen had similar hepatic fat fraction increases as compared to individuals without diabetes on mipomersen.

Table 29. Change in Average Liver Fat Fraction (%) From Baseline to Week 28/ET and Post-treatment Week 50 – CS12– Patients With and Without Diabetes

Time point Statistic	Patients With Diabetes		Patients Without Diabetes	
	Placebo (N = 30)	Mipomersen (N = 58)	Placebo (N = 22)	Mipomersen (N = 47)
Baseline				
N	26	45	18	41
Mean (SD)	2.7 (7.4)	3.9 (7.4)	3.4 (6.9)	0.0 (6.0)
Median (Q1 , Q3)	-0.2 (-2.4 , 4.8)	1.2 (-0.9 , 7.7)	1.0 (-1.6 , 10.1)	-1.5 (-2.5 , 5.0)
Min , Max	-6.6 , 20.1	-9.6 , 29.3	-9.3 , 15.7	-9.0 , 17.6
Week 28/ET				
n	19	26	17	26
Mean (SD)	3.4 (8.5)	22.2 (15.4)	3.1 (9.0)	15.0 (11.5)
Median (Q1 , Q3)	0.4 (-2.0 , 7.2)	22.5 (11.4 , 33.6)	-0.64 (-1.5 , 4.9)	15.96 (5.2 , 22.3)
Min , Max	-4.0 , 28.8	-8.4 , 53.0	-8.8 , 29.5	-1.9 , 37.2
Change from baseline				
n	18	24	15	24
Mean (SD)	1.3 (8.7)	17.6 (13.5)	-0.2 (4.6)	14.3 (8.3)
Median (Q1 , Q3)	0.2 (-1.2 , 2.0)	15.2 (6.0 , 27.2)	-0.6 (-2.4 , 0.5)	16.2 (8.7 , 19.9)
Min , Max	-14.7 , 28.3	0.1 , 46.0	-6.3 , 13.8	-0.1 , 30.2
95% CI	(-3.0 , 5.7)	(11.9 , 23.2)	(-2.8 , 2.3)	(10.8 , 17.8)
Week 50 (post-trt)				
n	18	36	13	29
Mean (SD)	4.1 (7.3)	10.7 (11.2)	6.9 (12.6)	5.0 (7.1)
Median (Q1 , Q3)	2.5 (-1.8 , 8.5)	8.2 (1.5, 17.2)	0.3 (-1.0 , 13.0)	3.38 (0.0 , 7.4)
Min , Max	-5.5 , 21.7	-7.3 , 36.3	-2.4 , 40.4	-3.8 , 27.3
Change from baseline				
n	16	31	11	27
Mean (SD)	0.5 (7.5)	5.7 (8.9)	2.4 (8.1)	4.4 (5.3)
Median (Q1 , Q3)	1.0 (-3.0 , 2.2)	3.9 (1.8 , 9.6)	-0.1 (-1.0 , 4.7)	3.0 (0.3 , 7.7)
Min , Max	-17.0, 20.0	-21.8, 29.2	-7.1 , 24.7	-3.4 , 18.4
95% CI	(-3.5, 4.5)	(2.4 , 9.0)	(-3.01 , 7.9)	(2.3 , 6.5)

Looking at all the subjects in CS12, assessments of hepatic fat fraction following discontinuation of mipomersen treatment were performed at the end of the 24-week post-treatment period (Week 50). The median change from baseline to Week 28/ET for the 48 individuals with paired assessments in the mipomersen group was 15.4% and -0.1% for the 33 individuals with paired assessments in the placebo group. From baseline to Week 50, the median change in average liver

fat fraction was 3.5% for the 58 individuals in the mipomersen group with paired assessments, and 0.8% for the 27 individuals in the placebo group with paired assessments. This suggests that the hepatic fat fraction is decreasing and trending towards baseline upon discontinuation of mipomersen.

In ISIS 301012-CS5 and MIPO3500108, there were no scheduled MRI assessments but only 'for cause' assessments (evaluation for ALT elevations ≥ 3 x ULN). In general, increases in hepatic fat, as measured by MRI, occurred in these individuals.

MRI assessments were also performed in the OLE study ISIS 301012-CS6. For the individuals with HoFH, liver MRI data were available at baseline and Week 26 for 7 individuals, at baseline and Week 52 for 5 individuals, at baseline and Week 76 for 5 individuals, and at baseline and Week 104 for 3 individuals. For the 7 with available data at baseline and Week 26, the baseline median average liver fat fraction was -2.25%; the median nominal change in liver fat fraction from baseline to Week 26 was 0.79% (Q1, Q3: -0.75%, 1.73%). For the 5 with available data at baseline and Week 52, the baseline median average liver fat fraction was -1.33%; the median nominal change in liver fat fraction from baseline to Week 52 was 2.35% (Q1, Q3: 0.01%, 3.04%). For the 5 with available data at baseline and Week 76, the baseline median average liver fat fraction was -1.26%; the median nominal change in liver fat fraction from baseline to Week 76 was 0.34% (Q1, Q3: -0.77%, 1.46%). For the 3 with available data at baseline and Week 104, the baseline median average liver fat fraction was -0.38%; the median nominal change in liver fat fraction from baseline to Week 104 was -2.08% (Q1, Q3: -3.59%, 4.58%). Of note, there was one individual (Patient 1501-6012) with liver fat content assessments at baseline and at 12 months or longer on mipomersen treatment who had an average liver fat fraction >20% on at least 1 occasion. This individual also had elevations in ALT ≥3 × ULN. The patient was asymptomatic but mipomersen was discontinued due to the elevated ALT.

For all individuals in the OLE trial, there were 60 individuals with available data, the median change in liver fat fraction from Baseline to Week 26 was 4.9%, and the mean was 9.3%. For the 31 individuals with available data, the median nominal change in liver fat fraction from Baseline to Week 52 was 12.6%. As seen in ISIS 301012-CS12, in ISIS 301012-CS6 liver fat fraction was observed to return to near baseline upon cessation of mipomersen treatment. For the 28 individuals with available data, the median nominal change in liver fat fraction from Baseline to Week 24 post-dose was 0.3%. Due to differences between trials and amendments to the ISIS 301012-CS6 protocol, the individuals included in each of these analyses are not always the same individuals included at later time points, which limits the interpretation of the results.

Table 30. Liver Fat Fraction (%) by Magnetic Resonance Imaging - Individuals In OLE CS6 Trial With Baseline and Post-Baseline Data

Time Point	Baseline Summary (%)	Nominal Change from Baseline (%)
Week 26		
n	60	60
Mean (SD)	-0.3 (3.7)	9.3 (10.5)
Median (P25, P75)	-1.2 (-2.5, 1.9)	4.9 (1.4, 17.3)
Min, Max	(-10.0, 10.7)	(-5.0, 37.1)
95% CI	(-1.2, 0.7)	(6.6, 12.1)
Week 52		
n	31	31
Mean (SD)	-0.7 (4.1)	12.5 (10.6)
Median (P25, P75)	-1.3 (-3.0, 1.4)	12.6 (2.4, 21.8)
Min, Max	(-10.0, 8.4)	(-1.9, 33.9)
95% CI	(-2.2, 0.8)	(8.6, 16.4)
Week 76		
n	45	45
Mean (SD)	-0.4 (3.5)	9.3 (9.0)
Median (P25, P75)	-0.9 (-2.5, 1.4)	6.6 (1.9, 16.1)
Min, Max	(-9.9, 8.4)	(-3.6, 32.0)
95% CI	(-1.5, 0.6)	(6.6, 12.1)
Week 104		
n	42	42
Mean (SD)	-0.5 (3.4)	7.9 (8.2)
Median (P25, P75)	-0.8 (-2.5, 1.4)	4.6 (2.2, 13.6)
Min, Max	(-9.9, 8.4)	(-3.6, 32.8)
95% CI	(-1.6, 0.6)	(5.4, 10.5)
Week 130		
n	20	20
Mean (SD)	-1.1 (2.7)	8.8 (9.1)
Median (P25, P75)	-1.3 (-2.6, 0.5)	6.9 (1.9, 14.4)
Min, Max	(-8.4, 3.3)	(-2.1, 33.2)
95% CI	(-2.4, 0.2)	(4.5, 13.0)
24 Weeks Post Dose		
n	28	28
Mean (SD)	-0.2 (3.7)	-0.1 (3.6)
Median (P25, P75)	-0.1 (-2.1, 2.2)	0.3 (-1.2, 1.8)
Min, Max	(-10.0, 8.3)	(-11.8, 7.9)
95% CI	(-1.3, 1.6)	(-1.5, 1.3)

Source: NDA 203568: ISIS 301012-CS6 Statistical Table 14.3.6 Spring 2012 Analysis
Baseline data are for patients who had baseline and post-baseline data at the time point specified.

Hepatic Fat Fraction >20%

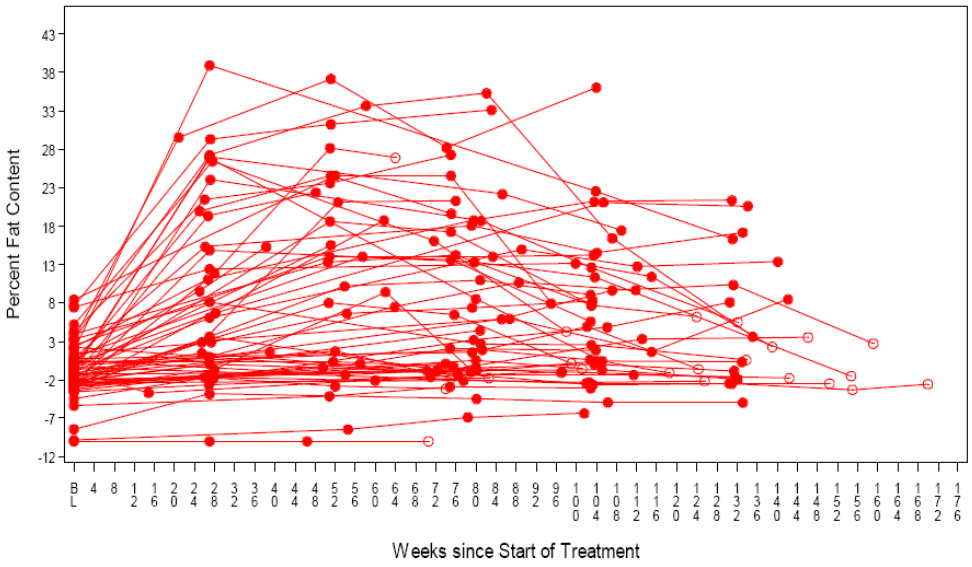
In CS6, twenty-two individuals (10 female and 12 male) out of 141 (16%) had an average liver fat fraction >20% on at least 1 occasion.[60] Nine out of 22 (41%) had elevations in ALT ≥3 × ULN.61 Thus, the majority of individuals (~60%) with average liver fat fraction >20% on at least 1 occasion could not be indentified by monitoring ALT levels. One individual (Patient 1587-6136) underwent a liver biopsy 415 days after his first dose of mipomersen for further assessment. Additional details are provided in Appendix 9.4.

As of 30 March 2012, among individuals in CS6 with a measurement at baseline and at 12 months or longer on treatment, 16 out of 65 individuals (25%; 6 female, 10 male) had an average liver fat fraction > 20% on at least 1 occasion. Of these 16 individuals, 4 had an average liver fat fraction that ranged from 33 to 39% on at least one occasion. One patient (#1577-6084) had an ALT that was 3.5xULN associated with the elevated fat fraction; 2 individuals had ALTs 2.6-2.8xULN and one subject had an ALT 1.3xULN at the time of maximal fat fraction. No one had a liver fat fraction > 39%.

For individuals administered mipomersen, the accumulation of fat in the liver was varied. For some individuals, liver fat content increases continued over time. For other individuals who had an increase in liver fat and continued mipomersen treatment, extended treatment with mipomersen was associated with liver fat stabilization, or decrease. The liver fat content over time in the OLE trial ISIS 301012-CS6 for individuals with assessments at baseline and at 12 months or longer on mipomersen treatment is displayed graphically in the figure below.

60 Patient ID# 1503-6039, 1503-6048, 1505-6082, 1520-6097, 1534-6062, 1538-6096, 1574-6077, 1577-6074, 1578-6142, 1579-6088, 1590-6121, 1597-6070, 1577-6084, 1578-6122, 1589-6126, 1608-6080, 1608-6089, 1622-6085, 1622-6133, 1623-6137, 1623-6138, and 1623-6140.
61 Patient ID# 1503-6048, 1574-6077, 1590-6121, 1597-6070, 1577-6084, 1589-6126, 1608-6080, 1622-6085, and 1622-6133.

Figure 11. Liver Fat Content Over Time – Liver Fat Content Assessments at Baseline and at 12 Months or Longer on Mipomersen Treatment for ISIS 301012-CS6



Source: NDA 203568: ISIS 301012-CS6 Winter 2012 Analysis Figure 14.3.4.7-2
Note: data are presented as of database cut off of 30 November 2011
N=64. Baseline (BL) represents the last value prior to receiving the first dose of ISIS 301012. For percent fat content data, BL is presented as 0 weeks since the start of treatment though for some patients this value represents a pre-treatment value taken weeks prior to the start of dosing. Solid circles represent values during the evaluable dosing period and open circles represent values during the post-treatment assessment period.

The details of some of the liver fat increases in individuals are summarized below.

- Patient 1503-6039: liver MRI in the ISIS 301012-CS7 index trial on Day -20 (baseline) with average liver fat fraction of 1.9% and by Day 191 (Week 26) it had increased to 27.7%.
- Patient 1505-6082: liver MRI in the ISIS 301012-CS7 index trial on Day -16 (baseline) with average liver fat fraction of 2.2% and on Day 188 (after 27 weeks of mipomersen treatment) it was 11.1%. Liver MRI in the ISIS 301012-CS6 extension trial on Day 558 (after 80 weeks of mipomersen treatment) was 18.8% and on Day 726 (after 104 weeks of mipomersen treatment), it was 21.2%.
- Patient 1520-6097: liver MRI in the ISIS 301012-CS7 index trial on Day 1 (baseline) with average liver fat fraction of -3.5% and on Day 191 (after 27 weeks of mipomersen treatment) it was 24.1%. Liver MRI in the ISIS 301012-CS6 extension trial on Day 568 (after 81 weeks of mipomersen treatment) was 18.7% and on Day 722 (after 103 weeks of mipomersen treatment), it was 12.6%.

- Patient 1534-6062: liver MRI in the ISIS 301012-CS7 index trial on Day 1 (baseline) with average liver fat fraction of 1.8% and on Day 190 (after 27 weeks of mipomersen treatment) it was 38.9%. The liver MRI in the ISIS 301012-CS6 extension trial on Day 728 (after 104 weeks of mipomersen treatment) showed an average liver fat fraction of 22.6%.
- Patient 1538-6096: liver MRI in the ISIS 301012-CS7 index trial on Day -6 (baseline) with average liver fat fraction of -0.9% and Day 190 (after 27 weeks of mipomersen treatment) it was 27.1%. The liver MRI in the ISIS 301012-CS6 extension trial on Day 598 (after 85 weeks of mipomersen treatment) showed an average liver fat fraction of 22.2% and on Day 764 (after 109 weeks of mipomersen treatment) it was 17.5%.
- Patient 1577-6074: liver MRI in the ISIS 301012-CS7 index trial on Day 1 with average liver fat fraction of 0.09% and Day 198 (Week 26) it was 6.69%. The liver MRI in the ISIS 301012-CS6 extension trial on Day 739 (Week 104) showed an average liver fat fraction of 21.1%.
- Patient 1578-6122 had a liver MRI in the ISIS 301012-CS7 index trial on Day -12 (baseline) with an average liver fat fraction of 8.4%. The liver MRI in the ISIS 301012-CS6 extension trial on Day 365 (after 52 weeks of mipomersen treatment) showed an average liver fat fraction of 24.6%.
- Patient 1578-6142: liver MRI in the ISIS 301012-CS7 index trial on Day -161 showed an average liver fat fraction of 4.3%. The liver MRI in the ISIS 301012-CS6 extension trial on Day 183 (Week 26) showed an average liver fat fraction of 21.5%.
- Patient 1579-6088: liver MRI in the ISIS 301012-CS7 index trial on Day 1 showed the average fat fraction was -0.6% and by Day 190 it was 34.6%. The liver MRI in the ISIS 301012-CS6 extension trial at treatment discontinuation (Day 568 [Week 8 post-dose] showed an average liver fat fraction of 30.4%.
- Patient 1608-6089: liver MRI in the ISIS 301012-CS6 extension trial on Day 355 (after 51 weeks of mipomersen treatment) showed an average fat fraction of 21.3% and Day 530 (after 76 weeks of treatment) it was 11.6%.
- Patient 1623-6137: liver MRI in the ISIS 301012-CS7 index trial on Day -77 (baseline) showed an average liver fat fraction of -1.5%. The liver MRI in the ISIS 301012-CS6 extension trial on Day 188 (after 27 weeks of mipomersen treatment) showed an average liver fat fraction of 19.3% and by Day 338 (after 48 weeks of mipomersen treatment) it was 22.4%.
- Patient 1622-6085: liver MRI in the ISIS 301012-CS7 index trial on Day -2 the average liver fat fraction was 10.7% and on Day 191 it was 20.6%. The liver MRI in the ISIS 301012-CS6 extension trial at treatment discontinuation (Day 392) showed an average liver fat fraction of 11.9%.
- Patient 1623-6138: liver MRI in the ISIS 301012-CS7 index trial on Day -58 (baseline) showed an average liver fat fraction of 7.6%. The liver MRI in the ISIS 301012-CS6 extension trial on Day 191 (after 27 weeks of

mipomersen treatment) showed an average liver fat fraction of 29.3% and Day 359 (after 51 weeks of mipomersen treatment) it was 31.3%.

- Patient 1623-6140: liver MRI in the ISIS 301012-CS7 index trial on Day -119 (baseline) showed an average liver fat fraction of 0.1%. The liver MRI in ISIS 301012-CS6 on Day 176 (after 25 weeks of mipomersen treatment) showed an average liver fat fraction of 20.0% and by Day 359 (after 51 weeks of treatment) it was 24.6%.

Reviewer comment: In ISIS 301012-CS6, 16% of subjects had an average liver fat fraction >20% on at least 1 occasion. 41% of these subjects who developed liver fat fractions > 20% had elevations in ALT ≥3 × ULN. Thus, liver fat fraction >20% cannot be consistently identified by monitoring liver transaminases. While it may be reasonable to monitor patients on mipomersen with AST/ALT testing at regular intervals and to temporarily hold dosing while evaluating liver function (assessing bilirubin, INR, PT) and investigating for other causes of hepatic transaminase elevation, ALT/AST monitoring alone is not an adequate method to determine which individuals are developing significant hepatic fat elevations on mipomersen. If mipomersen is approved, consideration should be given to monitoring all patients with an ultrasound or MRI at baseline and every 6 months to assess for liver fat accumulation. The physician will then need to evaluate the individual's LDL-C reduction as well as liver fat and transaminase elevations in the calculation of the patient's benefit:risk profile when determining whether to continue therapy.

7.3.5.1.4 Hepatic Triglyceride Content in Phase 2 Trial ISIS 30102-CS10

Title of Study: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effect of ApoB Reduction by ISIS 301012 on Liver Triglyceride Content in Subjects with Varying Degrees of Hyperlipidemia

Study Centers: 1 site in The Netherlands

Publication: Visser ME, Akdim F, Tribble DL, Nederveen AJ, Kwoh TJ, Kastelein JJ, et al. Effect of apolipoprotein-B synthesis inhibition on liver triglyceride content in patients with familial hypercholesterolemia. J Lipid Res 2010;51(5):1057-62.

This was a randomized, double-blind, placebo-controlled study to measure the effect of treatment with mipomersen on liver TG content in patients with varying degrees of hyperlipidemia and risk for hepatic steatosis. The original study design included 4 cohorts (Cohorts A through D). Subsequent protocol amendments added 3 cohorts (Cohorts E, F, and G) to the study, truncated the enrollment of Cohort D, and eliminated Cohorts B and C. The study consisted of up to a 3-week screening period; a 4-week (Cohorts A and D), 13-week (Cohort E), or 52-week (Cohort G) treatment period; and a 20-week post-treatment follow-up period. Cohort F was an observational cohort, and therefore, was not

treated with study drug. Patients in this cohort underwent a 15-week MRS and ultrasound evaluation period. The study cohorts are described below.

Cohort A: Healthy volunteers with LDL-C <140 mg/dL, serum TG <200 mg/dL, hemoglobin A1c (HbA1c) <6.0%, and hepatic TG content <5% (as measured by MRS at screening).
Cohort B: Cohort B was eliminated in Amendment 3 to the protocol.
Cohort C: Cohort C was eliminated in Amendment 3 to the protocol.
Cohort D: In Amendment 3 to the protocol, Cohort D was closed to enrollment.
Cohort E: Patients with uncomplicated HeFH, ALT ≤1.5 × ULN, no evidence of insulin resistance or metabolic syndrome, and hepatic TG content <5% by magnetic resonance spectroscopy (MRS) at screening. Patients were to remain on their baseline statin ± ezetimibe regimen but were to wash out from other lipid-lowering agents (e.g., fenofibrate, non-dietary omega-3 fatty acids, and niacin) at least 8 weeks prior to the MRS at screening.
Cohort F: Patients with familial hypobetalipoproteinemia (FHBL). FHBL is a documented APOB gene mutation that results in the expression of a truncated form of apo B, apo B concentrations approximately 25% of those without the mutation and elevated hepatic TG levels, presumably due to the impairment of incorporation of TG into nascent VLDL particles. Patients in this cohort were evaluated by MRS, ultrasound, and laboratory tests; however, they were not treated with mipomersen or placebo.
Cohort G: Patients with well-controlled type 2 diabetes mellitus (HbA1c ≤8.0%), hypercholesterolemia (LDL-C >100 mg/dL), and normal serum TG levels (≤200 mg/dL). Patients were to have been on a stable dose of antidiabetic and lipid-lowering medications >3 months prior to screening and were expected to remain stable for the duration of the study. Note: At the time of this CSR, Cohort G had not yet completed all study procedures and is not included in this CSR.

Duration of Treatment:
Cohorts A = 4 weeks
Cohort E = 13 weeks
Cohort F was not treated with study drug.

Number of Patients:
Randomized:
Cohort A = 6 patients
Cohort E = 21 patients
Cohort F = 6 patients

Discontinued: 2 patients (1 patient from Cohort A for withdrawal of consent and 1 patient from Cohort E due to an AE of influenza-like illness)

Efficacy:

Efficacy analyses were performed using the comparison between the 13-week treatment mipomersen group and the placebo group of Cohort E.

- The median percent change in apo B from baseline to Day 99 with LOCF was 6.0% in the placebo group and -16.3% in the mipomersen 200 mg/week group (p=0.0006).
- The median percent change in LDL-C from baseline to Day 99 with LOCF was 0.7% in the placebo group and -15.9% in the mipomersen 200 mg/week group (p=0.0028).
- The median percent change in TC from baseline to Day 99 with LOCF was -0.8% in the placebo group and -11.8% in the mipomersen 200 mg/week group (p=0.0048).

Liver TG Content:
Hepatic triglyceride levels were measured by magnetic resonance spectroscopy (MRS) at baseline and after 4 and 13 weeks of treatment. Summary statistics were calculated for nominal changes in liver TG content using the 13-week treatment Cohort E and the observational Cohort F. From baseline to Day 99, the median change in liver TG content was -0.0% in the placebo group and 0.4% in the mipomersen group. The treatment comparisons between placebo and mipomersen at both time points were not statistically significant (p=0.0513). From baseline to Day 99, the mean change in liver TG content was -0.1% in the placebo group and 0.8% in the mipomersen group. The median change in liver TG content from baseline to Day 99 in the observational Cohort F (a control group with FHBL) was 0.8% (mean change was 0.7%). Following treatment with mipomersen 200 mg, 2 patients (1 patient in Cohort A and 1 patient in Cohort E) had a liver TG content >5.6% (clinically relevant threshold for ULN liver TG content), as measured by MRS.

For the majority of patients in Cohort E, abdominal ultrasound revealed no liver steatosis at baseline, Day 26, or Day 99. Three patients in Cohort E in the mipomersen group with no liver steatosis at baseline, as measured by abdominal ultrasound, were considered to have mild liver steatosis during the treatment period and post-treatment follow-up period as determined by abdominal ultrasound findings. Most patients in Cohort F had moderate to severe liver steatosis at baseline, Day 26, and Day 99.

Reviewer comment: This study shows a trend toward a small increase in hepatic triglyceride accumulation over time in the mipomersen group compared with the placebo group. The study is limited by the small sample size, a study population that was not at increased risk for fatty liver at baseline, and a short treatment duration (13 weeks).

7.3.5.1.5 Hepatic Safety Issues in Trial ISIS 301012-CS19

ISIS 301012-CS19 was a randomized, double-blind, placebo-controlled Phase 2 trial to assess the safety and efficacy of mipomersen in high-risk statin-intolerant individuals with hypercholesterolemia. A total of 34 individuals were randomized in a 2:1 ratio to receive mipomersen 200 mg (N = 22) or placebo (N = 12) in SC injections weekly, for 26 weeks of treatment, followed by a 24-week post-treatment follow-up period. One mipomersen subject was randomized but not treated.

ALT increases ≥3 × ULN on at least 1 occasion occurred in 8 (38.1%) individuals in the mipomersen group. Two of the 8 individuals had an elevation in ALT ≥5 × ULN during the treatment period and 1 individual (Patient 1497-1073) had an elevation in ALT ≥10 × ULN during the treatment period. Seven (33.3%) patients in the mipomersen group had 2 consecutive elevations in ALT ≥3 × ULN at least 7 days apart. Among patients with ALT increases ≥3 × ULN, none of the elevations was associated with significant increases in bilirubin. No patients in the placebo group experienced ALT increases ≥3 × ULN. Levels of ALT decreased and returned to normal levels during post-treatment.

Table 31. ISIS 301012-CS19: Incidence of Liver Transaminase Elevations

Parameter	Events n (%)	Placebo (N = 12) n (%)	Mipomersen (N = 21) n (%)
ALT maximum	>ULN and <2 × ULN	2 (16.7)	3 (14.3)
	≥2 × ULN and <3 × ULN	1 (8.3)	6 (28.6)
	≥3 × ULN and <5 × ULN	0 (0.0)	5 (23.8)
	≥5 × ULN and <10 × ULN	0 (0.0)	2 (9.5)
	≥10 × ULN	0 (0.0)	1 (4.8)
ALT	ALT ≥3 × ULN, 2 consecutive results (at least 7 days apart)	0 (0.0)	7 (33.3)
	≥3 × ULN in presence of bilirubin >ULN	0 (0.0)	0 (0.0)
AST maximum	>ULN and <2 × ULN	4 (33.3)	12 (57.1)
	≥2 × ULN and <3 × ULN	0 (0.0)	4 (19.0)
	≥3 × ULN and <5 × ULN	0 (0.0)	0 (0.0)
	≥5 × ULN and <10 × ULN	0 (0.0)	1 (4.8)
	≥10 × ULN	0 (0.0)	0 (0.0)
AST	≥3 × ULN, 2 consecutive results (at least 7 days apart)	0 (0.0)	1 (4.8)

Source: NDA 203568: CSR CS19: Table 14.3.4.3

The narratives for the individuals with ALT ≥10 × ULN and ALTs ≥5 × ULN and <10 × ULN are detailed in Appendix 9.4.

Liver fat content was evaluated in all individuals with an ALT levels ≥2 × ULN or for medical reasons. No individual underwent baseline hepatic MRS. Seventeen individuals [16 in the mipomersen group (73%) and 1 in the placebo group (8%)] had at least 1 post randomization hepatic MRS performed (see following table). For 11 of the 17 individuals, the first hepatic MRS was performed during treatment (range of treatment duration prior to MRS: 4 weeks to 26 weeks); the remaining 6 individuals received their first hepatic MRS during the post-treatment follow-up period. The range of fat fraction recorded in MRS assessments was 0.8% to 47.3%. All MRS assessments repeated after more than 20 weeks following dosing cessation showed reductions in hepatic fat fraction. There was no consistent association between ALT elevations and hepatic fat fraction but there appeared to be an association between hepatic fat increases and greater decreases in LDL-C and apo B.

Table 32. Hepatic Magnetic Resonance Spectroscopy Results in Individuals with ALT ≥2 × ULN in ISIS 301012-CS19

Patient no.	MRS Day	MRS Result: Liver fat fraction %	PET Day	% Change in Apo B From Baseline to PET	% Change in LDL-C From Baseline to PET
1497-1008	155	24.2	190	-56.5	-53.1
	197	28.3			
	350	9.9			
1497-1022	70	23.7	190	-67.1	-64.6
	205	47.3			
	345	27.1			
1497-1023	190	31.5	190	-76.1	-71.7
	346	5.0			
1497-1036	257	12.3	190	-56.0	-54.6
	345	5.9			
1497-1037	288	26.6	190	-69.3	-70.1
	344	17.7			
1497-1043	85	3.5	190	-36.3	-41.3
	133	8.2			
	190	13.3			
1497-1046	191	1.7	191	-23.2	-18.5
1497-1047	141	22.6	190	-57.5	-62.6
	190	33.0			
	344	21.9			
1497-1050	221	10.5	193	-33.0	-37.5
	359	4.7			
1497-1052	177	3.1	190	-26.2	-20.2
1497-1058	22	17.8	169	-45.8	-57.2

Patient no.	MRS Day	MRS Result: Liver fat fraction %	PET Day	% Change in Apo B From Baseline to PET	% Change in LDL-C From Baseline to PET
	120	34.7			
	176	42.0			
	337	28.4			
1497-1066	192	9.2	192	-49.9	-45.1
	351	1.4			
1497-1068	162	16.5	191	-34.4	-37.7
	246	19.8			
	345	9.5			
1497-1071	68	25.6	92	-75.5	-77.2
	95	37.0			
	250	18.3			
1497-1073	61	0.8	57	-35.2	-28.5
1497-1088	142	16.7	191	-67.1	-65.7
	191	22.2			
	352	7.2			
1497-1007*	128	24.7	190	-8.3	2.2

*Patient 1497-1007 received treatment with placebo. All other patients received mipomersen treatment.
Apo B = apolipoprotein B; LDL-C = low-density lipoprotein cholesterol; MRS = magnetic resonance spectroscopy; PET = primary efficacy time point.
Sources: NDA 203568; CSR CS19: Table 12-15

Liver biopsies were performed on 2 individuals who had elevations in ALT >3 × ULN and average liver fat fractions >20% on at least 1 occasion. Steatosis, mild steatohepatitis, and no appreciable fibrosis were observed. See Appendix 9.4 for additional details.

7.3.5.1.6 Hepatic Biopsies

During the clinical development program, 5 individuals had liver biopsies. All patients had increases in hepatic fat on MRS or MRI, and 4 of 5 had elevations in ALT ≥ 3 x ULN. Narratives for all patients with hepatic biopsies are provided in Section 9.4.3. These 5 biopsies showed hepatic fat with minimal signs of inflammation and with minimal to no liver fibrosis. There was no evidence of necrosis or severe inflammation in the biopsies. Although these findings are somewhat reassuring, the mipomersen treatment duration was short and necrosis or fibrosis develops over time.

Table 33. Results for Hepatic Biopsies Performed in Five Individuals in the Mipomersen Treatment Group

Patient ID Number	Trial Number	Days on Treatment Prior to Biopsy; ALT/AST	Findings
1497-7002	ISIS 301012-CS10	235; ALT 103 U/L (2.5xULN) AST 43 U/L	Lobular architecture with severe steatosis, more than 66%. Predominantly macrovesicular steatosis, mostly located in zones 2 and 3 and locally panlobular. Some microvesicular steatosis (PAS staining). Scattered ballooning hepatocytes were observed, predominantly perivenular, and degenerated hepatocytes with Mallory bodies. Lobular aggregates of lymphocytes were present in places, and Kupffer cells were present in the PAS-O with large quantities of cytoplasm with PAS-D-resistant tissue. There was slight pericellular fibrosis in zone 3. No iron. Grade 2 and stage I according to Brunt. NAFLD activity score 5 out or 8 with fibrosis score la. Conclusion: Severe steatosis and a minor steatohepatitic component with clearance reaction. Slight pericellular fibrosis (grade 2, stage 1 according to Brunt).
1497-7003	ISIS 301012-CS10	322	Steatosis present, mainly in a perivenular location with extension in the direction of the portal triads, on average moderate (up to 66%). Steatosis was predominantly rnacrovesicular, but in places hepatocytes were seen with much smaller fat drops in the cytoplasm. There were a few scattered ballooning hepatocytes where the nucleus was displaced towards the periphery and the cytoplasm is clumped together. Centrolobular focal occurrence of small groups of inflammatory cells, mixed mono- en polynuclear, and in places a degenerated or apoptotic hepatocyte. In the portal fields, no increased inflammatory infiltrate. Scattered lobular and portal field Kupffer cells were observed with large quantities of cytoplasm that was PAS-D positive. There was no appreciable fibrosis. The iron staining was negative. NASH grading according to Brunt: grade 1 (steatosis up to 66%, minimal ballooning, slight lobular inflammation and no portal inflammation), stage I. NAFLD grading according to NASH Clinical Research Network: 4/8. Fibrosis score: 0. Conclusion: Moderate steatosis and minor lobular inflammation without significant fibrosis
1497-1022	ISIS 301012-CS19	92; ALT max 160 U/L (3.9 x ULN)	Macrovesicular steatosis present in approximately three quarters of the hepatocytes. Slight increase in lymphocytes and segmental nuclear granulocytes in the liver parenchyma. In the portal triads, very slight increase, predominantly in lymphocytes, without affecting the parenchyma .Very minor fibrosis around the central veins. Minor steatohepatitis, although in accordance with Brunt, on the basis of the degree of steatosis (score 3), this could be called a moderate steatohepatitis. The

Patient ID Number	Trial Number	Days on Treatment Prior to Biopsy; ALT/AST	Findings
			iron and copper stains were negative. Conclusion: Severe steatosis (>66%) and mild steatohepatitis; no significant fibrosis
1497-1058	ISIS 301012-CS19	148; ALT 126 U/L (3.1 x ULN) AST 67 U/L	Conclusion: extensive macrovacuolar steatosis (<66%) (Bunt 3) with a minor steatohepatitic component, consistent with NASH. No appreciable fibrosis.
1587-6136	ISIS 301012-CS6	415; ALT 51 U/L AST 45 U/L	Marked macrovesicular and microvesicular steatosis, mild portal and lobular chronic inflammation, no fibrosis seen

Source: ISIS 301012-CS10 CSR, ISIS 301012-CS19 CSR, and ISIS 301012-CS6 CSR
Note: data are presented as of database cut off of 30 November 2011

7.3.5.1.7 Serum Biomarkers of Hepatic Fibrosis

Measurements of exploratory biomarkers of liver fibrosis, which included the Enhanced Liver Fibrosis (ELF) panel and cytokeratin 18 (CK18), measured as M30 (caspase-cleaved CK18) and M65 (measures both capsase-cleaved and intact CK18), were evaluated retrospectively. In populations with known chronic liver disease (e.g., nonalcoholic steatohepatitis or hepatitis C virus), elevations of these biomarkers have been correlated with liver biopsy fibrosis grade[62]. The ELF panel has not been prospectively studied in patients without known liver disease or in patients with FH or high-risk hyperlipidemia. This analysis used data from individuals in ISIS 301012-CS7 and ISIS 301012-CS6 (individuals originally enrolled in ISIS 301012-CS7). The ELF panel includes measurements of serum concentrations of hyaluronic acid (HA), amino-terminal propeptide of type III collagen (PIIINP), and tissue inhibitor of matrix metalloproteinase 1 (TIMP-1), and an algorithm is used to derive an ELF score from these results. Baseline ELF scores were similar in the 2 treatment groups (medians of 8.4 in the mipomersen-treated group and 8.6 in the placebo-treated group), but higher than the applicant anticipated. The applicant notes that in other, non-FH populations in which the ELF panel has been more extensively studied,[63] similar scores were generally associated with mild to moderate fibrosis. Hepatic fibrosis, however, has not been reported to be a significant finding in the FH population.

62 Parkes J, Guha IN, Roderick P, Harris S, Cross R, Manos MM, et al. Enhanced Liver Fibrosis (ELF) test accurately identifies liver fibrosis in patients with chronic hepatitis C. J Viral Hepat. 2011;18(1):23-31.
63 Rosenberg WM, Voelker M, Thiel R, Becka M, Burt A, et. al. Serum Markers Detect the Presence of Liver Fibrosis: A Cohort Study. Gastroenterology 2004;127:1704–1713

With mipomersen treatment, ELF scores increased above baseline values as early as Week 5 (the first time point tested), and continued to increase through up to 2 years of treatment (median scores throughout treatment in the mipomersen-treated group ranging from 8.7 to 9.5 in ISIS 301012-CS7 and from 8.7 to 10.2 in ISIS 301012-CS6). These changes were primarily driven by changes in HA (a major factor in the algorithm), although changes in PIIINP and TIMP-1 also contributed. In those patients who stopped dosing, ELF scores declined back towards baseline values within 24 weeks after dosing was discontinued. There appeared to be no association of maximum changes in ELF with maximum changes in ALT or AST, maximum absolute or percent change in hepatic fat, or percent change in apo B at PET.

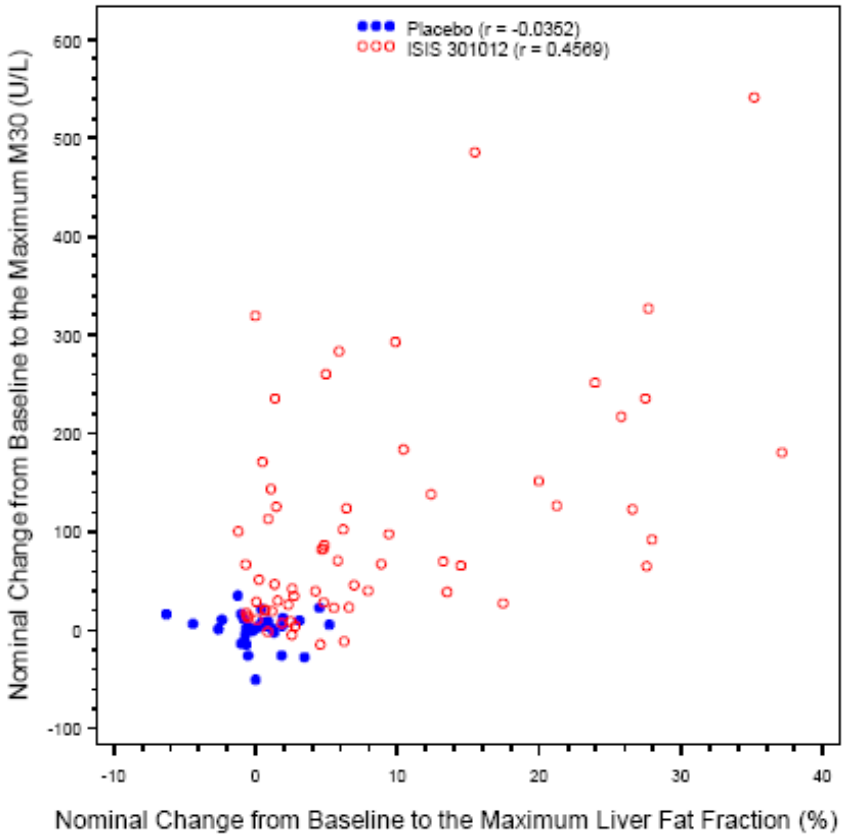
ELF scores were determined for the 5 individuals with liver biopsy data (treatment durations of approximately 3 to 14 months prior to biopsy), none of which were reported to show significant fibrosis. The ELF scores in these five cases increased with mipomersen administration. The ELF scores were not predictive of the histological fibrosis grade reported in the individuals biopsied. This reviewer agrees with the applicant that the rapid onset of the changes in ELF score (after 4 doses of mipomersen, at Week 5), the uniformity of the response, and the reversal toward baseline of mean and median values (within 24 weeks of cessation of treatment) do not reflect the development or subsequent resolution of liver fibrosis. In addition, the high baseline levels in both the mipomersen and placebo groups and the absence of fibrosis in those individuals where biopsy was performed suggest that the ELF scores do not reliably indicate underlying pathology in this population.

Baseline CK18 levels, as measured by median M30 and M65 concentrations, were similar in the 2 treatment groups (M30: medians of 138.5 U/L and 135.1 U/L in the placebo- and mipomersen-treated groups, respectively; M65: medians of 337.0 U/L and 344.7 U/L in the placebo- and mipomersen-treated groups, respectively). During the trial, median levels of M30 and M65 remained relatively stable in placebo-treated group, but increased in the mipomersen-treated group. Values trended towards baseline levels during the post-treatment period but the number of individuals in this analysis was smaller than earlier time points because many enrolled in OLE trial ISIS 301012-CS6. The M30/M65 ratio was approximately 0.4 in both treatment groups at baseline, and remained relatively constant throughout treatment and generally was at or above 0.35. The applicant comments that values > 0.20 are generally associated with a greater degree of apoptosis rather than necrosis in cell death events, while a ratio < 0.2 implies more necrosis than apoptosis may be taking place[64].

64 Linder S, Havelka AM, Ueno T, Shoshan MC. Determining tumor apoptosis and necrosis in patient serum using cytokeratin 18 as a biomarker. Cancer Lett. 2004; 214:1-9

Additional analyses were done to evaluate whether CK 18 concentrations were associated with hepatic fat or hepatic transaminase changes. Correlation coefficients for the comparison of nominal change from baseline to maximum M30 concentrations versus nominal change from baseline to maximum liver fat fraction, maximum liver fat fraction, and maximum ALT value were -0.0352, 0.2397, and -0.1894, respectively, for placebo-treated patients and 0.4569, 0.5712, and 0.5238, respectively, for mipomersen-treated patients (see figures below), suggesting moderate correlation between these variables in mipomersen-treated patients. Correlation coefficients for the comparison of nominal change from baseline to maximum M65 concentrations versus nominal change from baseline to maximum liver fat fraction, maximum liver fat fraction, and maximum ALT value were -0.0354, 0.1034, and -0.1053, respectively, for placebo-treated patients and 0.5163, 0.5862, and 0.6789, respectively, for mipomersen-treated patients, again suggesting moderate correlation between these variables in mipomersen-treated patients.

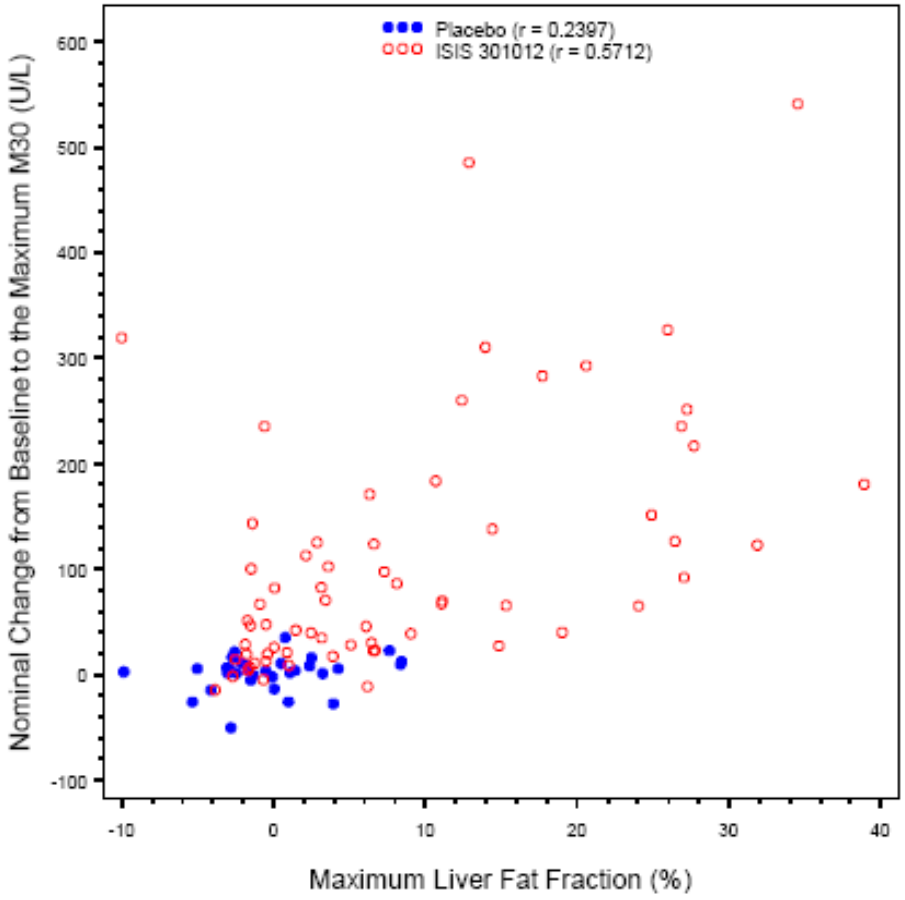
Figure 12. Scatterplot of Nominal Change from Baseline to Maximum M30 Concentration versus Nominal Change from Baseline to Maximum Liver Fat Fraction in ISIS 301012-CS7



r = Spearman correlation coefficient

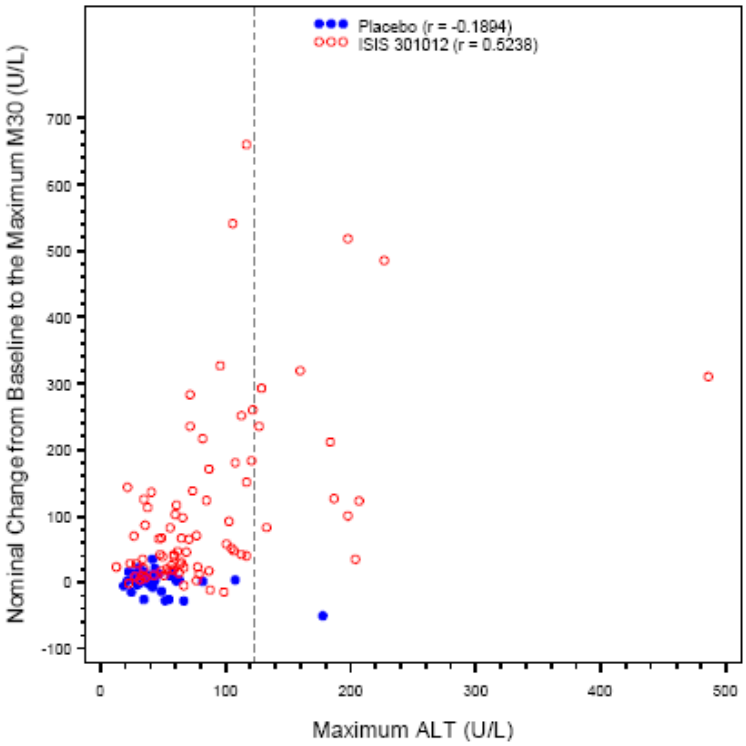
Source: NDA 203568; ISIS 301012-CS7 Figure 14.3.5.3.2

Figure 13. Scatterplot of Nominal Change from Baseline to Maximum M30 Concentration versus to Maximum Liver Fat Fraction in ISIS 301012-CS7



Source: ISIS 301012-CS7 Figure 14.3.5.3.1

Figure 14. Scatterplot of Nominal Change from Baseline to Maximum M30 Concentration versus Maximum ALT Value in ISIS 301012-CS7



Source: NDA 203568; ISIS 301012-CS7 Figure 14.3.5.3.3

Although moderate correlations were observed between CK18 concentrations and maximum absolute or nominal change in hepatic fat and maximum ALT, AST, and apo B values within the overall study populations, this was not consistently shown on an individual basis. There were 17 patients with the highest CK18 values (defined as M65 > 1000 U/L) and an examination of the individual data for these outliers showed that while mean CK18 elevations for the overall study populations generally paralleled with elevations in ALT values, some individual increases in CK18 values were observed in the absence of increases in ALT values. Similarly, individual increases in ALT values were not always accompanied by corresponding increases in CK18 values on an individual basis. The same issue occurred with liver fat increases. Increases in mean CK18 concentrations generally tracked with mean liver fat increases in the overall population; however, some individual increases in CK18 values were observed in the absence of increases in liver fat or with decreases in liver fat, and individual increases in liver fat values were not always accompanied by corresponding increases in CK18 values.

In conclusion, concentrations of CK18 were more variable in mipomersen-treated individuals than in placebo-treated individuals. Moderate correlations were

observed between CK18 concentrations and maximum absolute or nominal change in hepatic fat and maximum ALT, AST, and apo B values within the overall study populations. Marked increases in CK18 concentrations were not found to be consistently predictive of increases in other hepatic biomarkers or liver fat fraction in individuals. Maximum changes in CK18 (as measured by M65) did not appear to correlate with maximum changes in ELF components. In this trial, ELF scores and CK18 measurements did not prove to be useful in indentifying individuals with hepatic toxicity or abnormalities.

7.3.5.1.8 Applicant's Proposed Labeling for Hepatic Issues

7.3.5.2 Injection Site Reactions

ISRs were the most commonly reported AE in the clinical development program. In the pooled Phase 3 trials, 84.3% (220/261) of mipomersen-treated individuals experienced 3,683 ISR events and 33.3% (43/129) of individuals in the placebo group experienced 139 ISR events. ISRs were reported in 76.5% (26/34) of mipomersen-treated individuals in ISIS 301012-CS5 (individuals with HoFH). The most frequent ISR AEs for SC administration of mipomersen compared with placebo were injection site erythema (58.6%; 153/261 vs. 6.2%; 8/129), injection site pain (56.3%; 147/261 vs. 16.3%; 21/129), injection site haematoma (31.8%; 83/261 vs. 14.0%; 28/129), injection site pruritus (29.1%; 76/261 vs. 3.1%; 4/129), injection site swelling (17.6%; 46/261 vs. 0.0%), and injection site discolouration (17.2%; 45/261 vs. 2.3%; 3/129). Severe injection site erythema was reported in 1.9% of mipomersen-treated individuals, severe injection site pain in 3.1%, severe injection site hematoma in 0%, severe injection site pruritus in 0.8%, severe injection site swelling in 0.4%, and severe injection site discolouration in 0%.

In the pooled Phase 3 trials, 7.7% (20/261) of individuals experienced reactions such as erythema, pain, tenderness, or pruritus, at a previous injection site when subsequent injections were administered at a different site (AE term of “Injection site recall reaction”). No individuals who received placebo reported such reactions.

In the pooled Phase 3 trials, 13 of the 47 mipomersen-treated individuals (28%) who discontinued study treatment due to an AE did so because of an ISR. Thus, 5% (13/261) of all mipomersen-treated individuals discontinued due to a ISRs in these 6-month trials.

For individuals with HoFH, ISRs were reported in 76.5% (26/34) of mipomersen-treated individuals in ISIS 301012-CS5. For the HoFH individuals in the open-

label treatment extension trial, ISIS-301012-CS6, 36 (94.7%) had 441 injection site-related events. Two (5.3%) individuals had a severe injection site reaction. Four individuals discontinued treatment with study drug due to an injection site reaction: 2 individuals with Injection site pain, 1 patient with Injection site pain and Injection site swelling, and 1 patient with Injection site reaction.

For all individuals in the open-label treatment extension trial, ISIS-301012-CS6, 138 (97.9%) had 2970 injection site-related events. Nine (6.4%) individuals had a severe injection site reaction. Thirteen individuals discontinued treatment with study drug due to an injection site reaction.

In MIPO3500108, additional information regarding ISRs was collected. Over the 26-week treatment period, the mipomersen group had an average of 25 injection site reactions per patient; 10% of individuals in the mipomersen group had no AEs of injection site reactions and 90% of individuals had ≥1 AE of injection site reaction. The placebo group had an average of 6 injection site reactions per patient; 68% of individuals in the placebo group had no AEs of injection site reactions and 32% of individuals had ≥1 AE of injection site reaction. The most commonly reported ISR AEs were injection site erythema, which had a mean duration of 6 days in the mipomersen group compared to 2 days in the placebo group; injection site pain, with a mean duration of 4 days in the mipomersen group and no events in the placebo group; and injection site pruritus, with a mean duration of 5 days in the mipomersen group compared to 2 days in the placebo group. Injection site discoloration, which can involve persistent hypo- or hyper-pigmentation changes of the skin, was reported by 3 mipomersen-treated individuals in MIPO3500108 with a maximum average duration of 28 days.

ISIS 301012-CS301 was a Phase 1 study designed to assess local skin responses to mipomersen after a single dose (2 injections), to assess the effect of corticosteroid treatment to decrease potential local skin responses, and to determine whether local skin responses to mipomersen were lessened by dividing a single dose into multiple, small-dose, subcutaneous injections administered simultaneously in a non-contiguous manner. A total of 32 individuals had post-treatment skin biopsies of mipomersen-alone injection sites. Histological analyses of the mipomersen-alone injection sites revealed that 9 of the 32 individuals biopsied (28% [4/12 (33%) and 5/20 (25%) of individuals treated with 100 mg mipomersen and 200 mg mipomersen, respectively]) had findings consistent with leukocytoclastic vasculitis, containing the characteristic features of infiltrating neutrophils, prominent nuclear dust, lymphocytes, and eosinophils, as well as infiltration by local macrophages. There were no histopathologic findings in internal control skin biopsies taken from sites remote to the injection site. There was no evidence for necrosis, abscess, ulceration, subepidermal bulla, amyloidosis, acanthosis, or giant cell reaction.

Coadministration of corticosteroids (either topically or admixed with mipomersen) did not have an effect on the dermatological responses.

An evaluation of ISRs in the Phase 3 trials shows that for both placebo- and mipomersen-treated individuals, the first onset of ISRs was within 4 weeks of starting treatment. However, the percentage of individuals experiencing an ISR within the first 4 weeks was 3.5 times greater and the average time to onset of the AE was approximately 3 times shorter in the mipomersen group.

Table 34. Time-to-Onset of TEAEs-ISRs: Pooled Phase 3 Trials ISIS 301012-CS5, -CS7, -CS12 and MIPO3500108

	Total Placebo (N=129)	Total Mipomersen (N=261)
Time-to-onset of TEAEs ISR, n (%)		
>0 to 4 weeks	26 (20.2)	188 (72.0)
>4 to 8 weeks	6 (4.7)	17 (6.5)
>8 to 12 weeks	2 (1.6)	4 (1.5)
>12 to 16 weeks	2 (1.6)	5 (1.9)
>16 to 20 weeks	3 (2.3)	2 (0.8)
>20 to 24 weeks	2 (1.6)	1 (0.4)
>24 to 28 weeks	1 (0.8)	1 (0.4)
Unknown	1 (0.8)	2 (0.8)
n	42	218
Mean (SD)	5.79 (7.35)	1.94 (3.90)
Median	2.6	0.3

Only events started during the treatment period are included. The treatment period spans the time during which the study treatment is administered until the later of the primary efficacy timepoint (PET, date of the efficacy assessment closest to 14 days beyond the last study medication date) and 14 days beyond the last study medication date.

7.3.5.2.1 Applicant's Proposed Labeling for Injection Site Reactions

7.3.5.3 Flu-like Symptoms

Flu-like symptoms (FLS) were defined in the Mipomersen Pooled Data Analysis Plan by the preferred terms Influenza-like illness, Pyrexia, Chills, Myalgia, Arthralgia, Malaise, or Fatigue starting within 2 days after an injection. The definition of FLS that includes a time constraint of these events to within 2 days after an injection was not used in the individual trial analyses.

Pooled Phase 3 Trials of 6 Months Duration: FLS were reported by 29.9% (78/261) of mipomersen-treated individuals and 16.3% (21/129) of placebo-treated individuals. The most frequently reported individual symptoms in mipomersen group compared with the placebo group were Fatigue (11.1%; 29/261 vs. 6.2%; 8/129) and Influenza-like illness (11.9%; 31/261 vs. 1.6%; 2/129). Severe Fatigue or Influenza-like illness symptoms were reported by 0.8% (2/261) of mipomersen-treated individuals and no placebo-treated individuals.

In the pooled Phase 3 trials, 7 of the 47 mipomersen-treated individuals (15%) who discontinued study treatment due to an AE did so because of FLS. Thus, 3% (7/261) of all mipomersen-treated individuals as compared to 0.8% (1/129) of placebo-treated individuals discontinued due to FLS in these 6-month trials.

An evaluation of FLSs in the Phase 3 trials shows that for both placebo- and mipomersen-treated individuals, the first onset of ISRs was within 4 weeks of starting treatment. The percentage of individuals experiencing FLS within the first 4 weeks is approximately 2 times greater and the average time to onset of the AE was similar in the mipomersen group as compared to the placebo group.

Table 35. Time-to-Onset of TEAEs-FLS: Pooled Phase 3 Trials ISIS 301012-CS5, -CS7, -CS12 and MIPO3500108

	Total Placebo (N=129)	Total Mipomersen (N=261)
Time-to-onset of TEAEs FLS*, n (%)		
>0 to 4 weeks	12 (9.3)	49 (18.8)
>4 to 8 weeks	3 (2.3)	4 (1.5)
>8 to 12 weeks	1 (0.8)	2 (0.8)
>12 to 16 weeks	1 (0.8)	5 (1.9)
>16 to 20 weeks	0	4 (1.5)
>20 to 24 weeks	1 (0.8)	4 (1.5)
>24 to 28 weeks	1 (0.8)	2 (0.8)
Unknown	2 (1.6)	8 (3.1)
n	19	70
Mean (SD)	5.83 (7.52)	5.15 (7.47)
Median	3.1	1.3

*Flu-like symptoms include events that started within 2 days after a preceding mipomersen dose.

Only events started during the treatment period are included. The treatment period spans the time during which the study treatment is administered until the later of the primary efficacy timepoint (PET, date of the efficacy assessment closest to 14 days beyond the last study medication date) and 14 days beyond the last study medication date.

ISIS 301012-CS5 (individuals with HoFH): In the mipomersen group, 20.6% (7/34) reported FLS at least once in the trial. The most common symptoms were Influenza-like illness and Pyrexia. None of these events led to treatment discontinuation.

OLE Trial ISIS 301012-CS6: FLS were reported by 66.0% (93/141) of individuals with the preferred terms of Influenza-like illness, Fatigue, and Myalgia being used most commonly. Thirteen (9.2%) individuals had severe FLS. In this trial, 24.8% (35/141) of individuals discontinued treatment with study drug due to FLS.

OLE Trial ISIS 301012-CS6 (HoFH Subset): For the HoFH individuals in this trial, 71.1% (27/38) reported 48 events of FLS and 23.7% (9/38) discontinued due to FLS. One (2.6%) patient had a severe FLS. The most frequently reported FLS by Preferred Term on were Influenza-like illness (17 [44.7%] individuals), Pyrexia (6 [15.8%] individuals), and Myalgia (4 [10.5%] individuals).

The cause of the FLS is not known. In the dose-escalation trial ISIS 301012-CS3, there was a suggestion of an increased incidence of flu-like symptoms at the higher doses. Although the patient numbers are small, ISRs and FLS were reported in a higher percentage of individuals with the highest trough plasma levels of mipomersen, as compared to the overall patient population. FLS do not seem to correlate with changes in plasma cytokines (IL-1β, IL-13, IL-6, interferon alpha or beta) or chemokines (MCP-1 and MIP-1α) as assessed in Protocol MIPO3200309.

7.3.5.3.1 Applicant's Proposed Labeling for Flu-like Symptoms

7.3.5.4 Inflammatory and Immunological Issues

Pre-clinical Findings: Inflammatory effects were observed in the pre-clinical toxicology studies with injection site inflammation in mice, rats, and monkeys following SC injection. Mice and rats exhibited a dose-dependent increase in lymphoid organ weight, lymphoid hyperplasia, and multi-organ lymphohistiocytic cell infiltrates which was associated with increases in plasma chemokines such as MCP-1 and MIP-2. Acute and was also observed, primarily in monkeys. In monkeys treated with 30 mg/kg/week mipomersen, there was evidence of splenomegaly, increases in immunoglobulin G, complement activation with complement C3 depletion, and vascular intimal cell infiltrates with intimal thickening after 12 months of treatment. These monkeys also had significant decreases in plasma C3 levels, and transient increases in plasma CRP or IL-1β. There was also a question of whether some infections in the animals may have contributed to some of the pathology that was observed.

7.3.5.4.1 High Sensitivity C-reactive Protein (hsCRP) Effects

Notable chronic changes in hsCRP over time (from study baseline to the primary efficacy time point) were not seen in either mipomersen-treated individuals or placebo-treated individuals in the 6-month Phase 3 trials. A summary of the shifts for hsCRP in the pivotal trial (ISIS 301012-CS5) and the supportive trials (MIPO3500108, ISIS 301012-CS7, and ISIS 301012-CS12) is shown in the table below. After 26 weeks of therapy, the proportion of individuals with shifts in hsCRP levels from <3 mg/L pre-dose to ≥3 mg/L post-dose in the mipomersen group as compared to the placebo group was only notably higher in CS12 (mipomersen 14% vs placebo 2%). The proportion of individuals with hsCRP levels ≥3 mg/L at pre-dose and post-dose was similar in the placebo and mipomersen group.

Table 36. Summary of Shifts for C-Reactive Protein in Pivotal and Supportive Trials

	ISIS 301012-CS5		MIPO108		ISIS 301012-CS7		ISIS 301012-CS12	
	Placebo (N=17)	**Mipo (N=34)**	**Placebo (N=19)**	**Mipo (N=39)**	**Placebo (N=41)**	**Mipo (N=83)**	**Placebo (N=52)**	**Mipo (N=105)**
Individuals Assessed	17	31	18	37	41	81	50	98
Baseline Value Final Value								
<3								
<3, n (%)	11 (64.7)	18 (58.1)	8 (44.4)	20 (54.1)	32 (78.0)	67 (82.7)	30 (60.0)	49 (50.0)

	ISIS 301012-CS5		MIPO108		ISIS 301012-CS7		ISIS 301012-CS12	
	Placebo (N=17)	**Mipo (N=34)**	**Placebo (N=19)**	**Mipo (N=39)**	**Placebo (N=41)**	**Mipo (N=83)**	**Placebo (N=52)**	**Mipo (N=105)**
≥3, n (%)	1 (5.9)	1 (3.2)	4 (22.2)	5 (13.5)	3 (7.3)	6 (7.4)	1 (2.0)	14 (14.3)
≥3								
<3, n (%)	1 (5.9)	7 (22.6)	2 (11.1)	4 (10.8)	4 (9.8)	5 (6.2)	7 (14.0)	9 (9.2)
≥3, n (%)	4 (23.5)	5 (16.1)	4 (22.2)	8 (21.6)	2 (4.9)	3 (3.7)	12 (24.0)	26 (26.5)

Source: NDA 203568: ISS Statistical Table 3.4.5.1 S

In ISIS 301012-CS12, pre- and post-dose levels of hsCRP were measured at Week 17 and Week 26 in a subset of individuals following an amendment to the protocol. Mean and median elevations in hsCRP occurred in the mipomersen group, particularly at Week 17. In contrast, the placebo group experienced small mean increases at Week 17 and decreases in hsCRP at Week 26. The distribution of changes in hsCRP in the mipomersen group is skewed as shown by the mean change being greater than the median change and the greater standard deviation and range in the mipomersen group values. The hsCRP changes are summarized in the following table:

Table 37. hsCRP Change from Pre- to Post-Treatment at Weeks 17 and 26 in CS12

C-Reactive Protein (mg/L)	Visit	Timepoint Statistic	Placebo (N=52)	Mipomersen (N=105)
	Week 17	**Pre-dose**	28	39
		Mean (SD)	2.27 (3.38)	3.72 (4.44)
		Median (P25, P75)	1.2 (0.6, 2.3)	2.6 (1.0, 5.0)
		Min, Max	0.3, 17.1	0.2, 20.2
		Post-dose		
		Mean (SD)	3.06 (5.91)	8.77 (21.47)
		Median (P25, P75)	1.5 (0.6, 2.6)	4.2 (1.8, 6.5)
		Min, Max	0.2, 31.1	0.2, 130.0
		Nominal Change		
		Mean (SD)	0.79 (2.84)	5.04 (20.43)
		Median (P25, P75)	0.0 (-0.1, 0.2)	0.4 (-0.2, 2.4)
		Min, Max	-0.6, 14.0	-4.6, 125.3
	Week 26	**Pre-dose**	31	38
		Mean (SD)	2.58 (4.27)	3.64 (6.79)
		Median (P25, P75)	1.6 (0.7, 3.1)	1.9 (0.9, 3.4)
		Min, Max	0.3, 24.4	0.2, 41.1
		Post-dose		
		Mean (SD)	1.75 (1.33)	3.80 (4.32)

		Median (P25, P75) Min, Max	1.3 (0.7, 2.6) 0.4, 6.0	2.3 (1.2, 5.4) 0.2, 23.5
		Nominal Change		
		Mean (SD) Median (P25, P75) Min, Max	-0.83 (3.32) -0.2 (-0.5, 0.0) -18.4, 0.9	0.16 (7.09) 0.1 (-0.4, 1.1) -34.1, 23.0

- Individual Patient Changes: Thirty-nine individuals in the mipomersen group and 28 individuals in the placebo group had pre- and post-dose levels of hsCRP measured at Week 17. Seven (17.9%) individuals in the mipomersen group and 2 (7.1%) individuals in the placebo group had shifts in hsCRP levels from <3 mg/L pre-dose to ≥3 mg/L post-dose. Thirty-eight individuals in the mipomersen group and 31 individuals in the placebo group had pre- and post-dose levels of hsCRP measured at Week 26. Six (15.8%) individuals in the mipomersen group and 0 (0.0%) individuals in the placebo group had shifts in hsCRP levels from <3 mg/L pre-dose to ≥3 mg/L post-dose. Among individuals with pre- and post-dose levels of hsCRP measured at Week 17 and Week 26, eleven of 28 (39.3%) individuals in the mipomersen group and 2 of 25 (8.0%) individuals in the placebo group had shifts in hsCRP levels from <3 mg/L pre-dose to ≥3 mg/L post-dose at either of the 2 post-treatment assessments (Week 17 or Week 26). Two of 28 (7.1%) individuals in the mipomersen group and 0 of 25 (0.0%) individuals in the placebo group had shifts in hsCRP levels from <3 mg/L pre-dose to ≥3 mg/L post-dose at both of the post-treatment assessments (Week 17 and Week 26).

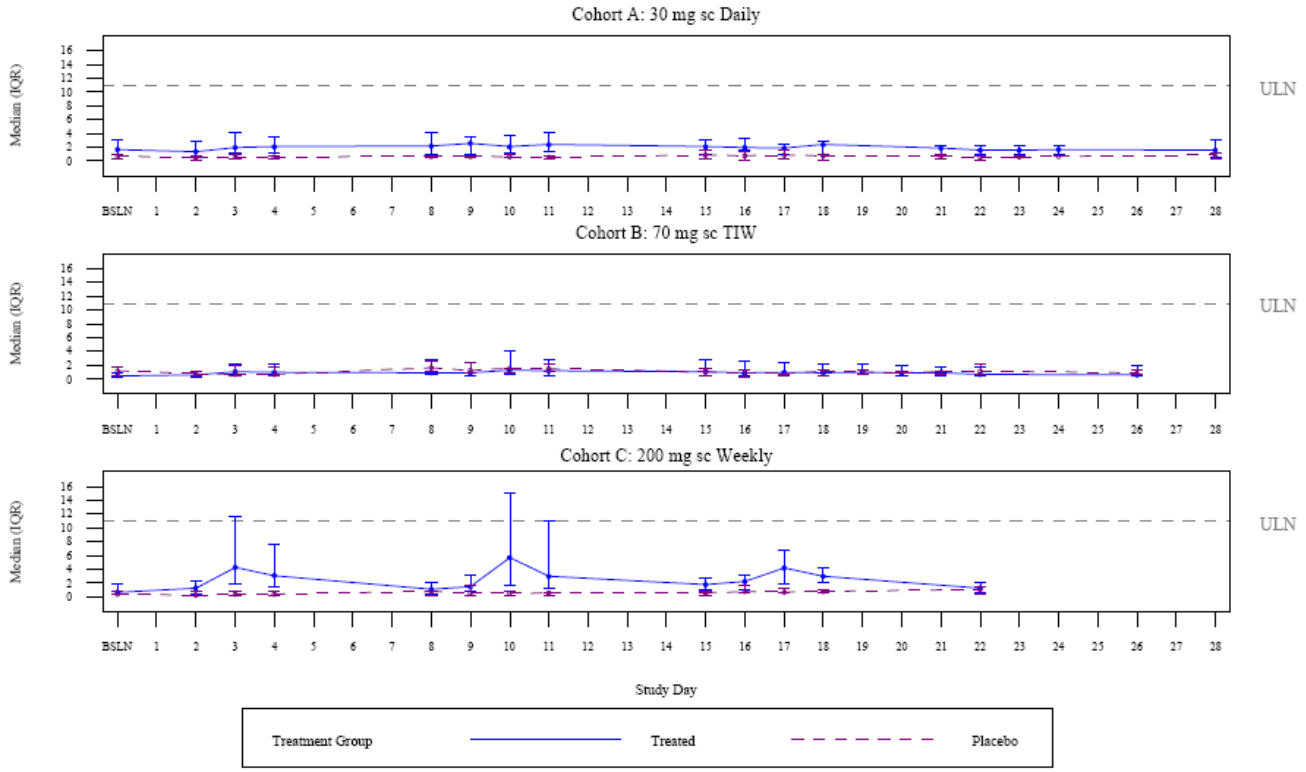
In OLE trial ISIS 301012-CS6, small increases in median hsCRP were seen between baseline and the end of treatment. Median hsCRP values returned to baseline by 24 weeks after the last dose of study drug. Specifically, the median hsCRP value was 0.8 mg/L at baseline. A small median increase was observed from baseline to Week 52 (0.1 mg/L; IQR: -0.3 mg/L, 0.7 mg/L) and from baseline to end of treatment (0.2 mg/L; IQR: -0.1 mg/L, 1.0 mg/L). Median hsCRP values returned to baseline 24 weeks after the last dose of study drug (median change 0.0 mg/L; IQR: -0.5 mg/L, 0.4 mg/L).

For the HoFH subset in the OLE trial ISIS 301012-CS6, the median hsCRP value was 1.1 mg/L (quartile 1 [Q1], quartile 3 [Q3]: 0.4 mg/L, 5.2 mg/L) at baseline. A small median increase was observed from baseline to end of treatment (0.2 mg/L; Q1, Q3: -0.3 mg/L, 1.6 mg/L). One patient (#1535-6005) had a severe AE of hsCRP increased. Treatment with mipomersen was interrupted and the event was resolved by the end of the trial. The patient also had an AE of gastrointestinal/viral symptoms that was moderate in severity around the same time as the hsCRP elevation.

Protocol MIPO3200309 was a Phase 1, randomized, double-blind, placebo-controlled trial designed to evaluate the relative bioavailability, pharmacokinetics (PK), safety, and tolerability of 3 weeks of dosing with different subcutaneous (SC) regimens of mipomersen (200 mg once weekly, 70 mg thrice weekly, and 30 mg daily), in healthy volunteers. This trial assessed high-sensitivity C-reactive protein (hsCRP), complement activation (Bb and C5a), and inflammatory markers (interleukin [IL]-1β, IL-6, IL-13, Interferon-α, Interferon-β, monocyte chemotactic protein [MCP]-1, and macrophage inflammatory protein-1α).

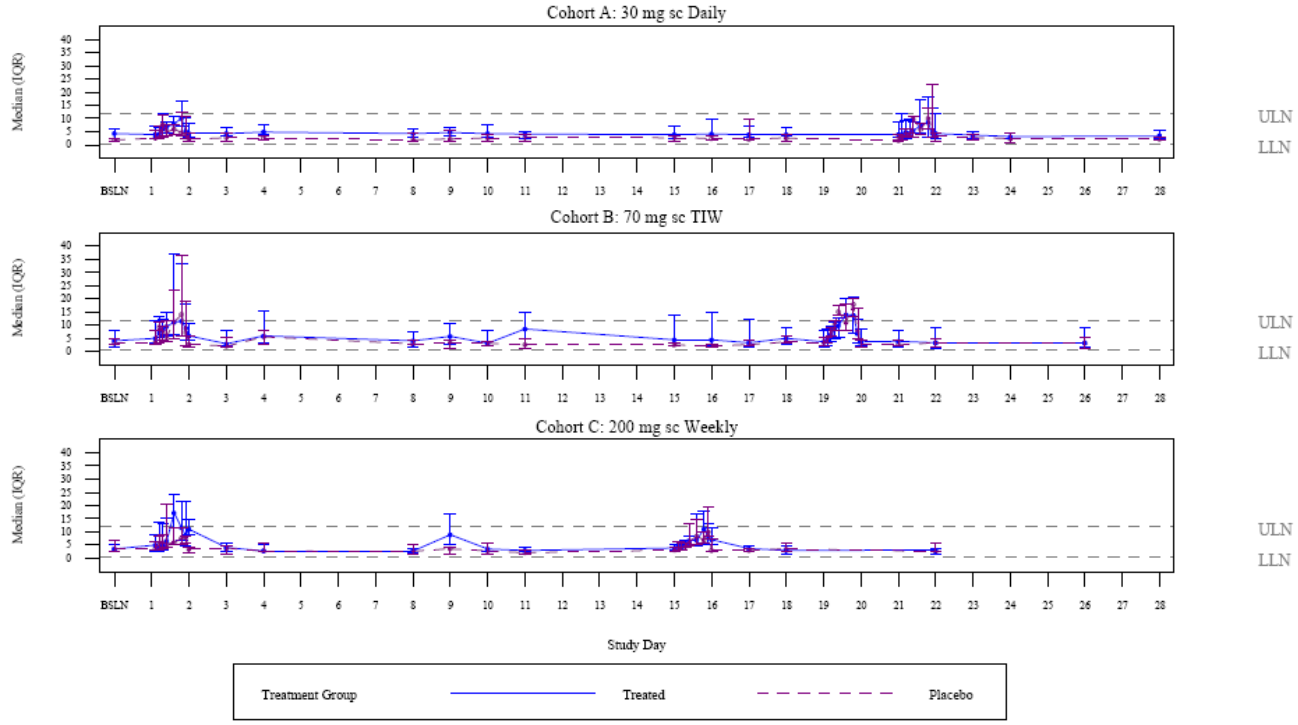
In MIPO3200309, acute transient elevations in hsCRP were seen post-dosing with a peak approximately 2 days after the administration of a 200 mg once weekly dose (median change; IQR: 3.8 mg/L; 0.8-9.8, n=21) with less effect on hsCRP seen at the lower doses (70 mg dose: 0.4 mg/L; 0.2-1.7, n=21 and 30 mg dose: 0.3 mg/L; -0.2-1.2, n=21). Changes did occur in IL-6 in the 200 mg mipomersen group, but they were not generally associated with hsCRP increases. Similar changes in IL-6 occurred across treatment groups, including placebo. Most changes in hsCRP were <10 mg/L or only slightly above; most changes in IL-6 were below or only slightly above the ULN. No increases in the cytokines IL-1β, IL-13, IL-6, interferon alpha or beta or the chemokines MCP-1 and MIP-1α were observed in mipomersen-treated subjects compared to placebo-treated subjects after the first or last dose in this 3-week trial.

Figure 15. Median (IQR) High Sensitivity CRP (hsCRP) (mg/L) Over Time



Source: NDA 203568: CSR MIPO3200309: Figure 14.3.4.6-1

Figure 16. Median (IQR) IL-6 (pg/mL) Over Time



Source: NDA 203568: CSR MIPO3200309: Figure 14.3.4.6-4

Reviewer comment: Mipomersen causes predominantly short-term elevations in the inflammatory marker hsCRP. These transient elevations in hsCRP in the mipomersen group are concerning and it is not known what the clinical significance of these elevations are and whether these changes in hsCRP negatively influence cardiovascular morbidity.

7.3.5.4.2 Complement Effects

Complement activation, as measured by an increase in complement split products (C5a and Bb), has not been seen following mipomersen administration at any dose in the selected Phase 1 and Phase 2 clinical trials in which complement was measured. Complement split product Bb, was measured in clinical trials because it was slowly cleared from plasma and was felt to provide a more accurate measure of alternative pathway activation. Bb is not biologically active, unlike C3a and C5a, but the latter are rapidly cleared and more difficult to follow over time.

In the Phase 1 trial MIPO3200309, baseline blood samples for the complement split products (C5a and Bb) were taken 5 minutes before dosing. Blood samples for complement split products were taken 4 hours post-dose on Dosing Days 1, 8, 15, and 21 for subjects in the mipomersen 30 mg QD group; 4 and 24 hours

post-dose on Dosing Days 1, 8, 15, and 19 for subjects in the mipomersen 70 mg TIW group; and 4 and 24 hours post-dose on Dosing Days 1, 8, and 15 for subjects in the mipomersen 200 mg QW group. There was no evidence of complement activation (an increase in C5a or Bb) in subjects who received mipomersen.

Circulating levels of an intact complement factor, C3, were measured in Phase 3 trials (excluding ISIS 301012-CS5) pre-dose and at specified post-dose times (a week after selected doses). Modest decreases in C3 were observed in both placebo and mipomersen treatment groups in the pooled Phase 3 placebo-controlled trials (median percent change in C3 in mipomersen-treated individuals was -7.2 vs. -3.0 in placebo-treated individuals at Week 28/ET, corresponding to median values of 1.31 g/L and 1.38 g/L, respectively; normal range 0.9 to 1.8 g/L. At Week 28, the mean change in C3 in the placebo group was -9.6 mg/dL in ISIS 301012-CS12, -6.4 mg/dL in ISIS 301012-CS7, and 13.8 mg/dL in MIPO3500108. The mean change in C3 in the mipomersen group was -10.6 mg/dL in ISIS 301012-CS12, -12.0 mg/dL in ISIS 301012-CS7, and -5.9 mg/dL in MIPO3500108.

In the supportive 6-month Phase 3 trials, the mean change in ESR in the mipomersen group ranged from -4.8 mm/hr in ISIS 301012-CS12 to 2.7 mm/hr in ISIS301012-CS7. The mean change in ESR in the placebo group ranged from -4.3 mm/hr in ISIS 301012-CS12 to 3.1 mm/hr in MIPO3500108.

Decreases in C3 occurred in OLE trial ISIS 301012-CS6 (mean 24.8 mg/dL decrease from baseline at Week 104, corresponding to a mean value of 111.8 mg/dL). In individuals from ISIS 301012-CS6 who discontinued treatment, mean C3 levels returned toward baseline by 24 weeks post-last dose.

The clinical significance of these findings is not known.

7.3.5.5 Renal Issues

In the clinical trials, renal function was assessed by evaluation of proteinuria, urine beta-2 microglobulin (increased urine levels are seen in proximal renal tubular damage), serum creatinine, urea and electrolytes, and changes in calculated glomerular filtration rate (GFR). GFR estimates were calculated using the Modification of Diet in Renal Disease (MDRD) formula based on isotope dilution mass spectrometry (IDMS)-calibrated creatinine.

As shown in the table below, in the pooled Phase 3 analyses, the numbers were small but there were numerically more renal-related adverse events, primarily proteinuria, in the mipomersen group as compared to the placebo group.

Table 38. Incidence of Renal Adverse Events Associated in the Pooled, Phase 3 Placebo-Controlled Trials of 6 Months Duration

System Organ Class Preferred Term	Treatment Arm	
	Placebo (N=129) n (%)	Mipomersen (N=261) n (%)
Investigations (Renal-related)		
Blood creatinine increased	2 (1.6)	3 (1.1)
Protein urine present	1 (0.8)	2 (0.8)
Blood urea increased	2 (1.6)	0 (0.0)
Red blood cells urine positive	0 (0.0)	2 (0.8)
White blood cells urine positive	1 (0.8)	1 (0.4)
Nitrite urine present	0 (0.0)	1 (0.4)
Urine leukocyte esterase positive	0 (0.0)	1 (0.4)
Renal and urinary disorders	**6 (4.7)**	**16 (6.1)**
Proteinuria	1 (0.8)	6 (2.3)
Renal cyst	1 (0.8)	4 (1.5)
Pollakiuria	1 (0.8)	2 (0.8)
Dysuria	1 (0.8)	1 (0.4)
Albuminuria	0 (0.0)	1 (0.4)
Azotaemia	0 (0.0)	1 (0.4)
Chromaturia	0 (0.0)	1 (0.4)
Haematuria	0 (0.0)	1 (0.4)
Micturition urgency	0 (0.0)	1 (0.4)
Nephrolithiasis	1 (0.8)	0 (0.0)
Nocturia	1 (0.8)	0 (0.0)
Stress urinary incontinence	0 (0.0)	1 (0.4)
Urge incontinence	0 (0.0)	1 (0.4)

Source: NDA 203568: ISS Statistical Table 3.2.2.1
On-treatment adverse events are defined as adverse events that started during the treatment period. The treatment period spans the time during which the study treatment is administered until the later of the primary efficacy time point (PET, date of the efficacy assessment closest to 14 days beyond the last study medication date) and 14 days beyond the last study medication date.
If a patient had >1 event within a particular system organ class or preferred term, he/she was counted only once for that system organ class or preferred term.

In the Phase 3 pooled trials, as shown the table below, there was no consistent trend for worsening GFR when assessed by shift analysis (baseline to end of treatment) between mipomersen and placebo individuals in these 6-month trials.

Table 39. Phase 3 Pooled Data Analysis of Shift in Glomerular Filtration Rate from Baseline to End of Treatment using MDRD Formula Based on IDMS-Calibrated Creatinine

Baseline Value Final Value	**Placebo** **(N=129)**	**ISIS 301012 200 mg** **(N=261)**
Individuals Assessed at both timepoints	**128**	**257**
<60 mL/min/1.73m^2		
<60 mL/min/1.73m^2	5 (3.9)	9 (3.5)
60-<90 mL/min/1.73m^2	2 (1.6)	10 (3.9)
90-<120 mL/min/1.73m^2	0	0
≥120 mL/min/1.73m^2	0	0
60 to < 90 mL/min/1.73m^2		
<60 mL/min/1.73m^2	2 (1.6)	9 (3.5)
60-<90 mL/min/1.73m^2	39 (30.5)	70 (27.2)
90-<120 mL/min/1.73m^2	14 (10.9)	26 (10.1)
≥120 mL/min/1.73m^2	0	0
90 to < 120 mL/min/1.73m^2		
<60 mL/min/1.73m^2	0	0
60-<90 mL/min/1.73m^2	9 (7.0)	17 (6.6)
90-<120 mL/min/1.73m^2	36 (28.1)	72 (28.0)
≥120 mL/min/1.73m^2	7 (5.5)	16 (6.2)
≥ 120 mL/min/1.73m^2		
<60 mL/min/1.73m^2	0	0
60-<90 mL/min/1.73m^2	0	0
90-<120 mL/min/1.73m^2	4 (3.1)	7 (2.7)
≥120 mL/min/1.73m^2	10 (7.8)	21 (8.2)

Source: NDA 203568: ISS Statistical Table PDAP 3 Ad hoc 9

As shown in Table 40, there was more proteinuria occurring in the pooled mipomersen-treated group (23/256; 9.0%) compared to placebo (4/128; 3.1%). As shown in Table 38, the differences in reported AEs of proteinuria in the Pooled Phase 3 analysis was smaller than the differences in the dipstick results (6/261 mipomersen-treated individuals; 2.3%, vs. 1/129 placebo-treated individuals; 0.8%). The median change in urine beta-2 microglobulin was 0 mg/mL in both treatment groups although the mean change was slightly increased in the pooled mipomersen group (0.10 in the mipomersen vs 0.01 in the placebo group). Urine albumin, urine quantitative protein, urine creatinine, and glomerular filtration rate were slightly increased in the pooled mipomersen

group as compared to the placebo group. Serum creatinine, serum albumin and blood urea nitrogen were not different between mipomersen and placebo.

Table 40. Change from Baseline to Week 28/Early Termination for RenalFunction-Associated Laboratory Parameters for ISIS 301012-CS5 and the Pooled, Phase 3 Placebo-Controlled Trials

Parameter Time Point, n Statistic	ISIS 301012-CS5		TOTAL Phase 3 Pooled	
	Placebo (N=17)	Mipomersen (N=34)	Placebo (N=129)	Mipomersen (N=261)
Albumin, Urine (mg/dL)				
Baseline Value, n	17	34	128	256
Mean (SD)	4.34 (8.29)	1.19 (1.26)	2.69 (7.80)	2.56 (10.34)
Median (P25, P75)	0.68 (0.45, 1.27)	0.77 (0.44, 1.24)	0.75 (0.45, 1.37)	0.73 (0.43, 1.39)
Week 28/ET, n	17	34	125	247
Mean (SD)	3.99 (14.51)	1.26 (1.11)	1.90 (5.94)	10.33 (118.56)
Median (P25, P75)	0.41 (0.33, 0.52)	1.03 (0.45, 1.51)	0.68 (0.40, 1.32)	0.88 (0.49, 1.70)
Nominal Change, n	17	34	125	243
Mean (SD)	-0.36 (11.21)	0.08 (1.00)	-0.84 (6.93)	0.20 (10.71)
Median (P25, P75)	-0.17 (-0.51, 0.09)	0.05 (-0.32, 0.61)	0.0 (-0.36, 0.25)	0.08 (-0.24, 0.56)
Albumin/Creatinine Ratio, urinalysis (mg/g)				
Nominal Change, n	17	34	125	243
Mean (SD)	-14.98 (74, 268)	-1.59 (7, 179)	-16.923 (134.916)	-16.923 (134.916)
Median (P25, P75)	-1.10 (-1.59, 0.47)	-0.71 (-2.65, 1.39)	-0.01 (-1.59, 1.78)	-0.08 (-2.49, 2.96)
Beta-2-Microglobulin, Urine (mg/L)				
Baseline Value, n	16	29	123	248
Mean (SD)	0.20 (0.00)	0.21 (0.05)	0.21 (0.04)	0.24 (0.30)
Median (P25, P75)	0.20 (0.20, 0.20)	0.20 (0.20, 0.20)	0.20 (0.20, 0.20)	0.20 (0.20, 0.20)
Week 28/ET, n	17	34	124	243
Mean (SD)	0.20 (0.00)	0.23 (0.09)	0.21 (0.05)	0.33 (1.05)
Median (P25, P75)	0.20 (0.20, 0.20)	0.20 (0.20, 0.20)	0.20 (0.20, 0.20)	0.20 (0.20, 0.20)
Nominal Change, n	16	29	120	232
Mean (SD)	0.00 (0.00)	0.02 (0.07)	0.01 (0.04)	0.10 (1.09)
Median (P25, P75)	0.0 (0.0, 0.0)	0.0(0.0, 0.0)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Quantitative Protein, Urine (mg/dL)				
Baseline Value, n	17	34	128	256
Mean (SD)	13.4 (14.5)	8.4 (3.5)	12.4 (11.6)	13.2 (19.3)

Parameter Time Point, n Statistic	ISIS 301012-CS5		TOTAL Phase 3 Pooled	
	Placebo (N=17)	Mipomersen (N=34)	Placebo (N=129)	Mipomersen (N=261)
Median (P25, P75)	7 (6, 11)	6 (6, 11)	9 (7, 13)	9 (6, 13)
Week 28/ET, n	17	34	125	247
Mean (SD)	13.0 (22.0)	12.1 (6.2)	11.7 (13.1)	26.6 (157.7)
Median (P25, P75)	7 (6, 8)	10 (7, 14)	9 (6, 12)	12 (9, 17)
Nominal Change, n	17	34	125	243
Mean (SD)	-0.4 (22.1)	3.7 (5.1)	-0.8 (14.5)	3.4 (22.7)
Median (P25, P75)	0 (-2, 2)	4 (0, 5)	0 (-2, 2)	3 (0, 7)
Creatinine, Urine (mg/dL)				
Baseline Value, n	17	34	128	256
Mean (SD)	140.95 (70.14)	129.67 (77.42)	140.32 (75.49)	141.16 (84.65)
Median (P25, P75)	148.9 (87.0, 177.8)	127.2 (62.0, 163.0)	138.1 (80.8, 186.3)	130.3 (81.7, 178.7)
Week 28/ET, n	17	34	125	247
Mean (SD)	110.64 (69.72)	157.93 (77.04)	137.14 (80.43)	153.56 (86.41)
Median (P25, P75)	92.9 (68.0, 138.0)	163.8 (95.4, 217.0)	125.0 (71.0, 175.6)	143.5 (87.9, 201.3)
Nominal Change, n	17	34	125	243
Mean (SD)	-30.31 (86.02)	28.25 (82.55)	-4.84 (84.60)	12.02 (87.18)
Median (P25, P75)	-25.0 (-73.8, 50.9)	43.9 (-30.9, 88.6)	-2.7 (-51.8, 41.1)	9.2 (-34.9, 62.4)
Glomerular Filtration Rate (mL/min/1.73 m2)				
Baseline Value, n	17	34	129	261
Mean (SD)	123.33 (52.11)	111.86 (24.60)	99.630 (30.491)	97.646 (25.039)
Median (P25, P75)	108.87 (96.00, 117.50)	110.80 (97.94, 128.31)	97.26 (80.94, 110.33)	97.34 (80.73, 112.94)
Week 28/ET, n	17	34	128	257
Mean (SD)	123.92 (49.23)	119.50 (27.46)	101.29 (30.01)	100.22 (25.37)
Median (P25, P75)	119.02 (90.33, 132.98)	117.86 (98.52, 136.81)	98.11 (81.41, 111.49)	98.59 (84.20, 116.39)
Nominal Change, n	17	34	128	257
Mean (SD)	0.59 (12.72)	7.64 (14.44)	1.64 (13.14)	2.90 (14.90)
Median (P25, P75)	-1.88 (-8.10, 12.09)	8.20 (0.00, 15.47)	1.73 (-5.44, 11.66)	2.40 (-6.13, 12.39)
Urine Protein Dipstick Result at Baseline				
<1+, n/N (%)	14 / 17 (82.4)	34 / 34 (100.0)	119/129 (92.2)	247/260 (95.0)
≥1+, n/N (%)	3 / 17 (17.6)	0 / 34 (0.0)	10/129 (7.8)	13/260 (5.0)
Urine Protein Dipstick				

Parameter Time Point, n Statistic	ISIS 301012-CS5		TOTAL Phase 3 Pooled	
	Placebo (N=17)	Mipomersen (N=34)	Placebo (N=129)	Mipomersen (N=261)
Result at Week 28/ET				
<1+, n/N (%)	16 / 17 (94.1)	33 / 34 (97.1)	124/128 (96.9)	233/256 (91.0)
≥1+, n/N (%)	1 / 17 (5.9)	1 / 34 (2.9)	4/128 (3.1)	23/256 (9.0)
Albumin (Serum) (g/dL)				
Baseline Value, n	17	34	129	261
Mean (SD)	4.51 (0.27)	4.58 (0.30)	4.52 (0.30)	4.54 (0.31)
Median (P25, P75)	4.5 (4.4, 4.6)	4.6 (4.5, 4.8)	4.5 (4.3, 4.7)	4.5 (4.4, 4.7)
Week 28/ET, n	17	34	128	257
Mean (SD)	4.52 (0.28)	4.52 (0.36)	4.48 (0.29)	4.51 (0.32)
Median (P25, P75)	4.5 (4.4, 4.7)	4.6 (4.3, 4.7)	4.5 (4.3, 4.6)	4.5 (4.3, 4.7)
Nominal Change, n	17	34	128	257
Mean (SD)	0.02 (0.24)	-0.06 (0.31)	-0.05 (0.27)	-0.03 (0.26)
Median (P25, P75)	0.0	0.0 (-0.3, 0.1)	0.0 (-0.3, 0.1)	0.0 (-0.2, 0.1)
Creatinine (Serum) (mg/dL)				
Baseline Value, n	17	34	129	261
Mean (SD)	0.74 (0.16)	0.79 (0.20)	0.83 (0.20)	0.83 (0.21)
Median (P25, P75)	0.71 (0.61, 0.81)	0.76 (0.65, 0.87)	0.80 (0.67, 0.97)	0.80 (0.69, 0.93)
Week 28/ET, n	17	34	128	257
Mean (SD)	0.73 (0.16)	0.74 (0.18)	0.82 (0.21)	0.81 (0.19)
Median (P25, P75)	0.74 (0.61, 0.79)	0.72 (0.62, 0.80)	0.79 (0.66, 0.93)	0.78 (0.68, 0.92)
Nominal Change, n	17	34	128	257
Mean (SD)	-0.01 (0.06)	-0.05 (0.09)	-0.01 (0.10)	-0.03 (0.11)
Median (P25, P75)	0.02 (-0.03, 0.03)	-0.03 (-0.08, 0.00)	-0.01 (-0.07, 0.04)	-0.02 (-0.08, 0.05)
Blood Urea Nitrogen (mg/dL)				
Baseline Value, n	17	34	129	261
Mean (SD)	12.1 (3.2)	11.9 (3.9)	14.7 (4.7)	15.2 (5.3)
Median (P25, P75)	12 (10, 15)	11 (9, 14)	14 (11, 17)	14 (12, 18)
Week 28/ET, n	17	34	128	257
Mean (SD)	11.6 (3.4)	11.8 (3.2)	15.1 (5.5)	15.3 (4.8)
Median (P25, P75)	12 (8, 14)	11 (10, 13)	14 (12, 18)	15 (12, 18)
Nominal Change, n	17	34	128	257
Mean (SD)	-0.5 (3.0)	-0.1 (3.8)	0.4 (3.8)	0.0 (3.9)
Median (P25, P75)	0 (-3, 2)	-1 (-2, 3)	0 (-2, 3)	0 (-2, 2)

Source: NDA 203568: ISS Statistical Tables 3.4.1-1a.1S, Table 3.4.1-7a.1S, Table 3.4.4.1 and Table 3.4.4.1S CI, confidence interval; ET, early termination; Max, maximum; Min, minimum; P25, 25th percentile, P75, 75th percentile, SD, standard deviation

For the HoFH population studied in ISIS 301012-CS5, no meaningful differences from the above results were noted.

- The mean change in BUN was -0.1 mg/dL (-0.042 mmol/L) in the mipomersen group and -0.5 mg/dL (-0.168 mmol/L) in the placebo group.
- The mean change in creatinine was -0.046 mg/dL (-4.0 µmol/L) in the mipomersen group and -0.005 mg/dL (-0.5 µmol/L) in the placebo group.
- The mean change in glomerular filtration rate was 7.638 mL/min/1.73 m^2 in the mipomersen group and 0.590 mL/min/1.73 m^2 in the placebo group.
- Both treatment groups had decreases in the mean albumin/creatinine ratio (ACR) from baseline to Week 28/ET (median change of -0.71 mg/g for the mipomersen group -1.10 mg/g for the placebo group).

Table 41. ISIS 301012-CS5: Shift Analysis for Renal Parameters

Parameter	Events n (%)	Placebo (N = 17) n (%)	Mipomersen (N = 34) n (%)
Proteinuria (dipstick)	≥1+	3 (17.6)	9 (26.5)
	≥2+	3 (17.6)	1 (2.9)
Serum creatinine (men) [a]	Increase ≥0.3 mg/dL above baseline [b]	0 (0.0)	1 (6.7)*
Serum creatinine (women) [c]	Increase ≥0.2 mg/dL above baseline	0 (0.0)	0 (0.0)

[a] There were 7 men in the placebo group, 15 in the mipomersen group, and 22 overall.
[b] Percentages are out of the total number of treated male individuals for the particular treatment group.
[c] There were 10 women in the placebo group, 19 in the mipomersen group, and 29 overall.
Source: NDA 203568: CSR ISIS 301012-CS5: Table 14.3.4.3
* At baseline, Patient 1501-8217 had a creatinine level of 1.3 mg/dL, BUN of 22 mg/dL, and a glomerular filtration rate of 67.1 mL/min/1.73 m^2. On 2 occasions during the trial, the patient's creatinine and BUN became elevated and glomerular filtration rate became lowered (Week 5: creatinine of 1.7 mg/dL, BUN 28 mg/dL, and glomerular filtration rate of 49.4 mL/min/1.73m^2; Week 26: creatinine of 1.6 mg/dL, BUN 26 mg/dL, and glomerular filtration rate of 53.5 mL/min/1.73m^2). After these occasions, renal function parameters returned to baseline levels.

In a Phase 3 trial, Trial ISIS 301012-CS12, analyses of renal function were compared in individuals with and without diabetes. Similar results after treatment were observed in individuals with and without diabetes.

- For individuals with diabetes, from baseline to Week 28/ET, the mean change in creatinine was -0.02 mg/dL for the mipomersen group and -0.02 mg/dL for the placebo group. For individuals without diabetes, from baseline to Week 28/ET, the mean change in creatinine was -0.04 mg/dL for the mipomersen group and -0.00 mg/dL for the placebo group.
- For individuals with diabetes, from baseline to Week 28/ET, the mean change in glomerular filtration rate was 2.13 mL/min/1.73m^2 for the

mipomersen group and 3.72 mL/min/1.73m^2 for the placebo group. For individuals without diabetes, from baseline to Week 28/ET, the mean change in glomerular filtration rate was 4.79 mL/min/1.73m^2 for the mipomersen group and 1.45 mL/min/1.73m^2 for the placebo group.

- In the combined diabetic and non-diabetic population, 28 individuals [26.7%] in the mipomersen group and 9 [17.3%] in the placebo group had proteinuria ≥1+. Five [4.8%] in the mipomersen group and 1 [1.9%] in the placebo group had proteinuria ≥2+.

In OLE trial ISIS 301012-CS6, 55/141 (39.0%) of individuals had proteinuria ≥ 1+ by dipstick measurement and 9/141 (6.4%) of individuals had proteinuria ≥ 2+. Of the 84 male individuals, 5 (6.0%) had an increase in serum creatinine ≥ 0.3 mg/dL above baseline, and of the 57 female individuals, 4 (7.0%) had an increase in serum creatinine ≥ 0.2 mg/dL above baseline. Four (2.8%) individuals had an increase in serum creatinine > 1.3 x baseline value without other functional changes. In individuals with HoFH in ISIS 301012-CS6, results were similar to the full ISIS 301012-CS6 population. Eleven (28.9%) individuals had proteinuria ≥1+. One (2.6%) patient had proteinuria ≥2+. Of the 17 male individuals, 1 (5.9%) had an increase in serum creatinine ≥0.3 mg/dL above baseline. Of the 21 female individuals, 1 (4.8%) had an increase in serum creatinine ≥0.2 mg/dL above baseline. One (2.6%) patient had an increase in serum creatinine >1.3 × baseline.

One SAE of glomerular nephritis (Patient ID 1506-6130) occurred in the OLE trial ISIS 301012-CS6. The patient is a 48-year-old male HeFH patient with a history of Reynaud's phenomena, intermittent microscopic hematuria and proteinuria who was seen by a urologist for assessment of one episode of macroscopic hematuria. The patient was previously enrolled in ISIS 301012-CS7 in which he received a total of 26 mipomersen (200 mg sc) injections. The urologist, after investigation including a normal cystosocpy, referred the patient to a nephrologist for continued assessment. Prior to being seen by the nephrologist, the patient had several tests done including a positive C-ANCA. Due to the microscopic hematuria, proteinuria, and positive ANCA results, a renal biopsy was done. Preliminary results of the renal biopsy are as follows: "Glomerulopathy with peripheral storage of IgG, C1q, Kappa, and Lambda with immunofluorescence for which a membranous glomerulonephritis was fostered. There was slight acute tubular damage focuses with fine microvacuolation of the cytoplasm of certain tubules, minimal tubular atrophy, slight interstitial fibrosis, and moderate atherosclerosis". See Appendix 9.4.7 for a more detailed patient narrative.

In the population PK analysis, creatinine clearance was found to be a covariate of mipomersen clearance. In the range of creatinine clearance in the population PK analysis dataset, mipomersen clearance is lower by approximately 31% at

lower creatinine clearances in the range of 150 mL/min, the capped value, to 42.2 mL/min.

7.3.5.6 Cardiovascular Issues

Cardiac SAEs are presented in the table below by SOC and preferred term for ISIS 301012-CS5 and the pooled Phase 3 trials. Although the number of cardiac SAEs is small, there are a slightly greater percentage of mipomersen-treated individuals with cardiac SAEs as compared to the placebo-treated individuals. There was only one vascular SAE of hypertension that occurred in a mipomersen-treated subject in trial ISIS 301012-CS12. Narratives for some of the individuals with SAEs reported as Major Adverse Cardiac Events (MACE) in the pooled Phase 3 trials are provided in Appendix 9.4.2.

Table 42. On-Treatment Serious Adverse Events by System Organ Class and Preferred Term for CS5 and the Four Pooled Phase 3 Placebo-Controlled Trials

System Organ Class Preferred Term	CS5 Placebo (N=17)	CS5 Mipo (N=34)	TOTAL Placebo (N=129)	TOTAL Mipo (N=261)
Any AE, n (%)	**1 (5.9)**	**2 (5.9)**	**7 (5.4)**	**21 (8.0)**
Cardiac disorders	**0**	**1 (2.9)**	**4 (3.1)**	**10 (3.8)**
Acute myocardial infarction	0	0	1 (0.8)	2 (0.8)
Angina pectoris	0	0	0 (0.0)	3 (1.1)
Acute coronary syndrome	0	1 (2.9)	1 (0.8)	1 (0.4)
Angina unstable	0	0	0 (0.0)	2 (0.8)
Coronary artery disease	0	0	1 (0.8)	1 (0.4)
Cardiac failure	0	0	0 (0.0)	1 (0.4)
Cardiogenic shock	0	0	1 (0.8)	0 (0.0)
Prinzmetal angina	0	0	0 (0.0)	1 (0.4)
Supraventricular tachycardia	0	0	1 (0.8)	0 (0.0)

All cardiac and vascular system AEs are presented in the following table by SOC and preferred term for ISIS 301012-CS5 and the pooled Phase 3 trials. At the SOC level, more individuals had Cardiac Disorders (9.2% vs. 6.2%) and Vascular Disorders (11.1% vs. 5.4%) disorders in the mipomersen-treated group than in the placebo group, respectively. Of note, these events were not prospectively defined or adjudicated across the four Phase 3 trials or the OLE trial.

In the Cardiac Disorders SOC, a greater number of disorders occurred in the mipomersen-treated group as compared to the placebo group in ISIS 301012-CS5 [4 (11.8%) vs 0] and in MIPO3500108 [5 (12.8%) vs 1 (5.3%)]. Of the 4 individuals in the mipomersen group in ISIS 301012-CS5, 2 experienced angina pectoris, and 1 patient each experienced acute coronary syndrome, palpitations, and aortic valve disease. The relevant preferred term events for MIPO108 were angina pectoris, coronary artery disease, acute myocardial infarction, angina unstable, cardiac failure, prinzmetal angina, and supraventricular extrasystoles.

In the Vascular Disorders SOC, a greater number of disorders occurred in the mipomersen-treated group as compared to the placebo group in MIPO3500108 [6 (15.4%) vs 0], ISIS 301012-CS7 [7 (8.4%) vs 2 (4.9%)] and ISIS 301012-CS12 [16 (15.2%) vs 5 (9.6%)]. The relevant preferred term events for MIPO108 were hypertension, hot flush, flushing, peripheral arterial occlusive disease and orthostatic hypotension. Hypertension was also relevant for CS-12 with 12 individuals (11.4%) in the mipomersen-treated group reporting hypertension as compared to 3 (5.8%) in the placebo group.

Table 43. Cardiac and Vascular On-treatment Adverse Events by System Organ Class and Preferred Term for ISIS 301012-CS5 and Pooled Phase 3 Placebo-Controlled Trials

System Organ Class Preferred Term	ISIS 301012-CS5 Placebo (N=17)	ISIS 301012-CS5 Mipomersen (N=34)	TOTAL Placebo (N=129)	TOTAL Mipomersen (N=261)
Cardiac disorders	**0**	**4 (11.8)**	**8 (6.2)**	**24 (9.2)**
Angina pectoris	0	2 (5.9)	2 (1.6)	10 (3.8)
Palpitations	0	1 (2.9)	0 (0.0)	7 (2.7)
Coronary artery disease	0	0	1 (0.8)	3 (1.1)
Acute myocardial infarction	0	0	1 (0.8)	2 (0.8)
Acute coronary syndrome	0	1 (2.9)	1 (0.8)	1 (0.4)
Angina unstable	0	0	0 (0.0)	2 (0.8)
Myocardial ischaemia	0	0	1 (0.8)	1 (0.4)
Tachycardia	0	0	1 (0.8)	1 (0.4)
Aortic valve disease	0	1 (2.9)	0 (0.0)	1 (0.4)
Atrial flutter	0	0	1 (0.8)	0 (0.0)
Atrioventricular block	0	0	1 (0.8)	0 (0.0)
Bradycardia	0	0	0 (0.0)	1 (0.4)
Cardiac discomfort	0	0	1 (0.8)	0 (0.0)
Cardiac failure	0	0	0 (0.0)	1 (0.4)
Cardiogenic shock	0	0	1 (0.8)	0 (0.0)

System Organ Class Preferred Term	ISIS 301012-CS5 Placebo (N=17)	ISIS 301012-CS5 Mipomersen (N=34)	TOTAL Placebo (N=129)	TOTAL Mipomersen (N=261)
Left ventricular hypertrophy	0	0	0 (0.0)	1 (0.4)
Prinzmetal angina	0	0	0 (0.0)	1 (0.4)
Sinus bradycardia	0	0	1 (0.8)	0 (0.0)
Supraventricular extrasystoles	0	0	0 (0.0)	1 (0.4)
Supraventricular tachycardia	0	0	1 (0.8)	0 (0.0)
Vascular disorders	**0**	**0**	**7 (5.4)**	**29 (11.1)**
Hypertension	0	0	4 (3.1)	17 (6.5)
Hot flush	0	0	1 (0.8)	5 (1.9)
Flushing	0	0	1 (0.8)	2 (0.8)
Hypotension	0	0	0 (0.0)	3 (1.1)
Aortic aneurysm	0	0	0 (0.0)	2 (0.8)
Peripheral arterial occlusive dis.	0	0	1 (0.8)	1 (0.4)
Aortic stenosis	0	0	1 (0.8)	0 (0.0)
Infarction	0	0	0 (0.0)	1 (0.4)
Intermittent claudication	0	0	1 (0.8)	0 (0.0)
Orthostatic hypotension	0	0	0 (0.0)	1 (0.4)

On-treatment AEs were defined as AEs that started during the treatment period. The treatment period spanned the time during which the study treatment was administered until the later of the PET (the date of efficacy assessment closest to 14 days beyond the last study medication date) and 14 days beyond the last study medication date.
If a patient had more than one event within a particular system organ class or preferred term, he/she is counted only once for that system organ class or preferred term.
Source: NDA 203568: ISS Statistical Table 3.2.2.1

In OLE trial ISIS 301012-CS6, 25.5% of individuals (36/141) were reported to have AEs in the SOC of Cardiac Disorders (8.5% [12/141] had events starting 0-6 months after the start of mipomersen treatment, and 18.4 % [26/141] had events starting > 6 months after the start of mipomersen treatment). The most common event reported in this class was Angina pectoris, reported in 9.2% of individuals (13/141), followed by atrial fibrillation (7, 5%), coronary artery disease (5, 3.5%), palpitations (3, 2.1%) and tachycardia (3, 2.1%).

In the subset of individuals with HoFH enrolled in ISIS 301012-CS6, 10/38 individuals (26.3%) were reported to have AEs in the SOC of Cardiac Disorders. Angina pectoris was also the most common event reported in these individuals (5/38 individuals; 13.2%) followed by tachycardia (3, 7.9%) and aortic valve stenosis (2, 5.3%).

MACE

The frequency of major adverse cardiac events (MACE) was examined by the applicant post-hoc and without adjudication or blinding in the Phase 3 trials and included both the 26-week on-treatment period as well as the post-treatment follow-up period for those individuals not entering the OLE trial. The applicant retrospectively defined MACE with the following preferred terms in the Cardiac Disorder SOC (Acute coronary syndrome, Acute myocardial infarction, Angina unstable, Cardiac failure, Cardiogenic shock, Myocardial infarction); the Nervous System Disorders SOC (Cerebrovascular accident), and the Vascular Disorders SOC (Infarction). The MACE incidence was similar but still slightly higher in the mipomersen-treated group (3.4%) as compared to the placebo group (3.1%).

Table 44. Treatment-Emergent MACE Adverse Events Safety Set (Including posttreatment follow-up) for Protocols ISIS 301012-CS5, -CS7, -CS12 and MIPO3500108

	Treatment Arm	
Preferred Term	**Placebo (N=129) n (%)**	**Mipomersen (N=261) n (%)**
Patients with Events	**4 (3.1)**	**9 (3.4)**
Acute coronary syndrome	1 (0.8)	1 (0.4)
Acute myocardial infarction	2 (1.6)	3 (1.1)
Angina unstable	0 (0.0)	2 (0.8)
Cardiac failure	0 (0.0)	1 (0.4)
Cardiogenic shock	1 (0.8)	0 (0.0)
Cerebrovascular accident	0 (0.0)	2 (0.8)
Infarction	0 (0.0)	1 (0.4)
Myocardial ischaemia	1 (0.8)	1 (0.4)

FDA conducted an exploratory analysis of cardiac adverse events by searching cardiovascular adverse events included in pre-specified Broad and Narrow MedDRA SMQs in the four Phase 3 clinical trials for mipomersen. The Relative Risk was estimated comparing mipomersen to placebo based on the results of these Broad and Narrow CV searches. This analysis includes only the 26-week, placebo-controlled treatment period.

Adverse events with Preferred Terms listed in the following MedDRA v14.1 SMQs were included in the “Broad” CV search:

- Haemorrhagic cerebrovascular conditions SMQ
- Ischaemic cerebrovascular conditions SMQ
- Ischaemic heart disease SMQ

Adverse events with Preferred Terms listed in the following MedDRA v14.1 SMQs were included in the "Narrow" CV search:

- Ischaemic cerebrovascular conditions SMQ
- Myocardial infarction SMQ

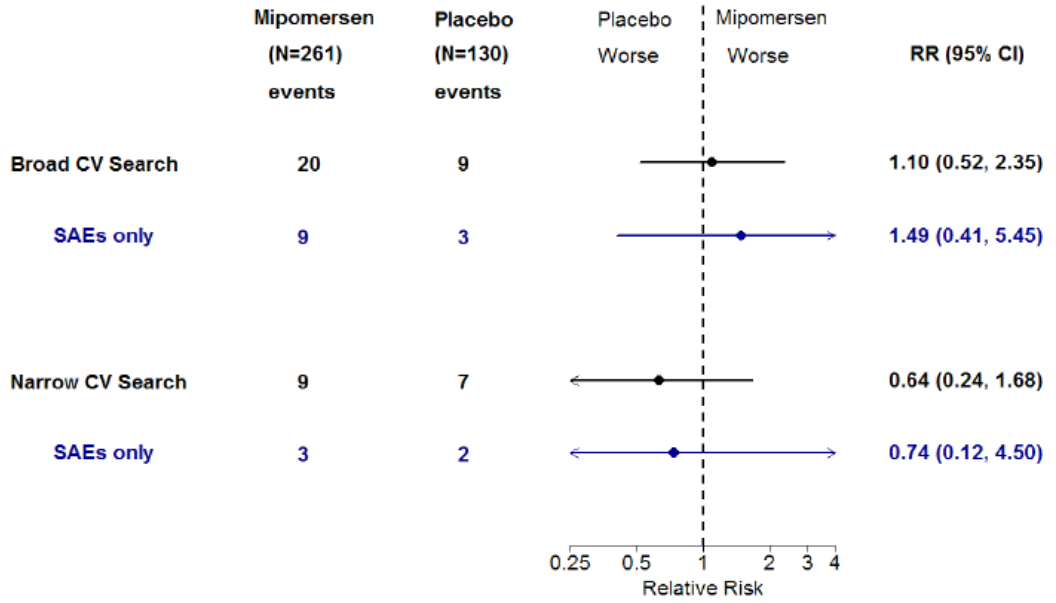
Note that the SMQs in the "Narrow" search are contained in the SMQs in the "Broad" search. All adverse events in the Broad and Narrow searches were also classified as "Serious" or "Non-Serious".

Twenty individuals on mipomersen (7.7%, N=261) and 9 individuals on placebo (6.9%, N=130) had a reported adverse event in the "Broad" SMQ search category. Nine individuals on mipomersen (3.5%) and 7 individuals on placebo (5.4%) had a reported adverse event in the "Narrow" SMQ search category. The figure below shows the estimated Relative Risk and corresponding 95% confidence intervals comparing mipomersen to placebo.

The estimated Relative Risk and 95% CI for the "Broad" CV search were 1.10 (0.52, 2.35). The estimated Relative Risk and 95% CI for the "Narrow" CV search were 0.64 (0.24, 1.68). There was no statistically significant evidence of a difference in risk between mipomersen and placebo in both the Broad and Narrow CV searches.

The estimates of the Relative Risk and corresponding 95% confidence intervals reported here are sensitive to small changes in the number of events in either randomized arm, reflects a treatment duration of only 6 months, and the adverse events were not formally adjudicated, nor were they prospectively defined. The results should therefore be interpreted with caution.

Figure 17. Relative Risk of Broad and Narrow Cardiovascular SMQs



Source: NDA 203568, ADAE.xpt datasets from trials CS5, CS7, CS12 and MIPO3500108. Analysis done by FDA statistical reviewer, Eugenio Andraca-Carrera, Ph.D.

7.3.5.6.1 Hypertension

In the pooled Phase 3 population, more AEs of hypertension have been reported in the mipomersen group vs. placebo (17/261 [6.5%] vs. 4/129 [3.1%]). This was more apparent in the subpopulation of individuals over age 65 (10/59 [16.9%] mipomersen-treated individuals ≥ 65 years vs 7/199 [3.5%] mipomersen-treated individuals age 18 to < 65 years). The individuals that reported a hypertension-related AE did not appear to have sustained blood pressure increases. The median change in systolic blood pressure (SBP) from baseline to Week 28/ET in these 17 mipomersen-treated individuals was -7 mmHg (mean= -4.0) and -2 mmHg (mean= 1.5) for the placebo-treated individuals. The median change in diastolic blood pressure (DBP) over the same timeframe was -2 mmHg (mean= -.04) for the mipomersen-treated and -3 mmHg (mean= -1.8) for the placebo-treated individuals. Thirteen out of 17 completed treatment and no individuals discontinued due to hypertension. Sixteen out of 17 of these individuals were on blood pressure medications at baseline and 6 out of 17 (35%) individuals required changes in blood pressure medications or dose associated with the AE of hypertension.

For the entire Phase 3 trial population, from baseline to Week 28/ET, the mean change in systolic blood pressure was 0.3 mmHg for the mipomersen group and -0.2 mmHg for the placebo group. The median change was 0 for both groups.

The mean change in diastolic blood pressure was 0.1 mmHg for the mipomersen group and -0.7 mmHg for the placebo group. The median change was 0 for both groups. The mean change in heart rate was 0.2 bpm (median=0) for the mipomersen group and -0.8 bpm (median= -1) for the placebo group.

As shown in the table below, there were no consistent shifts in categorical increases in blood pressure between mipomersen-treated vs placebo-treated individuals across the Phase 3 trials. For the HoFH population in CS5, there was a shift toward increases in SBP readings for most of the SBP categories in the mipomersen group but this did not occur for the DBP categories.

Table 45. Summary of Changes from Baseline for Blood Pressure Across the Phase 3 Trials of 6 Months Duration

	ISIS 301012-CS5		MIPO3500108		ISIS 301012-CS7		ISIS 301012-CS12	
Category	Placebo (N=17)	Mipo (N=34)	Placebo (N=19)	Mipo (N=39)	Placebo (N=41)	Mipo (N=83)	Placebo (N=52)	Mipo (N=105)
Systolic blood pressure								
≥140 mmHg for ≥2 consecutive values [1,2]	3/15 (20.0)	6/29 (20.7)	6/18 (33.3)	4/27 (14.8)	2/34 (5.9)	8/75 (10.7)	14/44 (31.8)	23/87 (26.4)
≥150 mmHg for ≥2 consecutive values [1,2]	0/16 (0.0)	3/33 (9.1)	1/19 (5.3)	5/36 (13.9)	3/37 (8.1)	5/80 (6.3)	3/49 (6.1)	10/96 (10.4)
≥160 mmHg for ≥2 consecutive values [1,2]	0/16 (0.0)	0/34 (0.0)	0/19 (0.0)	2/37 (5.4)	0/39 (0.0)	0/83 (0.0)	1/51 (2.0)	5/100 (5.0)
≥10 mmHg over baseline for ≥1 value	8/17 (47.1)	25/34 (73.5)	13/19 (68.4)	24/39 (61.5)	26/41 (63.4)	47/83 (56.6)	29/51 (56.9)	66/102 (64.7)
≥10 mmHg over baseline for ≥2 consecutive values [3]	5/17 (29.4)	16/34 (47.1)	10/19 (52.6)	14/39 (35.9)	17/41 (41.5)	34/83 (41.0)	19/51 (37.3)	46/102 (45.1)
≥15 mmHg over baseline for ≥1 value	5/17 (29.4)	17/34 (50.0)	9/19 (47.4)	19/39 (48.7)	18/41 (43.9)	32/83 (38.6)	19/51 (37.3)	43/102 (42.2)
≥15 mmHg over baseline for ≥2 consecutive values [3]	2/17 (11.8)	10/34 (29.4)	6/19 (31.6)	8/39 (20.5)	9/41 (22.0)	17/83 (20.5)	12/51 (23.5)	27/102 (26.5)
Diastolic blood pressure								
≥90 mmHg for ≥2 consecutive values [1,4]	0/17 (0.0)	0/33 (0.0)	4/17 (23.5)	3/35 (8.6)	2/40 (5.0)	2/78 (2.6)	6/49 (12.2)	10/95 (10.5)
≥95 mmHg for ≥2 consecutive values [1,4]	0/17 (0.0)	0/34 (0.0)	1/19 (5.3)	2/38 (5.3)	0/40 (0.0)	1/83 (1.2)	0/50 (0.0)	4/101 (4.0)
≥100 mmHg for ≥2 consecutive values [1,4]	0/17 (0.0)	0/34 (0.0)	0/19 (0.0)	2/38 (5.3)	0/41 (0.0)	0/83 (0.0)	0/51 (0.0)	1/102 (1.0)
≥5 mmHg over baseline for ≥1 value	14/17 (82.4)	22/34 (64.7)	12/19 (63.2)	28/39 (71.8)	23/41 (56.1)	53/83 (63.9)	38/51 (74.5)	59/102 (57.8)
≥5 mmHg over baseline	10/17	13/34	9/19	22/39	12/41	36/83 (43.4)	20/51	43/102

Category	ISIS 301012-CS5		MIPO3500108		ISIS 301012-CS7		ISIS 301012-CS12	
	Placebo (N=17)	Mipo (N=34)	Placebo (N=19)	Mipo (N=39)	Placebo (N=41)	Mipo (N=83)	Placebo (N=52)	Mipo (N=105)
for ≥2 consecutive values [3]	(58.8)	(38.2)	(47.4)	(56.4)	(29.3)		(39.2)	(42.2)
≥10 mmHg over baseline for ≥1 value	10/17 (58.8)	13/34 (38.2)	6/19 (31.6)	18/39 (46.2)	12/41 (29.3)	36/83 (43.4)	20/51 (39.2)	36/102 (35.3)
≥10 mmHg over baseline for ≥2 consecutive values [3]	7/17 (41.2)	9/34 (26.5)	5/19 (26.3)	11/39 (28.2)	6/41 (14.6)	23/83 (27.7)	9/51 (17.6)	24/102 (23.5)

1. At least 2 consecutive values during the treatment period or the last value within the treatment period. The treatment period spanned the time during which study drug was administered until the later of the primary efficacy time point [PET]) and 14 days beyond the date of the last dose of study drug. The PET was the date of the efficacy assessment closest to 14 days beyond the date of the last dose of study drug.
2. Individuals with a systolic blood pressure value ≥140 mmHg, or ≥150 mmHg, or ≥160 mmHg were excluded from the respective analysis.
3. At least 2 consecutive values during the treatment period or the last value within the treatment period.
4. Individuals with a diastolic blood pressure value ≥90 mmHg, or ≥95 mmHg, or ≥100 mmHg were excluded from the respective analysis.
Source: NDA 203568: ISIS 301012-CS5 Addendum, ISIS 301012-CS7 Addendum, MIPO3500108 Addendum, and ISIS 301012-CS12 Addendum.

7.3.5.7 Coagulation and Platelet Issues

In the mipomersen preclinical studies, changes in plasma clotting times were observed in monkeys of ~1.3-fold increase in aPTT during the first four hours after dosing. The largest change coincided with peak plasma concentrations after IV infusion or SC administration. The aPTT prolongation by mipomersen reversed within hours of treatment. No other clotting parameters (e.g., PT or fibrinogen) were affected, and the effect was not observed in monkeys treated with lower doses. In toxicology studies, decreases in platelet counts were observed in monkeys treated with 30 mg/kg/week mipomersen starting at the 6 month time point and in rats treated with 75 mg/kg/week for 3 months.

In the Phase 1 trial ISIS 301012-CS1, transient, reversible, dose-dependent increases within the normal range in aPTT were observed. During IV administration in the multiple-dose period, the mean aPTT showed an increase at 2 hours post-infusion (Cmax) in the 200 mg Cohort (from 30.6 to 35.7 seconds) and the 400 mg Cohort (from 26.0 to 38.0 seconds). Mean values had decreased at 4 hours. In the single-dose period with SC administration, these increases were not seen. In all subjects aPTT returned to baseline levels by the 24-hour blood draw.

In the pooled Phase 3 clinical trials, the aPTT, INR, and PT from baseline to Week 28/ET did not show any meaningful differences between the placebo and mipomersen groups. The mean change in platelets from baseline to Week 28/ET in the pooled Phase 3 trials was -23.8 x 10^3/µL in the mipomersen group and -3.5 x 10^3/µL in the placebo group. The mean change in platelets from baseline to Week 28/ET in ISIS 301012-CS5 was -30.6 x 10^3/µL in the mipomersen group and 8.1 x 10^3/µL in the placebo group.

Adverse events associated with effects on platelets occurred infrequently in the Phase 3 trials and there were no reports in the ISIS 301012-CS5 trial. Thrombocytopenia was not reported in any mipomersen-treated individuals in the 4 Phase 3 trials. The AE of platelet count decreased was reported in mipomersen-treated individuals in ISIS 301012-CS7 (2, 2.4%) and in ISIS 301012-CS12 (1, 1.0%) and in 1 (5.3%) placebo-treated individual in MIPO3500108.

In OLE trial ISIS 301012-CS6, no meaningful changes in aPTT and INR were reported from baseline to end of treatment. Seventeen (12.1%) individuals [5 (13%) with HoFH] had a PT > 1.2 x baseline. Two of the 17 individuals (one with HoFH, #1664-6123) met the protocol-defined coagulation monitoring rules (PT > 20 seconds or INR > 1.5).

7.3.5.8 Neoplasms

The tumorigenicity potential of mipomersen and species-specific analogs was assessed in standard 2-year carcinogenicity studies in mice and rats. There was a statistically significantly increased incidence (over control) of benign hepatocellular adenoma in female mice treated with either 60 mg/kg/week ISIS 147764 or 60 mg/kg/week mipomersen. In the rat, in the region of the subcutaneous sites, there was a statistically significant increased incidence of malignant fibrous histiocytoma in both males and females at 10 and 20 mg/kg/wk mipomersen and an increase in malignant fibrosarcoma in females at 10 and 20 mg/kg/wk mipomersen.

No malignant neoplasms related to the injection site and no fibrosarcomas or hepatic adenomas have been reported in mipomersen-treated individuals. No specific screening for malignancies was performed at the beginning of the mipomersen clinical trials. Baseline assessments included medical history, physical examination, and a clinical laboratory assessment, but did not include screening tests such as stool testing, colonoscopy, chest X-ray, digital rectal exam, prostate-specific antigen testing, mammogram, or other cancer screening tests.

In the entire mipomersen clinical development program there were 24 neoplasms in 23 mipomersen-treated individuals and 2 neoplasms in 2 placebo-treated individuals as of the database cut off of 30 November 2011. Neoplasms (benign and malignant) were reported in 3.1% (23/749) of mipomersen-treated individuals and 0.9% (2/221) of placebo-treated individuals. Malignant neoplasm was reported in 1.2% of mipomersen-treated subjects (9 malignant neoplasms/749 subjects), and in 0.5% of placebo-treated individuals (1 malignant neoplasm/221 subjects). The prevalence of basal cell carcinoma in mipomersen-treated individuals was 0.40% (3/749), which was similar to the prevalence in placebo-treated individuals, 0.45% (1/221).

Table 46. All Neoplasm Adverse Events by System Organ Class and Preferred Term

System Organ Class Preferred Term	Phase 3† Placebo (N=129)	Phase 3† Mipomersen (N=261)	TOTAL* Placebo (N=221)	TOTAL* Mipomersen (N=749)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**10 (3.8)**	**2 (0.9%)**	**24 (3.2%)**
Basal cell carcinoma	0	2 (0.8)	1 (0.5%)	3 (0.4%)
Seborrhoeic keratosis	0	1 (0.4)	0	3 (0.4%)
Angiomyolipoma	0	1 (0.4)	0	2 (0.3%)
Lipoma	0	2 (0.8)	0	2 (0.3%)
Melanocytic naevus	0	0	0	2 (0.3%)
Morton's neuroma	0	1 (0.4)	0	1 (0.1%)
Benign breast neoplasm	0	1 (0.4)	0	1 (0.1%)[a]
Breast cancer	0	0	0	1 (0.1%)[a]
Gastric cancer	0	0	0	1 (0.1%)
Lung neoplasm	0	1 (0.4)	0	1 (0.1%)
Malignant melanoma in situ	0	0	0	1 (0.1%)
Non-small cell lung cancer	0	1 (0.4)	0	1 (0.1%)
Prostate cancer	0	0	0	1 (0.1%)
Rectal cancer	0	0	0	1 (0.1%)
Skin papilloma	0	0	0	1 (0.1%)
Thyroid neoplasm	0	0	0	1 (0.1%)
Uterine leiomyoma	0	0	0	1 (0.1%)
Acrochordon	0	0	1 (0.5%)	0

Source: NDA 203568: LS-NEOPLASMS-MIPO-SELECT; LS-NEOPLASMS-PLACEBO-SELECT and ISS Statistical Table 3.2.2.1
*Data are presented as of database cut off of 30 November 2011 for individuals who were dosed subcutaneously.

† Pooled Phase 3 Placebo-controlled trials of 6 month duration. On-treatment AEs were defined as AEs that started during the treatment period. The treatment period spanned the time during which the study treatment was administered until the later of the PET (the date of efficacy assessment closest to 14 days beyond the last study medication date) and 14 days beyond the last study medication date.
[a] Benign breast neoplasm occurred in the same patient as Breast cancer

In the pooled analysis of AEs in the 6 month Phase 3 trials, there were more individuals with neoplasms (3.8%; 10/261) in the mipomersen group compared with the placebo group (0%) during the 6-month treatment period. In Trial ISIS 301012-CS5 (individuals with HoFH), no individuals had neoplasms in either treatment group.

In the entire mipomersen clinical development program, 15 of the 24 neoplasms in the mipomersen-treated individuals were classified as benign [Seborrhoeic keratosis (3); Angiomyolipomam (2); Lipoma (2); Melanocytic nevus (2); and single events of Benign breast neoplasm, Lung neoplasm, Morton's neuroma, Skin papilloma, Thyroid neoplasm, and Uterine leiomyoma). Nine of the 24 neoplasms in the mipomersen-treated individuals were classified as malignant (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. One event (basal cell cancer) was considered malignant in a placebo-treated individual. The prevalence of malignant neoplasm in mipomersen-treated individuals was 1.2% (9 malignant neoplasms/749 subjects), while the prevalence of malignant neoplasm in placebo-treated individuals was 0.5% (1 malignant neoplasm/221 subjects). The ten individuals that developed a malignant neoplasm during the course of the mipomersen clinical development program are summarized in the following table.

Table 47. Malignant Neoplasms in Mipomersen Clinical Development Program

Trial/Patient ID	Preferred Term/ AE Description	Age, Sex	Dosing Group	Days Since First Study Drug Dose[a]	Days on Drug Prior to Event[b]	Total Exposure to Mipomersen as of Event (mg)	Relevant Medical History
ISIS 301012-CS01/ 1375-1024	Gastric cancer / Gastric adenocarcinoma	64, F	200 mg	109	22	1200	Gastroscopy booked prior to 1st dose; history of smoking
ISIS 301012-CS12/ 1682-1317	Non-small cell lung cancer / Non-small cell squamous lung cancer	77, M	200 mg	113	112	3400	History of 24 smoking pack years;1st sx occurred within 2 mos. of starting mipo
ISIS 301012-CS12/ 1671-2157	Prostate cancer/ prostate cancer	77, M	200 mg	292	174	5200	
ISIS 301012-CS06/ 1589-6134	Breast cancer /New diagnosis: breast cancer	74, F	200 mg	384	350	10400	HeFH, 12 year hx of estrogen replacement therapy
ISIS 301012-CS06/ 1505-6082	Rectal cancer / rectal cancer	63, M	200 mg	795	771	21800	HeFH
ISIS 301012-CS17/ 1503-1208	Malignant melanoma in situ / Midsternal atypical melanocytic hyperplasia (melanoma in situ)	51, M	200 mg	1078	661	17800	HeFH; Discontinued study due to liver enzymes > 3x ULN
ISIS 301012-CS07/ 1503-7025	Basal cell carcinoma / Reoccurring of basal cell carcinoma (BCC) of left upper lip	74, F	200 mg	23	24	800	HeFH, Hx of BCCs at that site. After removal (5 days after 7th mipo dose, patient went on to complete dosing in CS7 and enroll in CS6; then

Trial/Patient ID	Preferred Term/ AE Description	Age, Sex	Dosing Group	Days Since First Study Drug Dose[a]	Days on Drug Prior to Event[b]	Total Exposure to Mipomersen as of Event (mg)	Relevant Medical History
							was followed for 6 months without an further reporting of neoplasias
ISIS 301012-CS07/ 1585-7068	Basal cell carcinoma / Basal cell cancer near corner of right eye	63, F	200 mg	173	169	5000	HeFH
ISIS 301012-CS04/ 1493-1035	Basal cell carcinoma / On back, right shoulder blade lesion fitting basal cellular carcinoma	63	placebo	22	N/A	N/A	
ISIS 301012-CS06/ 1608-6132	Basal cell carcinoma / Basal cell carcinoma, left hand	68	200 mg	405	344	9500	

a Calculated as AE start date – first dose date. For events that occur in an open-label extension trial, treatment gaps between the index trial and the open-label extension trial are included in this calculation
b Calculated as treatment duration (last dose date on or before AE start date – first dose date + 1) as of AE start date. For events that occur in an open-label extension trial, treatment gaps between the index trial and the open-label extension trial are not included in this calculation.
Source: NDA 203568: ISIS 301012-CS1, ISIS 301012-CS4, ISIS 301012-CS6, ISIS 301012-CS7, ISIS 301012-CS12, ISIS 301012-CS17, and LS-NEOPLASMS-MIPO-SELECT

In OLE trial ISIS 301012-CS6, Neoplasms, Benign, Malignant, and Unspecified (Including Cysts and Polyps) AEs were reported in 7.8% (11/141) of individuals. Two of these events were considered malignant (breast cancer in Patient 1589-6134 and rectal cancer in patient 1505-6082). No AEs of neoplasms were reported in the individuals with HoFH in ISIS 301012-CS6

The applicant comments that across the clinical development program for mipomersen, the overall incidence of malignant neoplasm in mipomersen-treated individuals was 2.60 per 100 patient-years (9 events/345.5 patient-years). Excluding basal cell carcinomas, the incidence of malignant neoplasm in mipomersen-treated individuals was 1.74 per 100 patient-years (6 events/345.5 patient-years). The applicant notes that patient-years of exposure include only the time that the patient is receiving weekly mipomersen, and do not include the follow-up time when the patient was not receiving drug. Due to the long-half life of the drug, the individuals receive continued exposure to drug during much of this 24-week follow-up time. The majority of these patient-years of exposure consist of multiple exposures of less than 6 months duration. The applicant cites two studies that provide estimates of the incidence rate of malignant neoplasm in comparable patient populations. In one published study65, the incidence rate of malignant neoplasms (excluding non-melanoma skin cancer) in individuals with hypercholesterolemia on statins, from 35 randomized studies of statins, ranged from 0 to 3.9 malignant neoplasms per 100 patient-years. Another meta-analysis66 that included 175,000 people in randomized trials of statin use, the cancer incidence was determined to be approximately 1.4% per year. Thus, the applicant contends that the incidence rate of malignant neoplasm in mipomersen-treated individuals is comparable to the expected range for a similar patient population. In addition, the tumors seen in this development program come from a variety of tissues without one type of cancer predominating.

Reviewer comment:
This imbalance in neoplasms will need to be assessed further in on-going and future studies and post-marketing (if approved). However, the interpretation of this data is limited by:

1) *Relatively short treatment duration and small sample size*
2) *No specific screening for malignancies was performed at the beginning of the mipomersen clinical trials. Baseline assessments included medical history, physical examination, and a clinical laboratory assessment, but did not include screening tests such as stool testing, colonoscopy, chest X-ray, digital rectal*

65 Bonovas S, Filioussi K, Tsavaris N, Sitaras N. Statins and Cancer Risk: A Literature-Based Meta-Analysis and Meta-Regression Analysis of 35 Randomized Controlled Trials. J Clin Oncol 2006. 24:4808-4817.
66 Cholesterol Treatment Trialists' (CTT) Collaboration. Lack of Effect of Lowering LDL Cholesterol on Cancer: Meta-Analysis of Individual Data from 175,000 People in 27 Randomised Trials of Statin Therapy. PLoS ONE 2012 Jan. 7(1): e29849.

exam, prostate-specific antigen testing, mammogram, or other cancer screening tests.

3) *The mipomersen subjects had significantly more adverse events from ISR, FLS, hepatic abnormalities and this may have biased toward more investigator evaluations and monitoring in the mipomersen group as compared to the placebo group with the potential for a greater opportunity in the mipomersen group to detect or evaluate for a neoplasm.*
4) *The tumors seen in this development program come from a variety of tissues without one type of cancer predominating. The nine individuals on mipomersen that developed a malignant neoplasm during the course of the mipomersen clinical development program had the following tumors: gastric adenocarcinoma, non-small cell lung cancer, prostate cancer, breast cancer, rectal cancer, melanoma, basal cell cancer (3 individuals). Not one tumor predominates except for basal cell carcinoma, which had a similar prevalence in both groups. In addition, two of the nine individuals were on mipomersen for < 30 days prior to diagnosis, making it highly unlikely that mipomersen played a role. The subject with lung cancer also had a 24-pack-year smoking history and symptoms started within 2 months of mipomersen therapy. The patient with breast cancer was on mipomersen for one year prior to diagnosis but also had a 12-year history of estrogen use.*

Thus, there are several confounding factors that make it difficult to conclude that mipomersen is playing a dominant role in this cancer imbalance.

7.3.5.9 Individuals with Higher Trough Concentrations

Mipomersen plasma trough levels (7 days post-dose/pre-next dose during treatment or 14 days post-last dose) were assessed in the following Phase 2 and Phase 3 trials: ISIS 301012-CS5, ISIS 301012-CS7, MIPO3500108, ISIS 301012-CS12, ISIS 301012-CS17, and ISIS 301012-CS6. With once weekly dosing, plasma trough levels increase over time and approach steady-state, typically within 6 months. Across these six trials, 35 out of 188 individuals (19%) were categorized as high trough (HT: plasma trough concentration of ≥ 100 ng/mL) in Phase 3 trials and 57 individuals (38%) were categorized as high trough in OLE trials. A subset of the high trough individuals was defined as highest trough (HHT), based on having high trough status and at least 1 measured mipomersen plasma trough concentration of ≥ 250 ng/mL in the relevant evaluation period. The safety profile of these highest trough individuals was evaluated further. Using PK data through March 2012, the applicant identified 29 individuals, 7 in the pooled Phase 3 trials and 22 in ISIS 301012-CS6, who were in the HHT group. None of the highest trough individuals from the pooled Phase 3 trials were individuals with HoFH, and 4/22 (18.2%) of the highest trough individuals from ISIS 301012-CS6 were individuals with HoFH. Two subjects from the pooled Phase 3 HHT group continued in ISIS301012-CS6. Thus, a total of 24 HHT individuals were included in the ISIS 301012-CS6 analyses.

In the pooled Phase 3 trials, 35/188 (18.6%) mipomersen-treated individuals were identified as high trough (including 7 highest trough) and 153 normal trough individuals. In the pooled Phase 3 trials, a greater percentage of the HHT individuals (100%, 7/7) experienced ISRs compared with HT (88.6%, 31/35) and normal trough (NT) individuals (84.3%, 129/153). Similarly, a greater percentage of the HHT individuals (85.7%, 6/7) experienced FLS compared with HT (42.9%, 15/35) and NT individuals (24.2%, 37/153). However, the incidence of liver transaminase values ≥ 3 X ULN was similar between HHT and NT individuals (14.3% and 11.8%, respectively) but lower in HHT individuals compared with HT individuals (14.3% versus 20.0%). HHT individuals had greater increases in hsCRP (median change from baseline at Week 28: 0.7 vs 0 vs 0.1 mg/L) and greater decreases in C3 (median change from baseline at Week 28: -47 vs -17 vs -11 mg/dL) than the HT and NT individuals, although the median values were still within the normal ranges for these parameters (normal range 0.0 to 3.0 mg/L for hsCRP and 90 to 180 mg/dL for C3).

In the OLE ISIS 301012-CS6, 24/141 patients (17.0%) were identified as highest trough individuals. Of these, 17 had received mipomersen in their index study, and 7 had received placebo. Of the highest trough patients, 50.0% (12/24) required dose adjustments due to AEs compared to 35.5% of patients (50/141) in the full ISIS 301012-CS6 population. The incidence of ISRs was similar in the highest-trough patients (91.7%, 22/24), the HT group (96.5%, 55/57) and the NT group (98.5%, 64/65). A higher percentage of patients in the highest trough population in ISIS 301012-CS6 experienced FLS (79.2%, 19/24) compared to the HT group (70.2%, 40/57) and the NT group (60.0%; 39/65). The incidence of liver transaminase values ≥ 3 X ULN was lower in the HHT group (12.5%) as compared to the HT group (15.8%) and the NT group (23.0%). The HHT group had greater increases in CRP than the HT and NT group (median change from baseline at Week 52: 0.7 vs 0.2 vs 0.1 mg/L, respectively). The HHT group had similar changes in C3 as the HT group (median change from baseline at Week 52: -24 mg/dL) but greater decreases in C3 than the NT group (-12 mg/dL). However, the median values were still within the normal ranges for hsCRP and for C3.

In the pooled Phase 3 trials, 22 of 35 (63%) HT individuals (including 7 HHT individuals) were classified as antibody-positive for anti-mipomersen antibodies as compared to 54 of 152 (36%) of NT individuals. Across the entire OLE trial ISIS-301012-CS6, 51 of 57 (90%) HT individuals (including 24 HHT) were classified as antibody-positive for anti-mipomersen antibodies as compared to 40 of 65 (62%) of NT individuals.

Thus, across the clinical program, ISR and, more notably, FLS terms were reported in a higher percentage of the highest-trough individuals compared to the full population. The discontinuation rate due to AEs in the highest-trough patients in ISIS 303012-CS6 was higher than that in the full patient population. Liver transaminase increases occurred in both groups to a similar degree. HHT individual had greater increases in hsCRP and greater decreases in C3 than the full patient population.

7.3.5.10 Individuals with Circulating Immune Complex

Circulating immune complexes (CIC) are formed when an antibody binds to a soluble antigen. Immune complexes are usually removed by the mononuclear phagocyte system. If the immune complex load saturates the system, the concern is that excess immune complexes may remain in the circulation. Immune complexes can cause disease when they are deposited in organs, such as in certain forms of vasculitis. Immune complex deposition is also a prominent feature of several autoimmune diseases. In the mipomersen clinical program, CIC testing was performed retrospectively on individuals participating in ISIS 301012- CS6.

CIC samples were tested from 116 of the 141 individuals in ISIS 301012-CS6. Of the 116 patients in the OLE ISIS 301012-CS6, 78% of individuals were negative for both assays (negative in all samples prior to the start of treatment and tested negative in all samples after the start of treatment: negative/negative subgroup). Twenty-two percent (26/116) tested CIC positive at 1 or more timepoint(s) during ISIS 301012-CS6. Fifteen of the 26 individuals were CIC negative prior to the start of treatment and subsequently tested CIC positive in at least one sample after the start of treatment (negative/positive subgroup): 7 individuals continued to test positive for CIC in multiple samples after the start of treatment, 6 individuals tested CIC positive at only the last sample evaluated, and 2 individuals only tested CIC positive in one isolated sample after the start of treatment. The remaining 11 of the 26 individuals tested CIC positive in at least one sample prior to the start of treatment in CS6: 2 were CIC positive only in samples collected prior to the start of treatment (positive/negative subgroup) and 9 tested CIC positive in at least one sample after the start of treatment (positive/positive subgroup). Of the 9 individuals who were CIC positive in at least one sample prior to the start of treatment and tested positive in at least one sample after the start of treatment, 6 patients tested CIC positive for all samples after the start of treatment and 3 patients tested CIC negative for intermittent samples after the start of treatment.

Flu-like symptoms were more common in the negative/positive subgroup and the positive/positive subgroup than in the negative/negative subgroup. ISRs occurred similarly in all 3 subgroups. Adverse events of ALT elevation and AST elevation were more common in the negative/positive subgroup versus the other 2 groups. However, there was no meaningful difference in terms of the number of patients with ALT ≥ 3x ULN or in terms of those who persisted with an ALT≥ 3x ULN.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Pooled Phase 3 Trials: In the pooled Phase 3 trials, 95.4% (249/261) of individuals in the mipomersen group experienced 5040 on-treatment AEs (OTAEs)67, and 84.5% (109/129) of individuals in the placebo group experienced 637 OTAEs. AEs that occurred notably more frequently in the mipomersen group as compared to the placebo group include Cardiac disorders (angina pectoris, palpitations); Gastrointestinal disorders (nausea, vomiting, abdominal pain); General disorders (ISRs, flu-like symptoms such as fatigue, pyrexia, and chills); Hepatobiliary disorders (hepatic steatosis); Investigations (ALT, AST or hepatic enzyme increased, liver function test abnormal); Nervous system disorders (headache, dizziness); Psychiatric disorders (anxiety, insomnia); and Vascular disorders (hypertension). By far, ISRs were the most common AEs in individuals receiving mipomersen. This included injection site erythema (58.6%), injection site pain (56.3%), injection site haematoma (31.8%), injection site pruritus (29.1%), injection site swelling (17.6%) and injection site discolouration (hypopigmentation or hyperpigmentation).

ISIS 301012-CS5: In the ISIS 301012-CS5 trial (individuals with HoFH), 88.2% (30/34) of individuals in the mipomersen group experienced 399 OTAEs, and 76.5% (13/17) of individuals in the placebo group experienced 48 OTAEs. As in the pooled Phase 3 population, the most common AEs in individuals who received mipomersen 200 mg SC once weekly were ISRs.

Table 48. Common On-treatment Adverse Events in ISIS 301012-CS5 and Pooled Phase 3 Placebo-Controlled Trials (Occurring in ≥ 2% of Individuals in Either Treatment Group) by System Organ Class and Preferred Term

System Organ Class Preferred Term	CS5 Placebo (N=17)	CS5 Mipo (N=34)	TOTAL Placebo (N=129)	TOTAL Mipo (N=261)
Any AE, n (%)	**13 (76.5)**	**30 (88.2)**	**109 (84.5)**	**249 (95.4)**
Blood and lymphatic system disorders	**1 (5.9)**	**2 (5.9)**	**6 (4.7)**	**13 (5.0)**
Anaemia	1 (5.9)	2 (5.9)	2 (1.6)	8 (3.1)
Cardiac disorders	**4 (11.8)**	**4 (11.8)**	**8 (6.2)**	**24 (9.2)**
Angina pectoris	0	2 (5.9)	2 (1.6)	10 (3.8)
Palpitations	0	1 (2.9)	0 (0.0)	7 (2.7)
Acute coronary syndrome	0	1 (2.9)	1 (0.8)	1 (0.4)
Aortic valve disease	0	1 (2.9)	0	1 (0.4)
Ear and labyrinth disorders	**0**	**1 (2.9)**	**4 (3.1)**	**4 (1.5)**
Ear pain	0	1 (2.9)	1 (0.8)	1 (0.4)

67 On-treatment AEs (OTAEs) are a subset of TEAEs (any AE occurring on or after the first dose of study treatment). OTAEs are AEs that occur between the first dose and the later of two weeks post-last dose and the PET date (defined as the laboratory assessment date closest to two weeks after the last dose).

System Organ Class Preferred Term	CS5 Placebo (N=17)	CS5 Mipo (N=34)	TOTAL Placebo (N=129)	TOTAL Mipo (N=261)
Endocrine disorders	**1 (5.9)**	**1 (2.9)**	**2 (1.6)**	**3 (1.1)**
Hypothyroidism	1 (5.9)	1 (2.9)	2 (1.6)	1 (0.4)
Gastrointestinal disorders	**1 (5.9)**	**11 (32.4)**	**37 (28.7)**	**78 (29.9)**
Nausea	1 (5.9)	6 (17.6)	10 (7.8)	36 (13.8)
Diarrhoea	0	1 (2.9)	9 (7.0)	18 (6.9)
Constipation	1 (5.9)	2 (5.9)	6 (4.7)	9 (3.4)
Abdominal pain upper	0	1 (2.9)	4 (3.1)	9 (3.4)
Vomiting	1 (5.9)	0	2 (1.6)	10 (3.8)
Dyspepsia	0	1 (2.9)	3 (2.3)	8 (3.1)
Abdominal pain	0	2 (5.9)	1 (0.8)	8 (3.1)
Gastrooesophageal reflux disease	0	1 (2.9)	2 (1.6)	6 (2.3)
Abdominal pain lower	0	0	3 (2.3)	1 (0.4)
Diverticulum	0	0	3 (2.3)	1 (0.4)
Haemorrhoids	0	0	3 (2.3)	0 (0.0)
Dry mouth	1 (5.9)	0	1 (0.8)	2 (0.8)
Toothache	0	1 (2.9)	1 (0.8)	2 (0.8)
General disorders and administration site conditions	**4 (23.5)**	**29 (85.3)**	**61 (47.3)**	**228 (87.4)**
Injection site pain	2 (11.8)	13 (38.2)	21 (16.3)	147 (56.3)
Injection site erythema	1 (5.9)	19 (55.9)	8 (6.2)	153 (58.6)
Injection site haematoma	2 (11.8)	12 (35.3)	18 (14.0)	83 (31.8)
Injection site pruritus	1 (5.9)	10 (29.4)	4 (3.1)	76 (29.1)
Fatigue	0	1 (2.9)	10 (7.8)	40 (15.3)
Injection site discolouration	0	10 (29.4)	3 (2.3)	45 (17.2)
Injection site swelling	0	4 (11.8)	0 (0.0)	46 (17.6)
Influenza like illness	0	3 (8.8)	4 (3.1)	34 (13.0)
Injection site nodule	0	0	4 (3.1)	22 (8.4)
Pyrexia	1 (5.9)	3 (8.8)	4 (3.1)	21 (8.0)
Injection site rash	0	2 (5.9)	0 (0.0)	22 (8.4)
Injection site warmth	0	1 (2.9)	0 (0.0)	22 (8.4)
Injection site induration	0	2 (5.9)	0 (0.0)	21 (8.0)
Injection site recall reaction	0	1 (2.9)	0 (0.0)	20 (7.7)
Injection site oedema	0	2 (5.9)	0 (0.0)	19 (7.3)
Injection site haemorrhage	0	1 (2.9)	2 (1.6)	16 (6.1)
Chills	0	1 (2.9)	1 (0.8)	16 (6.1)
Injection site discomfort	0	3 (8.8)	1 (0.8)	15 (5.7)

System Organ Class Preferred Term	CS5 Placebo (N=17)	CS5 Mipo (N=34)	TOTAL Placebo (N=129)	TOTAL Mipo (N=261)
Pain	0	0	5 (3.9)	11 (4.2)
Oedema peripheral	0	1 (2.9)	2 (1.6)	13 (5.0)
Injection site reaction	0	0	1 (0.8)	12 (4.6)
Injection site papule	0	4 (11.8)	0 (0.0)	11 (4.2)
Injection site inflammation	0	1 (2.9)	0 (0.0)	9 (3.4)
Injection site macule	0	5 (14.7)	0 (0.0)	8 (3.1)
Injection site vesicles	0	0	0 (0.0)	8 (3.1)
Injection site urticaria	0	0	0 (0.0)	7 (2.7)
Injection site pallor	0	2 (5.9)	0 (0.0)	3 (1.1)
Injection site paraesthesia	0	1 (2.9)	0 (0.0)	3 (1.1)
Injection site anaesthesia	0	1 (2.9)	0 (0.0)	1 (0.4)
Non-cardiac chest pain	0	4 (11.8)	1 (0.8)	6 (2.3)
Asthenia	0	1 (2.9)	2 (1.6)	5 (1.9)
Hepatobiliary disorders	**0**	**1 (2.9)**	**7 (5.4)**	**24 (9.2)**
Hyperbilirubinaemia	0	1 (2.9)	0 (0.0)	1 (0.4)
Hepatic steatosis	0	0	2 (1.6)	19 (7.3)
Hepatic cyst	0	0	3 (2.3)	1 (0.4)
Infections and infestations	**9 (52.9)**	**6 (17.6)**	**53 (41.1)**	**85 (32.6)**
Urinary tract infection	2 (11.8)	0	12 (9.3)	20 (7.7)
Upper respiratory tract infection	4 (23.5)	1 (2.9)	13 (10.1)	16 (6.1)
Nasopharyngitis	1 (5.9)	0	7 (5.4)	18 (6.9)
Influenza	2 (11.8)	2 (5.9)	6 (4.7)	14 (5.4)
Gastroenteritis	0	1 (2.9)	1 (0.8)	3 (1.1)
Ear infection	0	1 (2.9)	1 (0.8)	1 (0.4)
Fungal infection	1 (5.9)	0	1 (0.8)	1 (0.4)
Rhinitis	0	1 (2.9)	0 (0.0)	2 (0.8)
Tooth abscess	1 (5.9)	0	2 (1.6)	0 (0.0)
Sinusitis	0	0	7 (5.4)	6 (2.3)
Bronchitis	0	0	3 (2.3)	2 (0.8)
Cystitis	1 (5.9)	0	1 (0.8)	0 (0.0)
Injury, poisoning and procedural complications	**1 (5.9)**	**2 (5.9)**	**17 (13.2)**	**34 (13.0)**
Contusion	0	0	3 (2.3)	7 (2.7)
Muscle strain	0	0	3 (2.3)	2 (0.8)
Skin laceration	0	0	3 (2.3)	0 (0.0)
Procedural pain	0	1 (2.9)	1 (0.8)	3 (1.1)

System Organ Class Preferred Term	CS5 Placebo (N=17)	CS5 Mipo (N=34)	TOTAL Placebo (N=129)	TOTAL Mipo (N=261)
Ankle fracture	0	1 (2.9)	0 (0.0)	1 (0.4)
Head injury	1 (5.9)	0	1 (0.8)	0 (0.0)
Investigations	**2 (11.8)**	**6 (17.6)**	**19 (14.7)**	**77 (29.5)**
Alanine aminotransferase increased	0	4 (11.8)	1 (0.8)	25 (9.6)
Aspartate aminotransferase increased	1 (5.9)	4 (11.8)	3 (2.3)	16 (6.1)
Liver function test abnormal	0	0	1 (0.8)	14 (5.4)
Hepatic enzyme increased	1 (5.9)	0	1 (0.8)	9 (3.4)
Blood creatine phosphokinase increased	0	1 (2.9)	3 (2.3)	4 (1.5)
Protein urine present	1 (5.9)	0	1 (0.8)	2 (0.8)
Red blood cell macrocytes present	1 (5.9)	0	1 (0.8)	0 (0.0)
Metabolism and nutrition disorders	**2 (11.8)**	**1 (2.9)**	**10 (7.8)**	**12 (4.6)**
Decreased appetite	2 (11.8)	0	6 (4.7)	4 (1.5)
Hyperglycaemia	0	1 (2.9)	0 (0.0)	1 (0.4)
Musculoskeletal and connective tissue disorders	**2 (11.8)**	**4 (11.8)**	**34 (26.4)**	**69 (26.4)**
Myalgia	0	0	9 (7.0)	18 (6.9)
Pain in extremity	0	2 (5.9)	4 (3.1)	17 (6.5)
Arthralgia	1 (5.9)	0	8 (6.2)	9 (3.4)
Back pain	0	1 (2.9)	6 (4.7)	11 (4.2)
Musculoskeletal pain	0	1 (2.9)	2 (1.6)	10 (3.8)
Intervertebral disc protrusion	1 (5.9)	0	1 (0.8)	1 (0.4)
Nervous system disorders	**2 (11.8)**	**9 (26.5)**	**22 (17.1)**	**65 (24.9)**
Headache	2 (11.8)	5 (14.7)	12 (9.3)	31 (11.9)
Dizziness	0	2 (5.9)	5 (3.9)	13 (5.0)
Somnolence	0	1 (2.9)	0 (0.0)	3 (1.1)
Facial palsy	0	1 (2.9)	0 (0.0)	1 (0.4)
Neuralgia	0	1 (2.9)	0 (0.0)	1 (0.4)
Psychiatric disorders	**0**	**2 (5.9)**	**4 (3.1)**	**27 (10.3)**
Anxiety	0	1 (2.9)	2 (1.6)	8 (3.1)
Insomnia	0	0	1 (0.8)	8 (3.1)
Stress	0	1 (2.9)	0 (0.0)	2 (0.8)
Renal and urinary disorders	**1 (5.9)**	**1 (2.9)**	**6 (4.7)**	**16 (6.1)**
Proteinuria	0	1 (2.9)	1 (0.8)	6 (2.3)
Nephrolithiasis	1 (5.9)	0	1 (0.8)	0 (0.0)
Reproductive system and breast disorders	**1 (5.9)**	**3 (8.8)**	**4 (3.1)**	**7 (2.7)**
Menorrhagia	1 (5.9)	1 (2.9)	1 (0.8)	1 (0.4)

System Organ Class Preferred Term	CS5 Placebo (N=17)	CS5 Mipo (N=34)	TOTAL Placebo (N=129)	TOTAL Mipo (N=261)
Amenorrhoea	0	1 (2.9)	0 (0.0)	1 (0.4)
Galactorrhoea	0	1 (2.9)	0 (0.0)	1 (0.4)
Respiratory, thoracic and mediastinal disorders	**4 (23.5)**	**3 (8.8)**	**22 (17.1)**	**41 (15.7)**
Cough	1 (5.9)	0	5 (3.9)	14 (5.4)
Oropharyngeal pain	1 (5.9)	0	3 (2.3)	10 (3.8)
Sinus congestion	0	0	4 (3.1)	8 (3.1)
Nasal congestion	0	0	3 (2.3)	4 (1.5)
Rhinitis allergic	0	0	3 (2.3)	0 (0.0)
Upper respiratory tract congestion	0	1 (2.9)	2 (1.6)	3 (1.1)
Productive cough	0	1 (2.9)	1 (0.8)	3 (1.1)
Asthma	1 (5.9)	0	1 (0.8)	0 (0.0)
Epistaxis	1 (5.9)	0	1 (0.8)	0 (0.0)
Painful respiration	0	1 (2.9)	0 (0.0)	1 (0.4)
Skin and subcutaneous tissue disorders	**2 (11.8)**	**2 (5.9)**	**14 (10.9)**	**36 (13.8)**
Rash	0	1 (2.9)	5 (3.9)	4 (1.5)
Pruritus	1 (5.9)	0	4 (3.1)	4 (1.5)
Dermatitis allergic	0	1 (2.9)	1 (0.8)	2 (0.8)
Dry skin	1 (5.9)	0	1 (0.8)	1 (0.4)
Eczema	1 (5.9)	0	1 (0.8)	1 (0.4)
Vascular disorders	**0**	**0**	**7 (5.4)**	**29 (11.1)**
Hypertension	0	0	4 (3.1)	17 (6.5)

Source: NDA 203568: ISS Statistical Tables 3.2.2.1 and 3.2.2.1S
On-Treatment adverse events are defined as adverse events that started during the treatment period. The treatment period spans the time during which the study treatment is administered until the later of the primary efficacy timepoint (PET, date of the efficacy assessment closest to 14 days beyond the last study medication date) and 14 days beyond the last study medication date.
If a patient had more than one event within a particular system organ class or preferred term, he/she is counted only once for that system organ class or preferred term.

OLE Trial ISIS 301012-CS6: In the HoFH individuals in this trial, the most frequently reported TEAEs were Injection site erythema (28 [73.7%] individuals), Injection site pain (25 [65.8%] individuals), Influenza-like illness (18 [47.4%] individuals), and Injection site discoloration (17 [44.7%] individuals). Other frequent TEAEs were Headache (13 [34.2%] individuals), ALT increased (12 [31.6%] individuals), AST increased (11 [28.9%] individuals), and Nausea (8 [21.1%] individuals). For all individuals in this trial, the most frequently reported TEAEs were Injection site erythema (113 [80.1%] individuals), Injection site pain (102 [772.3%] individuals), and Injection site hematoma (72 [51.1%] individuals). Other frequently reported AEs were Influenza-like illness (58 [41.1%]

individuals), Fatigue (36 [25.5%] individuals), Nausea (35 [24.8%] individuals), Headache (31 [22.0%] individuals), and Myalgia (30 [21.3%] individuals).

Gender Subgroup: In the pooled Phase 3 trials of 6 months duration, the most frequently reported AEs for both subgroups within the mipomersen treatment arm were ISRs (Injection site erythema, Injection site pain, and Injection site hematoma). Adverse events in which there was an observed difference ≥ 5% between genders (mipomersen-treatment groups) include Nausea, Injection site erythema, Injection site haematoma, Injection site pruritus, Injection site swelling, Injection site discolouration, Urinary tract infection, Pain in extremity, Headache, and Cough, all reported more frequently in females, and Injection site rash, reported more frequently in males.

In OLE Trial ISIS 301012-CS6 as of the database cut off of 25 March 2011, the incidence of flu-like symptoms (FLS) was higher for female individuals than for male individuals in both the overall population (71.9% [41/57] of females and 57.1% [48/84] of males) and the sub-population of individuals with HoFH (81.0% [17/21] of females and 58.8% [10/17] of males). All other AEs were similar in incidence for female and male individuals.

Age Subgroup: As there were only seven individuals less than 18 years of age in the clinical development program, only comparisons between the 18 to <65 age group and ≥ 65 age group will be made. In the pooled Phase 3 trials of 6 months duration, individuals ≥ 65 years of age treated with mipomersen had a higher incidence of AEs of hypertension and peripheral edema compared to placebo individuals in this age group, as well as compared to the lower age groups for either treatment. In the mipomersen group, hepatic steatosis occurred more frequently in the ≥ 65 age group (10.2%) compared to the 18 to < 65 group (6.5%). Based on magnetic resonance imaging (MRI) assessment data, more individuals ≥ 65 years of age in the mipomersen group had liver fat elevations (defined as ≥ 5% change from baseline) [mipomersen (22/28, 78.6%); placebo (1/16, 6.3%)] compared to the 18 to < 65 age group [mipomersen (41/74, 55.4%); placebo (4/44, 9.1%)]. In the mipomersen group, individuals between the ages of 18 and 65 years had a higher incidence of ISRs than other age groups.

Race Subgroup: In the pooled Phase 3 trials, 84.4% (325/390) of individuals were white, which limits any evaluation of the affect of race on adverse events.

7.4.2 Laboratory Findings

Hematology
In monkeys treated for 12 months with ≤ 30 mg/kg/week mipomersen, there were no changes in platelet counts or any other hematologic parameters after 3 months of treatment, but platelet counts were lower than controls after 6 months of treatment.

In clinical trials, the mean change from baseline to Week 28/ET in hematology parameters in the pooled Phase 3 analysis showed no clinically meaningful differences between the treatment groups:

- The mean change in hemoglobin was -0.16 g/dL in the mipomersen group and -0.09 g/dL in the placebo group.
- The mean change in hematocrit was -0.4% in the mipomersen group and -0.2% in the placebo group.
- The mean change in platelets was -23.8 x 10^3/µL in the mipomersen group and -3.5 x 10^3/µL in the placebo group.
- The mean change in leukocytes was -0.86 x 10^3/µL in the mipomersen group and 0.16 x 10^3/µL in the placebo group.

Similar results were seen in ISIS 301012-CS5 (patients with HoFH) and OLE trial ISIS 301012-CS6.

For coagulation parameters, there were no clinically notable differences between the treatment groups in the pooled Phase 3 trials, ISIS 301012-CS5 (patients with HoFH), or ISIS 301012-CS6 with respect to mean changes in aPTT, INR and PT from baseline to Week 28/ET. For the pooled Phase 3 groups, the mean change from baseline to Week 28/ET in coagulation parameters were as follows:

- The mean change in aPTT was -0.93 secs in the mipomersen group and 0.00 sec in the placebo group.
- The mean change in INR was 0.02 in the mipomersen group and 0.04 in the placebo group.
- The mean change in prothrombin time (PT) was 0.01 sec in the mipomersen group and 0.25 sec in the placebo group.

Adverse events related to hematology are shown in Table 49. There was one AE of platelet count decreased (from ISIS 301012-CS12) that led to discontinuation in the mipomersen group in the pooled phase trials. Overall, adverse events related to hematology were infrequent and similar in number between mipomersen and placebo.

Table 49. Hematologic Adverse Events by System Organ Class and Preferred Term for ISIS 301012-CS5 and Pooled Phase 3 Placebo-Controlled Trials

System Organ Class Preferred Term	CS5 Placebo (N=17)	CS5 Mipo (N=34)	TOTAL Placebo (N=129)	TOTAL Mipo (N=261)
Blood and lymphatic system disorders	**1 (5.9)**	**2 (5.9)**	**6 (4.7)**	**13 (5.0)**
Anaemia	1 (5.9)	2 (5.9)	2 (1.6)	8 (3.1)
Lymphadenopathy	0	0	2 (1.6)	5 (1.9)
Iron deficiency anaemia	0	0	1 (0.8)	0

System Organ Class Preferred Term	CS5 Placebo (N=17)	CS5 Mipo (N=34)	TOTAL Placebo (N=129)	TOTAL Mipo (N=261)
Thrombocytopenia	0	0	1 (0.8)	0
Investigations				
Red blood cell macrocytes present	1 (5.9)	0	1 (0.8)	0 (0.0)
International normalised ratio increased	0	0	1 (0.8)	4 (1.5)
Platelet count decreased	0	0	1 (0.8)	3 (1.1)
Prothrombin time prolonged	0	0	2 (1.6)	1 (0.4)
Haematocrit decreased	0	0	0	2 (0.8)
Haemoglobin decreased	0	0	0	2 (0.8)
Eosinophil percentage increased	0	0	0	1 (0.4)
Red blood cell count decreased	0	0	0	1 (0.4)
White blood cell count decreased	0	0	0	1 (0.4)

Source: NDA 203568: ISS Statistical Tables 3.2.2.1 and 3.2.2.1S

Other chemistry laboratory data is discussed in the appropriate sections in Section 7.3.5.

7.4.3 Vital Signs

Across the four Phase 3 trials, from baseline to Week 28/ET, the mean change in SBP was 0.3 mmHg for the mipomersen group and -0.2 mmHg for the placebo group. Across the four Phase 3 trials, from baseline to Week 28/ET, the mean change in DBP was 0.1 mmHg for the mipomersen group and -0.7 mmHg for the placebo group. As shown in the table below, the mean baseline systolic and diastolic blood pressure of both mipomersen- and placebo-treated individuals in ISIS 301012-CS5 was lower relative to the baseline systolic and diastolic blood pressure of individuals in the other Phase 3 trials. This was likely due to the younger age of the individuals in ISIS 301012-CS5. There were no clinically meaningful changes in average blood pressure or heart rate between the two treatment groups across the Phase 3 trials. A discussion of adverse events related to hypertension and a shift table for systolic and diastolic blood pressures are located in *Section 7.3.5.6 Cardiovascular Issues*.

Table 50. Blood Pressure and Heart Rate Data Across the Four Phase 3 Trials

Parameter Time Point Statistic	ISIS 301012-CS5		MIPO3500108		ISIS 301012-CS7		ISIS 301012-CS12	
	Placebo (N=17)	Mipo (N=34)	Placebo (N=19)	Mipo (N=39)	Placebo (N=41)	Mipo (N=83)	Placebo (N=52)	Mipo (N=105)
Systolic Blood Pressure (mmHg)								
Baseline Value, n	17	34	19	39	41	83	52	105
Mean (SD)	120.9 (18.9)	119.1 (16.8)	124.6 (8.4)	127.7 (17.7)	122.7 (19.2)	121.8 (14.2)	126.4 (14.0)	127.0 (14.4)

Parameter Time Point Statistic	ISIS 301012-CS5		MIPO3500108		ISIS 301012-CS7		ISIS 301012-CS12	
	Placebo (N=17)	Mipo (N=34)	Placebo (N=19)	Mipo (N=39)	Placebo (N=41)	Mipo (N=83)	Placebo (N=52)	Mipo (N=105)
Min, Max	94, 173	94, 158	109, 140	96, 178	86, 188	92, 152	90, 154	90, 167
(95% CI)	(111, 131)	(113, 125)	(121, 129)	(122, 133)	(117, 129)	(119, 125)	(122, 130)	(124, 130)
Nominal Change, n	17	34	19	39	41	83	51	102
Mean (SD)	-2.4 (10.9)	1.1 (16.2)	5.1 (13.3)	-0.4 (15.0)	-1.0 (18.6)	-0.9 (12.4)	-0.7 (15.2)	1.3 (15.2)
Min, Max	-23, 17	-39, 30	-20, 29	-28, 50	-77, 40	-31, 26	-47, 35	-49, 33
(95% CI)	(-8, 3)	(-5, 7)	(-1, 11)	(-5, 4)	(-7, 5)	(-4, 2)	(-5, 4)	(-2, 4)
Diastolic Blood Pressure (mmHg)								
Baseline Value, n	17	34	19	39	41	83	52	105
Mean (SD)	66.3 (10.2)	67.6 (9.0)	78.6 (8.6)	74.1 (12.0)	75.0 (9.5)	73.8 (10.0)	76.8 (8.6)	78.2 (8.5)
Min, Max	53, 88	49, 90	60, 90	51, 102	56, 96	56, 94	59, 95	55, 98
(95% CI)	(61, 72)	(65, 71)	(74, 83)	(70, 78)	(72, 78)	(72, 76)	(74, 79)	(77, 80)
Nominal Change, n	17	34	19	39	41	83	51	102
Mean (SD)	2.5 (11.0)	-1.1 (9.4)	1.6 (7.4)	1.4 (9.3)	-4.0 (11.9)	-1.0 (9.3)	0.1 (8.1)	0.8 (7.9)
Min, Max	-20, 19	-20, 13	-15, 16	-19, 26	-36, 21	-23, 20	-35, 18	-18, 24
(95% CI)	(-3, 8)	(-4, 2)	(-2, 5)	(-2, 4)	(-8, 0)	(-3, 1)	(-2, 2)	(-1, 2)
Pulse Rate (beats/min)								
Baseline Value, n	17	34	19	39	41	83	52	105
Mean (SD)	73.4 (12.3)	71.8 (12.9)	69.8 (11.5)	67.4 (8.6)	63.3 (9.4)	64.8 (9.7)	69.9 (11.3)	69.0 (10.1)
Min, Max	58, 105	41, 96	54, 90	51, 88	44, 80	46, 101	54, 106	40, 94
(95% CI)	(67, 80)	(67, 76)	(64, 75)	(65, 70)	(60, 66)	(63, 67)	(67, 73)	(67, 71)
Nominal Change, n	17	34	19	39	41	83	51	102
Mean (SD)	-2.6 (9.7)	-1.6 (13.6)	1.4 (11.7)	2.3 (9.3)	-1.9 (8.1)	0.8 (8.8)	-0.2 (11.7)	-0.5 (10.5)
Min, Max	-19, 18	-24, 28	-22, 24	-14, 22	-20, 20	-18, 36	-32, 43	-34, 41
(95% CI)	(-8, 2)	(-6, 3)	(-4, 7)	(-1, 5)	(-4, 1)	(-1, 3)	(-3, 3)	(-3, 2)

7.4.4 Electrocardiograms (ECGs)

Mean changes in ECG parameters were generally small and there were no significant changes observed in either treatment group in the pooled Phase 3 analysis or in the individual trials.

In a thorough ECG study (MIPO2800209 CSR) conducted in 60 healthy volunteers, mipomersen had no significant effect on heart rate, PR, and QRS interval duration or cardiac repolarization. MIPO2800209 CSR 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 supra-therapeutic (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 moxifloxacin profile over time demonstrated that assay sensitivity was established. The overall summary of findings from the TQT team consult is presented in the following table.

Table 51. The Point Estimates and the 90% CIs for 200-mg Mipomersen s.c., 200-mg Mipomersen i.v. and Moxifloxacin

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
200-mg mipomersen SC	8	0.5	(-1.7, 2.7)
200-mg mipomersen IV	4	1.1	(-0.9, 3.1)
Moxifloxacin 400 mg*	2	16.9	(14.9, 18.9)

*Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 14.2 ms.
Source: FDA TQT review team analysis

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. No effect on Cmax or AUC was observed for food, age, gender or concomitant medications. However, PK studies have not been conducted for patients with either renal or hepatic impairment.

The mean change from baseline placebo-corrected HR for the 2 mipomersen doses showed an increase of 1.1 and 1.5 bpm for the SC and IV doses, respectively. Table 52 presents the categorical analysis of HR. Two subjects who experienced HR interval greater than 100 bpm were in mipomersen 200 mg s.c. and mipomersen 200 mg i.v.

Table 52. Categorical Analysis for HR

Treatment Group	Total N	HR < 100 bpm	HR ≥100 bpm
200-mg mipomersen IV / Placebo Subcutaneous	56	54 (96.4%)	2 (3.6%)
200-mg mipomersen Subcutaneous / Placebo IV	58	57 (98.3%)	1 (1.7%)
400-mg moxifloxacin IV / Placebo Subcutaneous	58	56 (96.6%)	2 (3.4%)
Placebo IV / Placebo Subcutaneous	59	59 (100%)	0 (0.0%)

Source: FDA TQT review team consult, Table 11

A search of the mipomersen phase 3 database was conducted to determine whether ECG changes were reported as adverse events. As shown in Table 53, the number of events is quite small with no meaningful difference between the two treatment groups. No subject in either treatment group discontinued due to an ECG-related adverse event and no clinically relevant ECG changes were reported.

Table 53. ECG-related Adverse Events by System Organ Class and Preferred Term for ISIS 301012-CS5 and Pooled Phase 3 Placebo-Controlled Trials

System Organ Class Preferred Term	CS5 Placebo (N=17)	CS5 Mipo (N=34)	TOTAL Placebo (N=129)	TOTAL Mipo (N=261)
Investigations				
Electrocardiogram PR prolongation	0	0	0	1 (0.4)
Electrocardiogram T wave inversion	0	0	0	1 (0.4)
Electrocardiogram abnormal	0	0	1 (0.8)	0
QRS axis abnormal	0	0	0	1 (0.4)

7.4.5 Special Safety Studies/Clinical Trials

The Thorough QT study is discussed in Section 7.4.4.

7.4.6 Immunogenicity

HoFH Population: To evaluate the formation of anti-mipomersen antibodies in mipomersen-treated individuals, second-generation assays for anti-mipomersen antibodies were used to test serum samples from individuals in ISIS 301012-CS5 and those individuals from ISIS 301012-CS5 who continued in the OLE ISIS 301012-CS6. In ISIS 301012-CS5, treatment duration of 26 weeks, antibodies assays were done at pre-treatment and Weeks 28 and 50. In ISIS 301012-CS6, antibodies assays were done in Years 1 and 2 at Weeks 13, 26, 52, 76, and 104. In Years 3 and 4, antibodies assays

were done at Weeks 1, 17, 34, 52, 68, 85, and 104. A total of 30 (60%) of the 50 mipomersen-treated individuals across ISIS 301012-CS5 and OLE ISIS 301012-CS6 tested positive for anti-mipomersen antibodies at some point during one of the trials. In ISIS 301012-CS5, no placebo-treated individuals were positive for anti-mipomersen antibodies. In ISIS 301012-CS5, a total of 11 of 34 (32%) mipomersen-treated individuals were positive for anti-mipomersen antibodies; 22 of 34 (65%) were negative for anti-mipomersen antibodies, and 1of 34 had no post-baseline assessment. In OLE ISIS 301012-CS6, 26 of 38 (68%) HoFH individuals had anti-mipomersen antibodies. Nineteen of these 26 individuals had been negative for anti-mipomersen antibodies in OLE ISIS 301012-CS5 and tested positive for anti-mipomersen antibodies in OLE ISIS 301012-CS6 and 7 individuals were positive in ISIS 301012- CS5 and continued into ISIS 301012-CS6. A summary of the findings comparing antibody-positive vs negative HoFH individuals treated with mipomersen in the CS5 and CS6 trials follows:

- In ISIS 301012- CS5, none of the 11 antibody-positive individuals discontinued treatment as compared to 5 out of 22 (23%) antibody-negative individuals that discontinued treatment (4 out of 22 [18.2%] discontinued due to AEs).
- Among the 30 individuals who tested positive for anti-mipomersen antibodies in either ISIS 301012-CS5 or ISIS 301012-CS6, 16 individuals (53%) discontinued from treatment. The main reasons for these discontinuations included FLS (7 individuals), nausea, vomiting and/or abdominal pain (3 individuals), withdrawal of patient or loss to follow up (3 individuals), hepatic transaminase tests (2 individuals), ISRs (1 patient), urticaria (1 patient), pregnancy (1 patient), depression (1 patient), and non-cardiac chest pain (1 patient).
- The most commonly reported AEs in both antibody-positive and antibody-negative individuals were ISRs and FLS. In ISIS 301012-CS5, ISRs were reported in 8/11 (73%) antibody-positive individuals and 18/22 (82%) antibody-negative mipomersen-treated individuals. In ISIS 301012-CS6, ISRs were reported in 24/26 (92%) antibody-positive individuals and 12/12 (100%) antibody-negative individuals.There was no increase in reports of Injection site recall reactions in antibody-positive individuals. All reports of Injection site recall reactions occurred in antibody-negative individuals [1/22, (4.5%) in ISIS 301012-CS5 and 2/12, (16.7%) in ISIS 301012-CS6].
- In ISIS- 301012-CS5, 1/11 (9%) antibody-positive patient reported FLS compared to 5/22 (23%) of antibody-negative mipomersen-treated individuals. An increase in the incidence of FLS was seen in the antibody-positive individuals in ISIS 301012-CS6 (77% in the antibody-positive group versus 58% in the antibody-negative group). In ISIS 301012-CS5, none of the individuals from either antibody group discontinued treatment due to FLS. In ISIS 301012-CS6, 7 out of 26 (27%) antibody-positive individuals discontinued treatment due to FLS as compared to 2 out of 12 (16.7%) antibody-negative individuals that discontinued treatment due to FLS.
- In CS5 and CS6, when looking at the small numbers of individuals with ALT or AST ≥ 3xULN, there was no difference in the number of antibody-positive individuals as compared to the antibody-negative individuals.

- An evaluation of albumin/creatinine ratio, C-reactive protein, glomerular filtration rate, platelets and Complement C3 in ISIS 301012-CS5 and ISIS 301012-CS6 was limited by the small number of individuals but did not reveal any clinically meaningful differences between the antibody-positive and antibody-negative individuals.

Pooled Phase 3 Trials: Of the mipomersen-treated patients in the pooled Phase 3 trials, 93 out of 248 mipomersen-treated individuals (37.5%) with post-baseline antibody results tested positive for anti-mipomersen antibodies during the 6-month trials while none of the 121 placebo-treated patients in the pooled Phase 3 trials with post-baseline antibody results tested positive for anti-mipomersen antibodies. A summary of the findings comparing antibody-positive vs negative individuals treated with mipomersen in the pooled Phase 3 trials follows:

- Efficacy results in individuals who tested positive for anti-mipomersen antibodies were similar to individuals who remained negative for anti-mipomersen antibodies (mean LDL% change from baseline was -32.4% for antibody-positive and -33.8% for antibody-negative).
- The majority of antibody positive and antibody negative individuals completed treatment with mipomersen (81.7% and 71.6%, respectively).
- The most common reason for treatment discontinuation among antibody positive and negative individuals was due to AEs or SAEs (16.1% and 19.4%, respectively).
- The most commonly reported AEs in antibody-positive and antibody-negative individuals were ISRs and FLS. 1677 ISR events were reported in 80/93 (86.0%) antibody-positive individuals and 1979 ISR events were reported in 133/155 (85.8%) antibody-negative individuals. The percentage of individuals with injection site recall reactions was similar between antibody-positive (7.5%; 7/93) and antibody-negative (8.4%; 13/155) individuals. Four antibody-positive individuals (4.3%; 4/93) and 9 (5.8%; 9/155) antibody-negative individuals discontinued treatment due to ISRs.
- The incidence of FLS AEs was higher in antibody-positive individuals (36/93 [38.7%]) compared with antibody-negative individuals (39/155 [25.2%]). However, only 1 antibody-positive individual (1.1%; 1/93) discontinued treatment due to FLS compared with 6 antibody negative individuals (3.9%; 6/155).
- One antibody-positive individual (1/93; 1.1%) and 1 antibody-negative individual (1/155; 0.6%) reported an AE of Urticaria.
- There were no meaningful differences in the number of antibody-positive individuals (19.4%; 18/93) with increases in ALT ≥ 3 X ULN as compared to the antibody-negative individuals (16.1%; 25/155), or in the percentages of patients with consecutive increases in ALT ≥ 3 X ULN (11.8% vs 7.1%).
- No median differences were observed in GFR, CRP or platelet count between the antibody positive and antibody negative individuals.

- Antibody-positive individuals had a median nominal change in albumin/creatinine ratio (ACR) of -0.40 mg/g to a median value of 5.85 mg/g from baseline to Week 28/ET, compared with a median nominal change in ACR of 0.27 mg/g to a median value of 7.25 mg/g in antibody-negative individuals.
- Antibody-positive individuals had a slightly greater median nominal change in complement C3 (C3) of -15 mg/dL to a median value of 126 mg/dL from baseline to Week 28/ET, compared with a median nominal change in C3 of -2 mg/dL to a median value of 134 mg/dL in antibody-negative individuals (normal range = 90-180 mg/dL).

OLE CS6 Trial: In the overall OLE CS6 trial, of the 83 individuals who received mipomersen treatment in the index trials, 26 individuals (31.3%) tested positive for anti-mipomersen antibodies during the index trials and an additional 37 individuals subsequently tested positive for anti-mipomersen antibodies in the OLE for a total of 63/83 individuals (75.9%) tested positive for anti-mipomersen antibodies during the OLE trial. Of the 58 individuals who received placebo in the index studies, 38 (65.5%) tested positive for antibodies in the OLE. Overall, of the 141 individuals who were treated with mipomersen in the OLE trial, 101 individuals (71.6%) tested positive for anti-mipomersen antibodies. A total of 60 individuals were treated with mipomersen for more than 2 years in the OLE study; 75% (45/60) of these tested positive for anti-mipomersen antibodies. The median maximum titer in anti-mipomersen antibody positive patients was 1:1600. A summary of the findings comparing antibody-positive vs negative individuals treated with mipomersen in the overall OLE CS6 trial follows:

- The overall incidence of AEs leading to treatment discontinuation was slightly higher in antibody positive individuals (48.5%; 49/101) compared with antibody negative individuals (40.0%; 16/40). The most common AEs leading to treatment discontinuation were in the MedDRA SOC of General Disorders and Administration Site Conditions (34.7% vs 17.5%).
- The most commonly reported AEs in both evaluable antibody-positive and antibody-negative individuals were ISRs and FLS: 2206 ISR events were reported in 98/101 (97.0%) antibody-positive individuals and 764 ISR events were reported in 40/40 (100.0%) antibody-negative individuals. The percentage of Injection site recall reactions in antibody-positive individuals was similar between antibody-positive (15.8%; 16/101) and antibody-negative (12.5%; 5/40). The incidence of treatment discontinuations due to ISRs was similar between antibody-positive individuals (8.9%; 9/101) and antibody-negative individuals (10.0% 4/40).
- Similar to the results in the pooled Phase 3 trials, the incidence of FLS AEs was higher in antibody-positive individuals (71.3% [72/101]) compared with antibody-negative individuals (52.5% [21/40]). There was also a higher incidence of treatment discontinuations due to FLS in antibody-positive individuals (29.7%; 30/101) versus antibody-negative individuals (12.5%; 5/40).
- Four antibody-positive individuals (4/101; 4.0%) and 2 antibody-negative individuals (2/40; 5.0%) reported an AE of Urticaria.

- There was one case of hypersensitivity reaction with angioedema that occurred in May 2012 and June 2012 in a 46-year old male individual with HeFH in OLE trial CS6. The patient had previously participated in trial CS17 and received treatment from July 2007 to February 2011. Prior to CS17, the patient was enrolled in trial CS9 and received 15 doses of 300 mg mipomersen from March 2007 to May 2007. During the CS9 trial, the patient had experienced a rash that resolved. During the CS17 trial, the patient had experienced ISRs consisting of discoloration and induration. During ISIS 301012-CS17 study, plasma ISIS 301012 concentrations ranged from 2.8 ng/mL to 57.3 ng/mL on-treatment and during ISIS 301012-CS6 study plasma concentrations ranged from 6.1 ng/mL to 46.7 ng/mL on-treatment. Antibody tests performed in ISIS 301 012-CS17 were all negative. However, in CS6 the patient had a titer of 400 for mipomersen antibodies in July 2011 but tested negative for mipomersen antibodies in November 2011, March 2012 and July 2012. Mipomersen has been discontinued after the self-injected Week 49 dosage in June 2012.
- The number of antibody-positive individuals (19.8%; 20/101) with increases in ALT ≥ 3 X ULN was somewhat smaller than the antibody-negative individuals (27.5%; 11/40); this was also the case with the percentages of individuals with consecutive increases in ALT ≥ 3 X ULN (10.9% vs 17.5%).
- No median differences were observed in GFR, CRP or platelet count between the antibody positive and antibody negative individuals.
- Antibody-positive individuals had a nominal median change in ACR of 1.08 mg/g to a median value of 6.20 mg/g from baseline to Week 104, compared with a median nominal change in ACR of -0.36 mg/g to a median value of 7.71 mg/g in antibody-negative individuals.
- Antibody-positive individuals had a nominal median change in C3 of -21 mg/dL to a median value of 111 mg/dL from baseline to Week 104, compared with a median nominal change in C3 of -3 mg/dL to a median value of 132 mg/dL in antibody-negative individuals (normal range = 90-180 mg/dL).

Although the numbers are small, there may be a small trend toward discontinuations from FLS in those individuals who become antibody-positive.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The Phase 3 trials all used the 200 mg SC per week dose. In the Phase 2 dose-ranging study CS4, a higher and dose-dependent incidence of tolerability and safety findings (such as injection site reactions, flu-like symptoms, and elevations in hepatic

transaminases) occurred with the higher 300 mg and 400 mg once weekly doses. See Section 4.4.2 for additional information.

7.5.2 Time Dependency for Adverse Events

An evaluation of time to onset for selected adverse reactions (ISRs and FLS) is presented in Sections 7.3.5.2 and 7.3.5.3.

7.5.3 Drug-Demographic Interactions

Adverse reactions analyzed in terms of gender, age and race is presented in Section 7.4.1. Common Adverse Events.

7.5.4 Drug-Disease Interactions

The effects of modest to severe degrees of hepatic or renal impairment on mipomersen efficacy and safety have not been studied. 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. Of the covariates studied, creatinine clearance was predictive of variability for mipomersen PK. Mipomersen clearance is lower by approximately 31% at lower creatinine clearances in the range of 42.2 mL/min compared with 150 mL/min.

7.5.5 Drug-Drug Interactions

Discussed in Section 4.4.3.3.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Refer to Section 7.3.5.8 Neoplasms.

7.6.2 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies of mipomersen use in pregnancy. It is not known whether mipomersen is excreted in human breast milk.

Reproductive and developmental toxicology studies were conducted in mice, rabbits and rats. According to the applicant, in mice, at doses up to 87.5 mg/kg/week, there was slight maternal toxicity as indicated by reduced hemoglobin and hematocrit values, increases in platelet counts, and some slight changes in serum chemistry parameters attributed to treatment. In rabbits given 52.5 mg/kg/week there were slight reductions in total serum protein, albumin, and AST. Maternal toxicity in rabbits was evident as reductions in body weight and feed consumption values and one early delivery. No effects on fertility or fetal development were observed in mice given up to 87.5 mg/kg/week mipomersen or in rabbits given up to 52.5 mg/kg/week mipomersen. There was little or no accumulation of drug in the fetus or the placenta after administration every other day during the gestation period. No effects on fetal development or fertility were observed in mice or in rabbits.

7.6.3 Pediatrics and Assessment of Effects on Growth

The inclusion criteria of ISIS 301012-CS5 allowed the enrollment of children 12 years of age and older. Of the 51 randomized patients, 7 were adolescents (12 to <18 years of age), 3 of whom were randomized to mipomersen and 4 to placebo. Although a dose adjustment was allowed for patients below 50 kg (to 160 mg mipomersen once weekly), all of the mipomersen-treated children in ISIS 301012-CS5 were above 50 kg (range, 55 to 61 kg; between 14 and 16 years of age), so all were treated with 200 mg mipomersen once weekly. Efficacy results for the mipomersen treated group were consistent with the overall mipomersen-treated population.

After Week 28, the 7 adolescent patients from ISIS 301012-CS5 enrolled in OLE study ISIS 301012-CS6. The 3 patients who were receiving mipomersen in ISIS 303012-CS5 continued to receive 200 mg mipomersen once weekly. The 4 placebo patients (aged 12 to 14 years of age) from ISIS 301012-CS5 were assigned to receive mipomersen at 200 mg once weekly (3 patients) or 160 mg once weekly (1 patient at 45.8 kg; 13 years of age) in ISIS 301012-CS6.

The safety and effectiveness of mipomersen in pediatric patients has not been established in these clinical trials. No assessments on growth were made in these trials.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There has been no known occurrence of a mipomersen overdose in humans to date. There have been no reports of patient abuse of or dependence on mipomersen. No formal studies for withdrawal or rebound effects have been conducted.

7.7 Additional Submissions / Safety Issues

The 4-Month Safety Update Report (submitted 25 July 2012) is discussed within the body of this review.

8 Postmarket Experience

Mipomersen has not been marketed in any country; therefore, there are no post-marketing safety data.

9 Appendices

9.1 Literature Review/References

Literature references were made throughout this document when relevant.

9.2 Labeling Recommendations

Some general label recommendations include:

- Indication: [redacted] (b) (4) add qualifier of 'adult' to patients with HoFH
- Include a Limitations of Use in the indication section describing that (1) the effect of mipomersen on cardiovascular morbidity and mortality has not been determined and (2) mipomersen has not been adequately studied as an adjunct to LDL-apheresis; therefore, the use of mipomersen as an adjunct to LDL-apheresis is not recommended.
- Contraindication section: add in known sensitivity to product components.
- Patients with known severe renal impairment, clinically significant proteinuria, or on renal dialysis have not been studied and use in these patients is not recommended.
- Section 2.2: Instructions for use: recommend adding that the injection should be given on the same day every week

[redacted] (b) (4)

- Section 6.1 Clinical trials: added additional information on demographics, adverse reactions that led to treatment discontinuation and notable adverse reactions seen in the OLE trial
- Section 8.5: added additional demographic information
- Section 12.2 Pharmacodynamics: deleted information [redacted] (b) (4)
- Section 14: Clinical Studies: remove [redacted] (b) (4)

Additional label comments will be made in a separate label review document.

9.3 Advisory Committee Meeting

An advisory committee meeting was held on 18 October 2012. The vote of whether mipomersen should be approved was 9 'yes' votes and 6 'no' votes. This reviewer's notes on the discussion comments and voting responses are included below.

Comments during meeting:
1) LDL-C reduction variability:

- What is the basis for LDL-C reduction variability and how would this be addressed in labeling? Consider evaluating after 4-6 months to see if there is a good response.
- One committee member asked if non-responders to LDL had evidence of response to other lipid parameters such as HDL-C or Lp(a).

2) LDL-apheresis:

- The average LDL-C is ~400 mg/dL. The post-treatment value was >300 mg/dL which leaves a huge treatment gap.
- Many members questioned why there were no patients on lipid apheresis in the trials.
- The sponsor states that LDL apheresis may affect mipomersen distribution. That every apheresis treatment is different in regard to how much cholesterol can be removed and this could confound efficacy. There is an on-going pilot study in Germany where mipomersen is given the day after LDL-apheresis.

3) One of the hepatologists believed that of the 5 biopsies presented, 4 out of 5 had signs of steatohepatitis based on the pathology report.

4) Immunogenicity:

- Is there any evidence of auto-antibodies? The sponsor did not have any evidence of binding to self-DNA in studies.

Discussion Questions:

1. Discuss whether you believe that the applicant has provided adequate evidence to support the efficacy of mipomersen as an adjunct to a low-fat diet and maximally tolerated lipid-lowering medications for the reduction of low-density lipoprotein cholesterol (LDL-C) in patients with homozygous familial hypercholesterolemia (HoFH).

Committee:

- Need to assess the effect of LDL apheresis on efficacy
- Poor responders may not have a positive benefit:risk profile

2. Provide your assessment of mipomersen's effect on high density lipoprotein cholesterol, triglyceride, apolipoprotein B, apolipoprotein AI, Lp(a), and C-reactive protein.

Committee:

- Transient hsCRP are less worrisome; long-term increases in hsCRP are concerning but this was not seen here

3. The reduction of LDL-C is a surrogate endpoint that is expected to correlate with a reduction in cardiovascular morbidity and mortality. The effect of mipomersen on cardiovascular outcomes will not be determined in the HoFH population given the rarity of this disease, and for the purposes of this discussion, assume that no additional outcomes data for mipomersen will be generated in other populations. Discuss whether you consider LDL-C an appropriate surrogate for reduced cardiovascular morbidity and mortality in mipomersen-treated patients with HoFH.

Committee:

- While LDL is an appropriate surrogate in the HoFH population, there may be off-target toxicities that may not be offset by the modest LDL lowering.
- Other endpoints that may be of interest include CIMT, resolution of xanthomas, coronary calcium score, aortic valve disease.
- The key issue here is that we don't have enough information to know whether lowering 400 to 300 is meaningful. So LDL does seem to be a reasonable surrogate, but it needs to be taken in the context of disease.
- The broader question of the adequacy of LDL as a surrogate is highly context dependent, so what the panel concluded about the HoFH setting, with all of its clinical trial challenges, may not be the same for other cholesterol medications in other settings.

4. Regarding the liver-related adverse effects observed in the mipomersen development program:
a. Discuss your level of concern for the hepatic steatosis associated with mipomersen and the potential for steatohepatitis with chronic use of mipomersen.

Committee:

- Moderate concern: variability in ALT elevations and they are not tightly linked to hepatic steatosis
- Moderate concern: There were early stopping rules for transaminase elevations; patients may have done worse if they had continued with drug treatment

b. Discuss your level of concern regarding a possible association between hepatic steatosis and increased risk for cardiovascular morbidity or mortality.

Committee:

- The mechanism for drug-induced vs nondrug-induced may not be the same; CV risk is in setting of increased insulin resistance and there is no evidence for that here
- The risk is unknown at this time
- Doubt that the potential increased CV risk from hepatic steatosis is a big issue

c. Discuss your level of concern for the transaminase abnormalities associated with mipomersen and the potential for drug induced liver injury.

Committee:

- High concern: 4 out of 5 of the biopsies showed steatohepatitis and had ballooning degeneration of hepatocytes
- We don't know what the baseline was for these biopsies so difficult to assess the drug affect

d. If approved for the treatment of HoFH,

- Discuss how patients treated with mipomersen should be monitored for liver-related adverse effects.
- Comment on dosing recommendations (dose lowering, interruption or discontinuation) based on quantitative thresholds of liver transaminase elevations or steatotic changes.
- Discuss population-based approaches to further characterize and assess liver safety post-approval.

Committee:

- ALT ULN should be 30 U/L; At 3xULN (90 U/L) consider holding or stopping drug at this level; ALT level of 90-150 U/L and patient to stay on drug, consider liver biopsy within 3-6 months; ALT> 150 U/L and a change from baseline in steatosis by MRI > 10%: discontinue or interrupt therapy
- Full liver panel to include bilirubin and GGT at baseline
- CT and ultrasound are not helpful longitudinally as they are not precise enough
- Consider non-contrast MRI to monitor for liver steatosis
- No clear threshold for concern but 10% or 20% was suggested as thresholds for clinical concern
- Recommend more frequent monitoring in the first 6 months and then could spread out monitoring
- Proceed cautiously in patients with increases in ALT and hepatic fat; not enough data to say more definitively

5. Mipomersen caused immunostimulatory effects including proinflammatory tissue changes in animal studies, which were associated with malignant fibrohistiocytic tumors (fibrosarcoma and/or fibrous histiocytoma) of the skin/subcutis in both genders in rats

and in male mice. Mipomersen also increased the incidence of hemangiosarcomas in mice (female) and hepatocellular adenomas/carcinomas in mice. Mipomersen-related tumors were all seen at clinically relevant exposures. Notably, the mouse surrogate (ISIS 147764) caused a further increase in the incidence of hepatocellular tumors over that seen with mipomersen. Discuss your level of concern regarding these mipomersen-related tumor findings.

Committee: Immunostimulatory effects may be concurrent rather than associative.

6. Across the entire mipomersen clinical development program, the incidence of reported neoplasms (benign and malignant) was 3.1% (23/749) in mipomersen-treated patients versus 0.9% (2/221) in placebo-treated patients. Provide your assessment of this reported imbalance in neoplasms.

Committee:

- Is 10/261 vs 0/129 statistically significant?
- This might be a signal. Animal data is concerning as well.
- Question of ascertainment bias. Could look at mipomersen-treated subjects without adverse events as they would not be subject to the ascertainment bias.
- Cancer screening should be done at baseline in future trials.

7. Based on the information provided in the briefing materials, the presentations today, and the proposed risk evaluation and mitigation strategy, do you believe that the potential benefits of mipomersen outweigh its potential risks in patients with homozygous familial hypercholesterolemia?
a. If YES, provide your rationale and any recommendations you have regarding risk management strategies, post-marketing studies and clinical monitoring.
b. If NO, provide your rationale and comment on what additional data you believe are required to potentially support approval

YES votes = 9; NO votes = 6

YES vote comments:

- Yes, but only in HoFH. Risk of liver related transaminase elevations and steatosis is warranted due to benefit
- Yes but weak. Issues of high discontinuation rates, liver toxicity, nagging carcigenicity concerns but are probably unlikely; if indication expanded, warrants imaging endpoint data
- Yes because we need more tools in this population; Antibody positivity and FLS are lingering concerns
- Yes, given that the risk for major clinical cardiovascular events is extremely high in homozygous-FH patients. It is a small group of patients, and they should be able to be monitored closely. Within that context, we view the efficacy a bit

differently. Even if a third of the group responded very well, then that's a major success. Can't hold HoFH population hostage to off-label use worry; the REMS should be more restrictive

- Yes but it was a very close call because of the uncertainty about the risk/benefit trade-off, and it mainly came down to the fact that there would be patients who would have a dramatic response to mipomersen. It didn't seem fair to not make it available for those patients. A rigorous postmarketing study is needed.
- Tumors seen in multiple species, both genders, and multiple sites is a cancer signal; mipomersen data did not rise to that level
- Effect size is modest. Retention is a concern. Unclear if steatosis seen on biopsy is caused by mipomersen. Absence of apheresis is unfortunate. Recommend stopping rules for side effects and lack of efficacy. For post-marketing, closely monitor patients and assess long-term consequences.

NO vote comments:

- LDL lowering is not particularly robust. We do not know if lowering the cholesterol by the amount seen in this study would be meaningful in this population. We also do not know if cardiovascular events will go down with this drug and may never know because of the limited population. Five patients had liver biopsies prompted by increases in hepatic fat, so we are actually able to have more information and we're able to see some steatohepatitis. The fact that it occurred so soon after the initiation of the drug is concerning that this isn't something we're going to see in 20 or 30 years, but maybe this is something we're going to see the effects of in five years. And then really, the trade-off between cardiovascular risk and liver disease is narrower than one would have liked. On-going studies could address some of these issues. Lipid apheresis needs to be done with mipomersen use; high drop-out rate
- Primary concern is safety (liver, systemic inflammation); only modest 20% LDL lowering
- Safety concerns along with increased discontinuation rate; need data on LDL apheresis
- Comes down to the risk:benefit ratio. Degree of LDL lowering not robust enough to be certain of a benefit. Who would benefit? Who would have toxicity? High discontinuation rate. Immune response concern. Steatosis and steatohepatitis developed in a short time.
- There are heterogeneity of treatment effects but decisions are based on mean. Modest reduction in LDL. Safety concerns. Concerned about off-label use, need to tighten up REMS. Requirement for monitoring and registry.

9.4 Patient Narratives

9.4.1 Individuals who Died during the Clinical Development Program

Patient ID: 1681-2132 (Trial ISIS 301012-CS12)
Patient 1681-2132 was a 68 year-old male with HeFH who received a total of 26 injections of blinded study drug (mipomersen) and completed the treatment period of the trial.

August 2010: 325 days after starting blinded study drug and 149 days after receiving his last dose, the patient awoke with severe epigastric and right upper quadrant pain, burning in nature, nonradiating and accompanied by nausea. History was obtained of a decrease in appetite and weight loss (20 pounds) over the previous 2-3 months and the patient stated he was drinking 2-3 beers per day, an increase over the amount documented during the trial. Liver function tests (LFTs) were performed on day 1, elevations of ALT 832 U/L (14.9xULN; reference range 7-56 U/L), AST 2775 U/L (60.3xULN; reference range 15-46 U/L), total bilirubin 3.2 mg/dL (2.5xULN; reference range 0.1-1.3 mg/dL), PT 26.6 secs (1.9xULN; reference range 11.0-14.4 secs) and INR 2.4 (D). Lipase at that time was 209 U/L (reference range of 23-300 U/L) and platelets were 67 x 103/mm3. The patient's initial cardiac enzymes and electrocardiograms (ECGs) were negative. He was admitted to the hospital with acute liver failure, thrombocytopenia, and acute chest pain.

Course in hospital: During the course of the first day, the patient became more symptomatic and liver function tests worsened over the next 24 hours. By early the next morning, ALT was 2526 (45xULN), AST peaked at 12555 (273xULN), total bilirubin 4.2 (3.2xULN), and INR 5.8. An acetaminophen level, first drawn at this time, (approximately 25 hours after first presentation in the emergency department) was 35 mcg/mL (reference range 5-20 mcg/mL). The patient's family denied any excessive acetaminophen use and no history regarding use prior to admission was given. From the submitted medication records no acetaminophen was administered or ordered in hospital. An infusion of N-acetylcysteine was started on the second day and the patient was given lactulose for rising ammonia levels, which had increased, from an admission normal of 9 umol/L to a peak of 333 umol/L on the second day (reference range 9-33 umol/L). The lipase level peaked at 1361 U/L at 20:00hrs of the first evening. The patient was on a number of medications in addition to acetaminophen that may have been hepatotoxic, including piroxicam, colchicines, furosemide, and fenofibrate.

The patient became increasingly acidotic with a lactic acid level of 17.4 mg/dL at 20:00hrs of the first day (reference range 0.5-2.2 mg/dL). At some point in the early morning of the second day, the patient was transferred to the intensive care unit, and shortly thereafter, suffered a cardio respiratory arrest from which he was resuscitated. The patient was intubated and ventilated. Arterial gases done just after intubation

showed a pH of 6.95 (reference range 7.35-7.45), pC02 of 63 (reference range 35-45 mmHg), p02 of 58 on 50% oxygen (reference range 80-100 mmHg on room air), HC03 of 14 (reference range 22-26 mmol/L). At presentation, creatinine was 1.5 mg/dL (reference range 0.66-1.25 mg/dL), BUN 15 mg/dL (reference range 7-21 mg/dL), and glomerular filtration rate (GFR) 47 mL/min (reference range 85-125 mL/min). On the second day, creatinine had increased to 3.86 mg/dL, BUN 15 mg/dL, and GFR 16 mL/min. The patient was diagnosed with acute on chronic renal failure due to liver failure as well as hemodynamic changes. Blood pressure during this time had remained in the 100 mmHg systolic range with diastolics of 50 to 60 mmHg, in a patient with a history of hypertension. The attending physician listed the following issues in the chart post-arrest; fulminant hepatitis, acidosis (metabolic/respiratory), acute renal failure on chronic renal failure, pancreatitis, severe coagulopathy, encephalopathy, non-ST-elevation myocardial infarction (NSTEMI) with increased troponins, and bilateral pneumonia. Given the patient's prognosis, the family requested comfort measures only. An hour later, the patient was pronounced dead. No autopsy was performed.

Studies during Hospitalization: On the first day of presentation, an ultrasound of the right upper quadrant showed a slight increased echogenicity to his liver. The gallbladder was contracted. There was no evidence of stone or sludge. The pancreas was unremarkable. The biliary ducts were not dilated. A CT scan of the abdomen and pelvis without contrast showed severe fatty infiltration of the liver with no pancreatic involvement or biliary dilatation. No free air was seen but consolidation of the right lung base was noted. The patient was diagnosed with fulminant liver failure of uncertain etiology.

- Day 1: Chest X-Ray: patchy bilateral pleural-based plaque seen in both lungs that look to be unchanged compared to the prior study. The lungs are otherwise clear. There is no evidence of pneumothorax, consolidative infiltrate, or otherwise negative. No change in appearance of the chest when compared to a previous study done approximately one month prior.
- Day 2: Ultrasound of the right upper quadrant showed the liver slightly increased in echogenicity, contracted gallbladder, no evidence of stones or sludge. The common bile duct was normal measuring 0.35 cm. The pancreas appears to be unremarkable. The right kidney was normal measuring 10 cm.
- CT of abdomen and pelvis without contrast showed significant patchy areas of ground-glass opacification and airspace consolidation involving the bilateral lung bases, nonspecific. Pneumonia should be considered. Multiple pleural plaques and calcifications, consistent with prior asbestos exposure. Severe diffuse fatty infiltration of the liver. Unremarkable non contrast appearance of the pancreas. No peripancreatic fluid collections. Decompressed gallbladder. Tiny nonobstructing calyceal stone versus vascular calcification within the left kidney. No ureteral stones. No hydroureteronephrosis. Very mild distended distal esophagus containing fluid.

Social History: The patient drank 2 to 3 beers a day; previously he drank more heavily. He was an ex-smoker for 45 years. Occupation was not specified and he had no history of illicit drug use. His brother died (age not specified) from liver failure secondary to

alcohol abuse. His mother was a smoker and died from lung cancer. His father died from an aneurysm of uncertain location.

Past Medical History:
PMH: hypercholesterolemia treated with Welchol (colesevelam) 625 mg 6 times per day, Tricor (fenofibrate) 145 mg daily, and Crestor (rosuvastatin) 40 mg daily; coronary atherosclerosis since March 2005, cardiac stent placement in March 2005, cardiac catheterizations in May 2004, June 2005, and July 2007 with stent placement to right coronary artery; carotid artery stenosis since May 2009; palpitations since 2001; mitral valve disorder since March 2005; grade 2/6 murmur since August 2008; hypertension since December 2004, treated with Toprol XL (metoprolol) 100 mg daily and Lasix (furosemide) 40 mg daily from April 2008 to June 2009; chronic obstructive pulmonary disease since April 2005, treated with Albuterol (salbutamol) inhalation 2 puffs as needed; reflux treated with Protonix (pantoprazole) 40 mg daily and Kapidex (dexlansoprazole) 125 mg daily ; gout since 08 September 2005, treated with allopurinol 300 mg daily po since February 2009, colchicine 0.6 mg daily po from September 2005 to 03 March 2010, and Percocet (oxycodone) 1 tab as needed po since September 2007; osteoarthritis since 2004, treated with piroxicam 20 mg daily po since October 2005; fatigue since May 2009; dizziness and headaches since April 2005; pleurisy in August 2009; hypernatremia from September 2005 to April 2009; elevated glucose from August 2006 to April 2009; history of weight loss in May 2009; wrist sprain in February 2009; Surgery: hernia repair in March 2005, right shoulder surgery in March 2005, right knee replacement in April 2009, spontaneous ecchymosis in November 2005, left eye cataract surgery in December 2008.

During participation in the study, the patient experienced worsening of gout in left foot and left hand which was treated with Feldene (piroxicam) 10 mg three times daily.

At study screening (Sept 2009), the patient's laboratory values included ALT 30 U/L (normal range 6-41 U/L) and AST 23 U/L (normal range 9-34 U/L). Hepatitis C antibody and hepatitis B surface antigen were both non-reactive. His hs-C-Reactive protein (hsCRP) was 0.7 mg/L (normal range 0-3 mg/L). His urine protein was trace. The patient's ALT and AST values increased during the first 3 months of treatment and reached maximum values in December 2009 with ALT 154 U/L (3.8 x upper limit of normal [ULN]) and AST 164 U/L (4.8 x ULN).

In March 2010, the patient was seen by a cardiologist regarding palpitations. The patient noted shortness of breath especially when his heart was racing and also some dizziness. His appetite had been poor over the previous couple of months. ECG showed sinus bradycardia without signs of acute injury or infarction. Due to worsening hypertension, lisinopril 5 mg qd po was added to his medication regimen. Stress echocardiogram was positive for symptoms but nondiagnostic. Cardiac catheterization revealed a left dominant system, the left anterior descending coronary artery contained minor disease proximally with a 75% stenosis in its most distal segment. The diagonal

branches were minimally involved. The left circumflex contained a 75% stenosis proximally. The right coronary artery contained minor disease only. A previously deployed stent remained widely patent. A 2.5 x 8 Promus stent was placed to the LAD and a 2.5 x 12 Promus stent was placed to a left circumflex lesion. The patient was discharged home in stable condition with the following discharge medications: Plavix 75 mg daily, nitroglycerin as needed, Aspirin 325 mg daily, Metoprolol 200 mg daily, Lisinopril 5 mg daily, Crestor 40 mg daily, Trilipix 135 mg daily, Lasix 40 mg daily, Allopurinol 3 mg daily, Colchicine 0.6 mg bid, Pepcid daily, Proventil inhaler 2 puffs as needed, Iron 65 mg daily, Vitamin C 1000 mg daily po, Vitamin D 400 international units 3 tabs tid, Tylenol Arthritis as needed

In March 2010 (day 176, last values on treatment) patient's ALT was 35 U/L and AST was 38 U/L. Serum albumin, total bilirubin, prothrombin time, partial thromboplastin time, and INR were within normal ranges throughout the trial.

In April 2010, 27 days after the patient received his last dose of blinded study drug, the investigator noted that the patient had severe hepatic steatosis based on an MRI imaging report (protocol required procedure). Baseline fat fraction was 2.2% and increased to 18.9% by Week 28 (17% units increase since first MRI).

In July 2010, 99 days after the patient received his last dose of blinded study drug, his ALT was 51 U/L (0.9xULN) and AST was 80 U/L (1.7xULN).

Reviewer comment: The cause of hepatic failure in this case is unlikely to be drug-induced due to the rapid progression, very high AST/ALT levels, discontinuation of mipomersen 21 weeks prior to event and his presentation with chest pain and subsequent NSTEMI/cardiac arrest. The past medical history of alcohol use and the elevated acetaminophen level at admission also confound the case. However, given that the hepatic transaminase levels and hepatic steatosis increased over the year in which the patient was treated with mipomersen, a contributing effect of the drug cannot be ruled out.

Patient ID: 3002-1027 (Trial MIPO3500108)
Patient 3002-1027, was a 43 year-old male HeFH patient randomized to mipomersen. Twenty-eight days after completing 26 weeks of mipomersen treatment (200 mg SC once weekly), the patient was admitted to the hospital after experiencing chest pain. His ECG and cardiac enzymes were positive for myocardial damage. He was admitted to the intensive care unit and was prescribed enoxaparin sodium, atenolol, enalapril, and morphine 3 mg IV. He refused further treatment at the local hospital and requested to be transferred to another hospital. The patient collapsed and died. The patient's medical history is significant for ischemic heart disease with 4-vessel CABG, two myocardial infarctions, stable angina pectoris and hypertension. Other risk factors included HeFH, obesity (BMI 38), ex-smoker (13 pack years). The screening ECG, on

17 August 2009, showed previous inferior myocardial infarction and anterior and lateral ischemia.

Patient ID: 1525-6001 (ISIS 301012-CS6)
Patient 1525-6001, was a 55-year-old male HoFH patient, who 434 days after receiving first dose of mipomersen and 630 days after receiving first dose of mipomersen in clinical trial ISIS 301012-CS5, was admitted to the hospital for an elective aortic valve replacement procedure. He had a history of angina pectoris, ischemic heart disease, stenosis of the carotid artery, hypertension, and type 2 DM. Following the procedure, the patient went into ventricular tachycardia and CPR was initiated. The patient became asystolic and, despite attempts at resuscitation, died. The patient's death certificate lists the cause of death as "Recurrent myocardial infarction."

Patient ID: 1547-1420 (ISIS 301012-CS12)
Patient 1547-1420, a 53-year-old female randomized to placebo was admitted with chest pain 112 days after starting treatment. On admission her ECG showed acute anterolateral ST segment elevation and she was taken directly to the cardiac catheterization lab for urgent coronary angiography and percutaneous transluminal coronary angioplasty (PTCA). The procedure revealed acute left main and left anterior descending coronary artery obstruction. A PTCA was performed but the patient developed ventricular ectopy and cardiogenic shock. She arrested and despite aggressive intervention including insertion of an intra-aortic balloon pump remained hypotensive, developed ventricular fibrillation with intermittent pulseless electrical activity and could not be resuscitated. No autopsy was performed.

9.4.2 Narratives for Individuals with Major Adverse Cardiac Events (MACE) Reported as SAEs - Pooled Phase 3

Trial No.	Patient ID	Treatment	MedDRA Preferred Term
301012-CS5	1523-8309*	Mipomersen 200 mg	Acute coronary syndrome
301012-CS7	1589-7479*	Mipomersen 200 mg	Acute myocardial infarction
301012-CS12	1681-1358	Mipomersen 200 mg	Angina unstable
301012-CS12	1681-2132	Mipomersen 200 mg	Acute myocardial infarction
MIPO3500108	3000-1046	Mipomersen 200 mg	Angina unstable
MIPO3500108	3002-1027*	Mipomersen 200 mg	Acute myocardial infarction
MIPO3500108	3002-1027*	Mipomersen 200 mg	Acute myocardial infarction
MIPO3500108	5002-1056*	Mipomersen 200 mg	Cerebrovascular accident
MIPO3500108	6000-1032	Mipomersen 200 mg	Cardiac failure
301012-CS12	1535-2369	Placebo	Acute coronary syndrome
301012-CS12	1547-1420	Placebo	Acute myocardial infarction
301012-CS12	1547-1420	Placebo	Cardiogenic shock
301012-CS12	1664-2055	Placebo	Acute myocardial infarction

*Narratives are provided for the Patient ID numbers in this table below.

301012-CS5: 1523-8309; Mipomersen 200 mg; Acute coronary syndrome
Patient 1523-8309 is a 24-year-old female with HoFH who experienced acute coronary syndrome 44 days after receiving her first dose of blinded study treatment (mipomersen). The patient's medical history was significant for hypertension (since 2008), aortic stenosis (since 1996), bilateral carotid artery stenosis (since 1996), thickened Achilles tendon (since 1993), and tendinous xanthomas (since 1993). Concomitant medications include atorvastatin 80 mg daily, ezetimibe 10 mg daily, atenolol 120 mg daily, ethinylestradiol and levonorgestrel 150 +30 mcg daily, acetylsalicylic acid 100 mg daily, amlodipine 5 mg daily, and hydrochlorothiazide 100 mg daily, all taken orally. The patient received her first weekly subcutaneous injection of blinded study treatment in August 2008 and her last dose prior to the event was given in September 2008. In October 2008 (44 days after starting blinded study treatment), the patient was admitted to hospital after presenting with crushing precordial chest pain radiating to the left arm, accompanied by nausea, vomiting, and inferior/lateral T wave changes on electrocardiogram. Initial troponin and creatine kinase (MB fraction) levels were reported as normal. Treatment included nitrates (not specified) and enoxaparin (dosages not specified). Coronary angiography demonstrated the following lesions: a 90% stenosis of the left main coronary artery, 50% stenosis of the mid left anterior descending artery, 70% stenosis of the proximal first diagonal branch, 50% stenosis of the right coronary artery and a 70% stenosis of the right posterior descending branch. Creatine kinase and troponin levels prior to the angiography were within normal levels but post procedure the troponin level was slightly elevated (value not specified). The patient underwent coronary artery bypass surgery, the left internal mammary artery was grafted to the left anterior descending artery and a saphenous vein graft was applied to the first diagonal branch. Surgery was uneventful and the patient was discharged. At clinic follow-up 10 days later, the patient was doing well. Study drug was temporarily interrupted and the patient continued on her usual hypercholesterolemia medications (atorvastatin 80 mg and ezetimibe 10 mg daily). The patient completed ISIS 301012-CS5.

MIPO3500108: 5002-1056; Mipomersen 200 mg; Cerebrovascular accident
Patient 5002-1056, a 21 year-old female, was randomized in November 2009. She experienced cardiac chest pain 99 days, 182 days, and 189 days after receiving her first dose of mipomersen study treatment. She also had a stroke 213 days after receiving her first dose of mipomersen study treatment. The patient's medical history includes heterozygous familial hypercholesterolemia (diagnosed July 1999) treated with atorvastatin and ezetimibe, possible angina since May 2005, possible acute coronary insufficiency since July 2007, asthma since August 2002, depression from November 2006 to April 2010, and ovarian cyst removal in November 2008. Her screening LDL-C prior to entry into the study was 199 mg/dl. Concomitant medications include salbutamol and becotide. She received a total of 15 mipomersen injections prior to experiencing her first episode of cardiac chest pain. Ninety-nine days after starting mipomersen study

treatment, the patient experienced pain in the chest and left arm. She was assessed in hospital and was noted to have a 1-2 mm ST segment elevation in her anterior leads on electrocardiogram. Serum troponin levels were negative. She was treated with oral glyceryl trinitrate, reassured and discharged home on the same day after 2 hours in hospital.

183 days after receiving her first dose of mipomersen study treatment and after having received 26 doses of study drug, with the last dose received 7 days previously, the patient again experienced chest pain of moderate intensity. The patient was admitted to her local hospital for investigation for 2 days. The patient recovered and was discharged. Five days later, the patient experienced another episode of cardiac chest pain of moderate intensity. The patient was assessed and admitted to her local hospital but self-discharged the next day. An ECG and troponin assay performed during this admission were reported as negative. The chest pain continued after leaving the hospital and the patient was advised by the Investigator to return to the study site hospital for further assessment. During this admission the patient underwent an emergency coronary angiography which did not demonstrate any acute lesions. The results were essentially normal and unchanged from a previous study done elsewhere in September 2008. The clinical diagnosis was vasospastic angina pectoris with no myocardial infarction. Most of the admissions for chest pain were inconclusive; they did not show ECG changes and did not have a rise in troponin levels, however, she did have findings of adenosine induced changes on her most recent stress perfusion scan in March 2010 and ST changes noted during some admissions. Thus, the patient was treated as having a form of unstable spastic angina. The calcium channel blocker diltiazem was added to her medication regimen. She was also referred for lipid aphaeresis since she had completed dosing, per protocol, in this trial. She continued in the post-treatment safety follow up period for this trial.

In June 2010, after having received 26 doses of study drug, with her last dose prior to the event given 37 days previously, the patient was admitted to her local hospital after suffering a possible cerebrovascular accident with left-sided arm and leg weakness. No dysarthria or facial changes were observed. She was assessed by the stroke team, who following a defined Acute Stroke Pathway, assessed her in part by using the National Institutes of Health Stroke Scale (NIHSS), a quantitative measure of stroke-related neurological deficit that spans key aspects of the neurological examination: level of consciousness, language function, neglect, visual fields, eye movements, facial symmetry, motor strength, sensation, and coordination. On this survey, the patient scored a 6 (best score is 0, worst is 42, with a severe unilateral complete stroke with hemi paresis, hemianopia, hemineglect, and aphasia scoring a 31). At all times the patient was alert, had no alterations in consciousness and was able to follow commands and answer questions with no aphasia, no visual changes or facial findings and no dysarthria. MRI noted no abnormalities detected. The patient was not treated with thrombolytics. She was discharged in June 2010. A notation on the discharge summary lists the primary diagnosis as being non-stroke and suggests that the presenting

symptoms of limb weakness were likely due to stress symptoms. At time of discharge, the patient had residual left-sided arm and leg weakness and was in a wheelchair. She was undergoing rehabilitation and physiotherapy at her local hospital. During a consultation in September 2010 with the stroke physician, the physician's assessment of the previous coronary angiogram and cardiovascular system was normal. The chest pain was diagnosed as atypical and the physician suspected absence of arteriosclerotic disease and thought both her cardiac and cerebral symptoms were functional. In the opinion of the stroke physician, there was no evidence of any structural brain lesion in relation to her symptoms and assessed the event as "non-organic stroke", which he confirmed by a brain MRI scan performed in September 2010. The brain parenchyma appeared normal; there was no obvious evidence of a large right MCA territory infarct in particular. Major intracranial arteries were patent. In September 2010 ultrasonic arteriography of the carotid and vertebral arteries was performed. Duplex scanning demonstrated minor disease in both internal carotid arteries. Vertebral and subclavian artery signals were within the normal range. The report concluded the presence of minor bilateral ICA disease 16% to 49% (nearer 35%). A consultant neurologist reviewed the patient in October 2010. The neurologist stated that the follow-up MRI did not show any evidence of vascular disease and that the carotid dopplers showed only minimal atheromatous disease. Full recovery was expected and referral to a psychiatrist was recommended, which the patient agreed to. The Investigator agreed that there was no evidence of ischemic or hemorrhagic stroke however the patient was still wheelchair bound with left sided weakness. The Investigator indicated that, although neither an ischemic stroke nor a hemorrhagic stroke is an accurate description of the event, for lack of a better term he maintains the current event term of stroke. The event of stroke was assessed by the Investigator as severe and possibly related to the study drug. At the time of this report, the patient had not yet recovered.

MIPO3500108: 3002-1027; Mipomersen 200 mg; Acute myocardial infarction
Patient 3002-1027, a 43 year-old male, was randomized in September 2009. He experienced acute coronary syndrome (ACS) 158 days later and a non ST-elevation myocardial (NSTEMI) 207 days later, which resulted in a fatal outcome (208 days after receiving his first dose of mipomersen study treatment). The patient's medical history included heterozygous familial hypercholesterolemia since 1975, which was treated with atorvastatin and bezafibrate. His medical history was also significant for ischemic heart disease since 1995 with 4-vessel coronary artery bypass graft in 1995; myocardial infarction in 2000 and 2004; stable angina pectoris (occasionally with severe exertion) since 2006, treated with glyceryl trinitrate and Aspirin (acetylsalicylic acid); hypertension since 1990 treated with perindopril, arcus cornealis; bilateral thickening of Achilles tendons; deformed left arm due to motorcycle accident since 2005; and obesity (BMI, 38) since 2000. The patient was a previous smoker (13 years).

The August 2009 screening ECG showed a previous inferior myocardial infarction and anterior and lateral ischemia. Beginning in September 2009, the patient received once

weekly subcutaneous injections of 200 mg mipomersen, with the last dose prior to the event in February 2010. He received a total of 23 injections of mipomersen prior to experiencing acute coronary syndrome. In February 2010 (158 days after starting mipomersen; 4 days after last dose) the patient experienced severe chest pain, central and radiating to the left arm. The pain was associated with dyspnea, diaphoresis, and nausea, and was exacerbated by exercise. Three days later, he was admitted to the hospital with severe chest pain. ECG showed inferior myocardial infarction, age undetermined, ST abnormality, possible subendocardial ischemia (inferior), as well as Q waves in inferior leads. Laboratory results included troponin I 1.62 µg/L (reference range .00-0.04 µg/L), additional troponin I values were 0.89 and 0.70 (dates not indicated), creatine kinase (MB-fraction) 8.8 µg/L (normal range 0.6-6.3 µg/L), creatine kinase 63 U/L (normal range 38-174 U/L), CRP quantitative 26.0 mg/L (normal range .1-7.5), and D-dimer (quantitative) 0.52 mg/L (normal range 0.00-0.25). The patient as seen by a cardiologist and was diagnosed with ACS-NSTEMI. A 99mTc-MIBI cardiac scan showed scintigraphic evidence of a large transmural infarct in the inferior, inferoseptal, inferolateral with moderate peri-infarct ischemia. Overall ventricular systolic function was compromised with regional wall motion abnormalities. Poor prognostic indicators included end systolic volume greater than 70ml (163ml), left ventricular ejection fraction greater than 35% (34), with multi-vessel disease involvement. The patient was continued on routine medications plus treatment for acute coronary syndrome: Clexane (enoxaparin) 80 mg BID subcutaneously, carvedilol 12.5 mg QD orally, isosorbide mononitrate 20 mg BID orally, and Tryptanol (amitriptyline) for insomnia 25 mg orally. The patient was discharged home asymptomatic 8 days after admission. He was scheduled for an angiogram procedure for March 2010. The patient continued on study drug and completed Week 26 in March 2010. In April 2010 (205 days after starting mipomersen, 29 days after last dose), the patient experienced chest pain and reported that he had collapsed at home. His ECG showed probable inferior myocardial infarction, suspected right ventricular hypertrophy, intraventricular block, prolonged QT (QT/QTc - 436/491 ms). The laboratory results included: troponin T 0.35 ng/ml (normal range < 0.4 ng/ml), creatinine kinase (MB-fraction) 113 U/L (normal range less than 24 U/L), % creatinine kinase (MB-fraction) 7.9%, and creatinine kinase (CK) 1437 U/L (38-174 U/L). He was admitted to the intensive care unit. He then refused further treatment and requested to be transferred to another hospital using his own transport. The patient collapsed and died of cardiac arrest 3 days after initial presentation (208 days after starting mipomersen study treatment).

301012-CS7: 1589-7479; Mipomersen 200 mg; Acute myocardial infarction
Patient 1589-7479 is a 58 year-old male who was randomized in May 2009. He experienced an ST-elevation myocardial infarction 178 days after receiving his first dose of mipomersen study treatment. This patient, with heterozygous familial hypercholesterolemia, has a medical history significant for coronary artery disease since 1999, myocardial infarction in 1999, angioplasty in 1999, coronary bypass graft surgery in 2000, hypertension since 2006, and metabolic syndrome since 2006. Concomitant medications include Aspirin (salicylamide), Altace (ramipril), metformin, rosuvastatin,

ezetimibe, and fish oil. The last dose of study drug prior to the event was in November 2009. The patient completed study treatment and received a total of 26 injections of mipomersen study drug prior to experiencing the ST-elevation myocardial infarction. In November 2009 (178 days after starting study treatment; 1 day since last dose), the patient experienced chest pain. In the local emergency department, cardiac markers were checked and were negative times 2. The patient was started on a nitroglycerin drip and became pain free. He had elevation of ST segment on ECG which was noted as a change from an ECG done the prior month. The patient was transferred and underwent urgent heart catheterization and percutaneous coronary intervention and was transferred to the coronary care unit. He had several episodes of ventricular fibrillation which required shocking. He was put on inderal and lidocaine and was taken back to the cardiac catheterization lab for further intervention. An intra-aortic balloon pump was inserted and a temporary pacemaker was placed. He became hemodynamically stable, not requiring pressor support. On the next day the intra-aortic balloon pump was pulled out. The patient spontaneously reverted to sinus rhythm with a first degree atrio-ventricular block on his third hospital day. The patient underwent 2-D Doppler echocardiography which showed left ventricular ejection fraction 54% with mild concentric left ventricular hypertrophy and mild inferior wall hypokinesis. The patient's hospital course was complicated by heparin-induced antibody negative thrombocytopenia. After discontinuing heparin, his platelet counts improved. The patient was discharged in November 2009 with a final diagnosis of ST-elevation myocardial infarction. After completing ISIS 301012-CS7, the patient enrolled in the open-label extension trial ISIS 301012- CS6 (An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 301012 in Subjects with Familial Hypercholesterolemia).

9.4.3 Narratives of Individuals Who Had Liver Biopsies

Patient Number: 1497-7002 (Trial ISIS 301012-CS10)

AE Description: 1. Mild steatohepatitis component and mild hepatic pericellular fibrosis
2. Severe hepatic steatosis

MedDRA Preferred Term: 1. Hepatic fibrosis
2. Hepatic steatosis

64 year-old female with the following medical conditions: hypertension, hypercholesterolemia, type 2 diabetes mellitus, subclinical hypothyroidism, frequent diarrhea, elevated urine albumin, and previous removal of a Bartholin's gland. Concomitant medications consisted of Lipitor, metoprolol, amlopin, glimepiride, metformin, seasonal influenza vaccinations, xylometazolin and noscapine. 99 days after receiving first dose of study treatment, she was diagnosed with moderate hepatic steatosis (triglyceride content on Magnetic Resonance Spectroscopy (MRS) was 33.9%. On repeat imaging done 196 days after receiving first dose of study treatment, her condition worsened to severe hepatic steatosis. Transaminase levels at the time were

elevated with ALT 103 U/L and AST 43 U/L. Because of severe liver steatosis on MRS and elevated ALT levels the patient underwent a liver biopsy 235 days after starting study treatment. Results demonstrated severe hepatic steatosis with mild steatohepatitis component and mild pericellular fibrosis (grade 2, stage 1 Brunt classification). Study treatment was last administered prior to the reported events 239 days after starting study treatment and was permanently discontinued ~ 1 week later. The patient received a total of 35 injections of mipomersen. The events were not treated with medication.

Patient Number: 1497-7003 (Trial ISIS 301012-CS10)
AE Description: Moderate steatosis
MedDRA Preferred Term: Hepatic steatosis
56 year-old female who began treatment with subcutaneous injections of mipomersen at a dose of 200 mg weekly in February 2009 and the last dose was prior to the onset date of the event in December 2009. In December 2009 (Week 44), the patient had elevated liver triglyceride content, as measured by MRS (>23%) and elevated ALT (99 U/L) and was referred to a hepatologist. The patient underwent a liver biopsy in December 2009 (Day 322), which revealed moderate steatosis and minor lobular inflammation without significant fibrosis. NASH (non-alcoholic steatosis) grading according to Brunt was grade 1 (steatosis up to 66%, minimal ballooning, slight lobular inflammation and no portal inflammation) and stage 1. NAFLD (non-alcoholic fatty liver disease) grading according to NASH Clinical Research Network was 4/8 and fibrosis score was 0. The subject completed the study and received her last mipomersen dose in January 2010.

Patient Number: 1497-1022 (Trial ISIS 301012-CS19)
AE Description: Hepatic steatosis
MedDRA Preferred Term: Hepatic steatosis
58 year old white male who began treatment with subcutaneous injections of mipomersen at a dose of 200 mg weekly in November 2009. In addition to hypercholesterolemia, this subject had a prior history of myocardial infarction and mitral valve surgery. Statin intolerance was evidenced by muscle pain and tendinitis after treatment was attempted with atorvastatin, pravastatin or rosuvastatin. Current medications, continued throughout the clinical trial, included colesevalam for hypercholesterolemia, carbasalaat calcium (salicylic acid acetate, calcium salt, compound with urea) for secondary prevention of myocardial infarction and amiodarone for cardiac arrhythmia. During the study this subjects ALT increased from normal at screening (ALT 44 and AST 33 U/L) to ALT of 57 U/L after two weeks on treatment then progressively increasing to a maximum of 160 U/L in June 2010 (2 weeks after the end of the treatment period). The AST at this time was 76 U/L and alkaline phosphatase was 126 U/L. ALT levels fell steadily after treatment was stopped reaching 38 U/L in December 2010. Bilirubin (total, direct and indirect) remained within normal limits throughout. Magnetic resonance spectroscopy (MRS) estimate of liver fat was 23.7% in February 2010 (Week 10) and 47.3% in June 2010 (5 weeks after the last dose); a baseline MRS study was not performed. A liver biopsy, performed in April 2010 (after 92

days on mipomersen), confirmed severe steatosis >66% and mild steatohepatitis with no fibrosis (Brunt classification = 0). No clinical sequelae were attributed to the increase of liver fat or liver enzyme elevations. Follow up MRI in November 2010 showed decreased fat fraction of 27%.

Patient Number: 1497-1058 (Trial ISIS 301012-CS19)
AE Description: Hepatic steatosis
MedDRA Preferred Term: Hepatic steatosis
59-year-old white male who began treatment with subcutaneous injections of mipomersen at a dose of 200 mg weekly in November 2009. In addition to hypercholesterolemia, the subject's medical history included hypertension, myocardial infarction, smoking and abuse of alcohol, amphetamines and cocaine. Concomitant medications included bisoprolol, aspirin, clopidogrel, candesartan, amlodipine, valsartan, hydrocholothiazide, oxazepam and pantoprazole. The patient had for-cause MRS assessments of liver fat content. The patient's average liver fat fraction was 17.8% at Day 22, 34.7% at Day 120, 42% at Day 176, and 28.4% at Day 337. The subject had a pre-treatment ALT of 54 U/L. In April 2010, while patient was still on study medication, the ALT level was 96 U/L. Serum bilirubin levels (total, direct and indirect) remained within normal limits throughout. At Week 32, the patient had an ALT value of 124 U/L; the patient's corresponding apo B was 90.0 mg/dL. In April 2010 (after 148 days on mipomersen), a liver biopsy was performed because of severe liver steatosis (per MRS) and increased ALT levels. The liver biopsy showed extensive macrovacuolar steatosis (categorized as Brunt 3) with a minor steatohepatitic component, consistent with nonalcoholic steatosis (NASH) and previous history of alcohol abuse. The subject discontinued study medication in May 2010, but ALT increased to peak levels of 124 U/L and 126 U/L in June 2010 and in July 2010 respectively, gradually returning to a level of 57 U/L in December 2010. Results from MRS performed in May 2010, showed an increasing in triglyceride content in the right lobus: 44.6% (voxel 1) and 39.4% (voxel 2) compared to the previous MRS. In October 2010, the MRS, off mipomersen, showed a decreasing triglyceride content in the right lobus: 29.4% (voxel 1) and 27.4% (voxel 2) compared to the previous examinations. No clinical sequelae were attributed to the increase of liver fat or liver enzyme elevations.

Patient Number: 1587-6136 (Trial MIPO3500108)
AE Description: Fatty Liver
MedDRA Preferred Term: Hepatic steatosis
62 year old male with severe hypercholesterolemia subject who began treatment with subcutaneous injections of mipomersen at a dose of 200 mg weekly in September 2009. The subject completed 26 weeks of treatment in this study followed by 30 weeks of treatment in the OLE study (ISIS 301012-CS6) in February 2010 at a dose of 200 mg weekly. The date of the last dose prior to the onset of the event was in October 2010. This subject has a history of CAD, type 2 diabetes mellitus, benign prostatic hypertrophy, depression, hiatus hernia, hypertension and hyperthyroidism. Current medications, continued throughout the clinical trial included aspirin, atenolol,

rosuvastatin, fenofibrate,fish oil, glipizide, L-thyroxine, duloxetine, aripiprazole, mirtazapine tamsulosin, vitamin D and pantoprazole. Liver MRI, performed July 2009 before mipomersen treatment, showed some liver fat (7.1%) which was interpreted as normal. A follow-up MRI done after the subject completed 26 weeks of treatment in MIPO3500108 followed by 30 weeks in ISIS 301012-CS6 in August 2010 showed that the liver fat had increased to 43.2%. In November 2010 his ALT was 51 U/L, AST 45 U/L, alkaline phosphatase 53 U/L and total bilirubin 0.7 mg/dL. At this time, treatment was stopped pending investigation of the increases in enzyme and liver fat. The subject had a liver biopsy in December 2010 which showed marked macrovesicular and microvesicular steatosis, mild portal and lobular chronic inflammation, no definite hepatitis, no Mallory's hyaline, and no fibrosis.

9.4.4 Select Narratives for Those with ALT Levels ≥3 X ULN on at Least 2 Consecutive Occasions at Least 7 Days Apart (Pooled Phase 3)

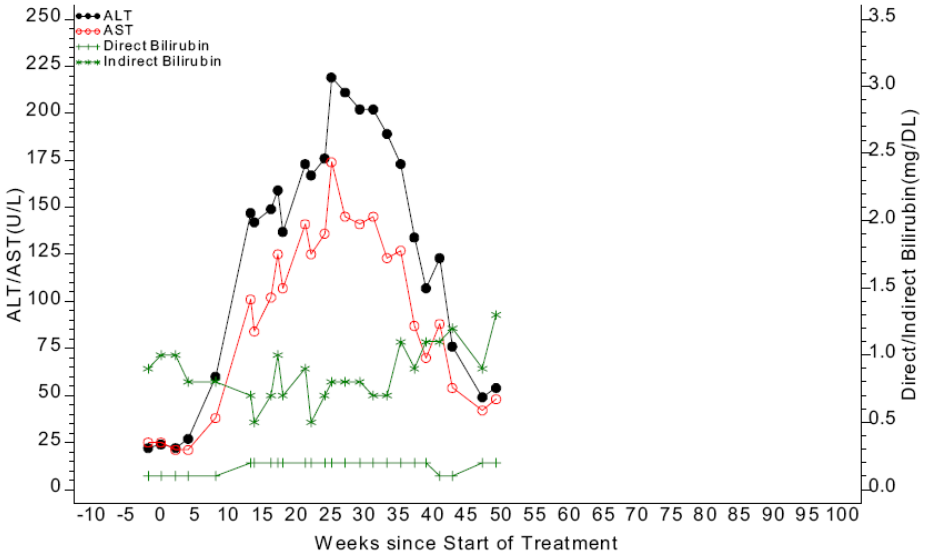
This table lists the individuals with ALT Levels ≥3 X ULN on at least 2 consecutive occasions at least 7 days apart. Narratives are included for these patients denoted with *.

Trial No.	Patient ID
301012-CS05	1536-8317*
MIPO3500108	1030-1006*
MIPO3500108	2002-1003*
MIPO3500108	3002-1027*
MIPO3500108	4000-1052*
MIPO3500108	5000-1049*
MIPO3500108	6000-1032*
301012-CS07	1505-7023
301012-CS07	1575-7387
301012-CS07	1608-7452
301012-CS07	1622-7323 †
301012-CS07	1664-7098
301012-CS12	1508-1336
301012-CS12	1520-2077
301012-CS12	1535-2133 †
301012-CS12	1553-1233 †
301012-CS12	1553-1297 †
301012-CS12	1556-2357
301012-CS12	1633-1370
301012-CS12	1646-1374 †
301012-CS12	1660-2310
301012-CS12	1660-2384 †

*Narratives are included for these patients
† Narratives for these patients appear in Section 9.4.5

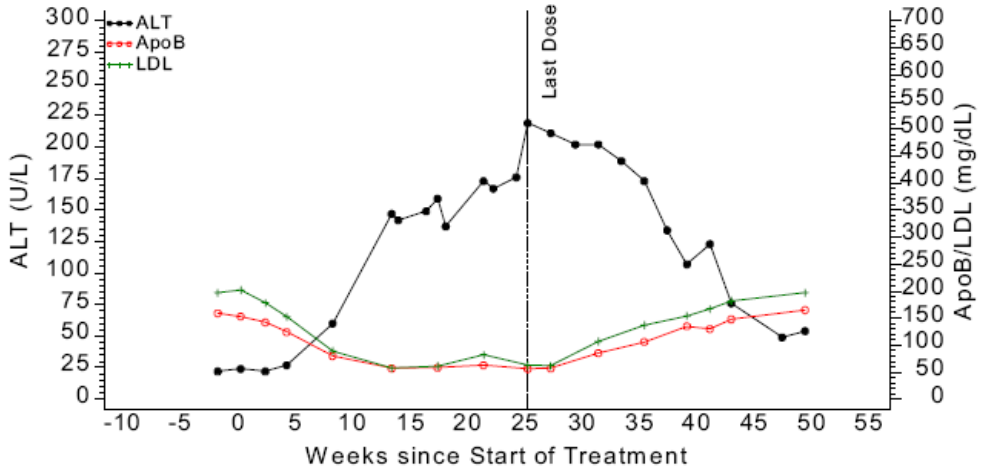
Patient 1536-8317 in the mipomersen group had an adverse event of ALT/AST increased (ALT/AST ≥5 x ULN) and an adverse event of mild hyperbilirubinemia. These events occurred on Day 176, coincident with the Week 26 visit at which the patient received the last dose of mipomersen. In this patient, ALT was normal at Screening and throughout week 9; at Week 13 ALT was ≥3 x ULN after which there was progressive increase with ≥5 x ULN occurring at the Week 26 visit. The ALT levels decreased gradually during follow-up, returning to 54 U/L by the last follow-up visit, 25 weeks after the last dose. These data are depicted in the following two figures. Direct bilirubin increased from a baseline value of 0.1 mg/dL to 0.2 mg/dL at Week 13, coinciding with the initial increase in ALT. The bilirubin level remained at 0.2 mg/dL throughout the treatment period and the first 6 weeks of follow-up after which it returned to the baseline value of 0.1 mg/dL. LDL and apo B levels decreased by up to 71% and 64%, respectively, reaching a minimum LDL-C of approximately 55 mg/dL by Week 13 of treatment, remaining at this level through the end of treatment (baseline levels were approximately 200 mg/dL).

Figure 18. Summary of ALT, AST, Direct Bilirubin, and Indirect Bilirubin Over Time for Patient 1536-8317



ALT = alanine aminotransferase; AST = aspartate aminotransferase; apo B = apolipoprotein B.
Source: NDA 203568: Data Listings 16.2.6.1a and 16.2.8.1-4a, CSR CS5 Figure 12-4

Figure 19. Summary of ALT, Apo B, and LDL Levels Over Time for Patient 1536-8317



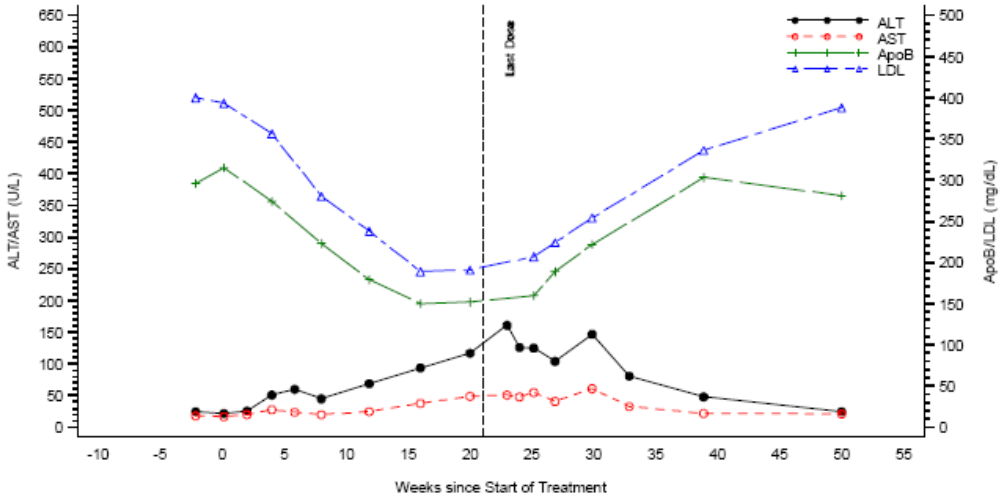
ALT = alanine aminotransferase; apo B = apolipoprotein B; LDL = low-density lipoprotein.
Source: NDA 203568: Data Listings 16.2.6.1a and 16.2.8.1-4a, CSR CS5 Figure 12-5

Patient 1030-1006 in the mipomersen group had ALT/AST elevations ≥3 × ULN and <5 × ULN. The patient's baseline ALT value was 29 U/L. The patient had ALT values of 141 U/L and 125 U/L at Week 17 and 146 U/L and 126 U/L at Week 21. Apo B values were 93.0 mg/dL at Week 17 and 102.0 mg/dL at Week 21, representing reductions

from the patient's baseline of approximately 50%. At baseline, the patient's AST value was 32 U/L. The patient had AST values of 133 U/L, 136 U/L, and 138 U/L at Week 17 and 151 U/L and 125 U/L at Week 21. Patient 1030-1006 met the liver chemistry safety monitoring rule, ALT/AST ≥3 × ULN, which was confirmed by retest; however, dosing was not stopped. The patient had 2 liver-related AEs (AST increased and ALT increased). The events were resolved by the end of the study. Paired liver imaging data are not available for this patient. The patient's baseline medications included acetylsalicyclic acid, lisinopril, lovastatin, Metamucil, and nicotinic acid. This patient also had proteinuria ≥2+. This patient 1030-1006 had a urine dipstick result of 30 mg/dL (proteinuria ≥1+) at Day 1 (baseline) and 100 mg/dL (proteinuria ≥2+) from Week 3 to Week 17 and at Week 21 (Day 141); all other urine protein dipstick results during the treatment period were 30 mg/dL (proteinuria ≥1+). The patient's baseline serum creatinine was 1.42 mg/dL; this male patient had an increase in serum creatinine ≥0.3 mg/dL above baseline at Week 3 (1.72 mg/dL). The patient had 2 renal-related AEs (2 events of Proteinuria). One event was resolved and 1 event was ongoing at the end of the study.

Patient 2002-1003 in the mipomersen group had ALT elevations ≥3 × ULN and <5 × ULN. The patient's baseline ALT value was 22 U/L. The patient had ALT values of 161 U/L, 126 U/L, and 125 U/L at Week 26 and 147 U/L at Week 32. Apo B values were 150.0 mg/dL at Week 17 and 189 mg/dL and 222 mg/dL at Week 32, representing reductions from the patient's baseline of approximately 50%. The patient had elevations in ALT throughout the study, returning towards normal range by Week 50. Patient 2002-1003 met the liver chemistry stopping rule ALT/AST ≥3 × ULN with the appearance/worsening of Fatigue, Nausea, Vomiting, Right upper quadrant pain or tenderness, Fever, Rash, or Eosinophilia. The stopping rule was presumed confirmed and dosing was stopped. The patient had a for-cause MRI assessment of liver fat content at Day 168 and Day 534. The patient's average fat fraction was 0.8% at baseline, 23.0% at Day 168, and 1.0% at Day 534. The patient had 2 liver-related AEs (ALT increased and AST increased). These events were resolved by the end of the study. The patient's baseline medications included acetylsalicylic acid, calcium with magnesium, cyanocobalamin, estradiol, paracetamol, and atorvastatin calcium. The following figure shows the ALT, AST, apo B, and LDL-C levels for Patient 2002-1003 over time.

Figure 20. Selected Laboratory Values for Patient 2002-1003



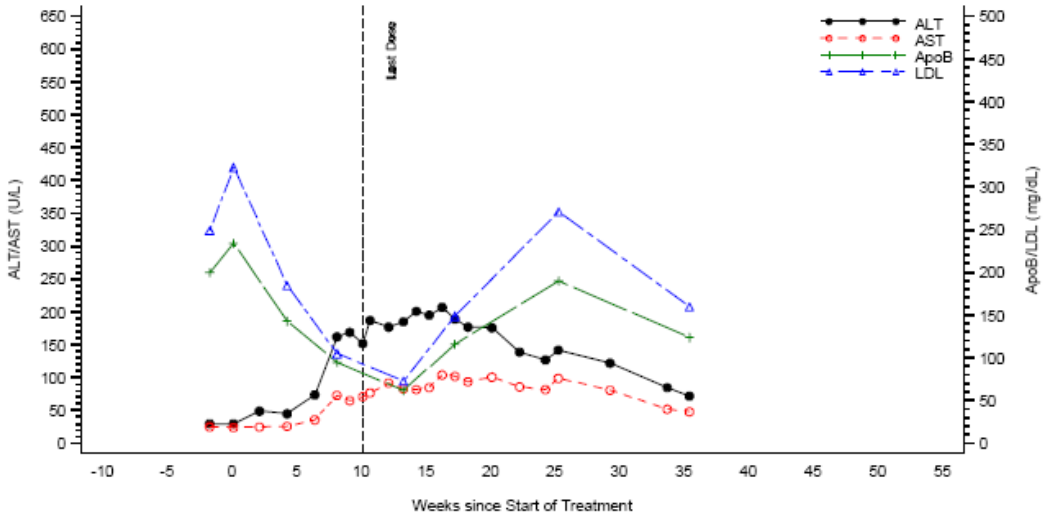
Source: NDA 203568: Figure 14.3.4.5-5, CSR MIPO108 Figure 12-5

Patient 3002-1027 in the mipomersen group had ALT/AST elevations ≥3 × ULN and <5 × ULN. The patient's baseline ALT value was 24 U/L. The patient had ALT elevations ≥3 × ULN at Weeks 17, 21, and 26 ranging from 129 U/L to 203 U/L. Apo B values ranged from 125.0 mg/dL to 173.0 mg/dL, representing reductions from the patient's baseline of up to approximately 30%. At baseline, the patient's AST value was 25 U/L. The patient had AST values of 122 U/L at Week 21 and 102 U/L at Week 26. Patient 3002-1027 met the liver chemistry safety monitoring rule, ALT/AST ≥3 × ULN, which was confirmed by a retest, and dosing was stopped. At baseline, this patient had a CT scan performed. This patient had increased fat fraction (estimated >30%) noted at baseline and a finding of hepatic steatosis at Day 155. The average liver to spleen ratio on CT was 0.74 at baseline and 0.06 at Day 155. The patient had 3 liver-related AEs (ALT increased, AST increased, and Hepatic steatosis). The events were ongoing at the time of the patient's death from a non ST-elevation myocardial infarction. The patient's baseline medications included acetylsalicylic acid, atorvastatin calcium, bezafibrate, glyceryl trinitrate, and perindopril.

Patient 4000-1052 in the mipomersen group had ALT elevations ≥3 × ULN and <5 × ULN. The patient's baseline ALT value was 30 U/L. The patient had ALT elevations ≥3 × ULN from Week 9 to Week 40, ranging from 127 U/L to 207 U/L. Apo B values ranged from 62.0 mg/dL to 190.0 mg/dL, representing reductions from the patient's baseline of approximately 55%. The patient had elevations in AST post-treatment. At baseline, the patient's AST value was 24 U/L, and at Week 32, the patient had AST values of 104 U/L and 102 U/L. Patient 4000-1052 met the liver chemistry safety monitoring rule, ALT/AST ≥3 × ULN, which was confirmed by a retest, and dosing was stopped. The patient had a for-cause MRI assessment of liver fat content at Day 93 and Day 332. The patient's average fat fraction was 7.2% at baseline, 46.7% at Day 93, and 12.7% at Day 332. The liver imaging results of the first post-baseline assessment

supported the finding of steatosis for this patient. The liver imaging results of the second post-baseline assessment showed a regression of steatosis for the patient. The patient had 3 liver-related AEs (ALT increased, AST increased, and Hepatic steatosis) which led to discontinuation of study drug. The patient's baseline medications included atorvastatin calcium, ezetimibe, isradipine, and levothyroxine sodium. The following figure shows the ALT, AST, apo B, and LDL-C levels for Patient 4000-1052 over time.

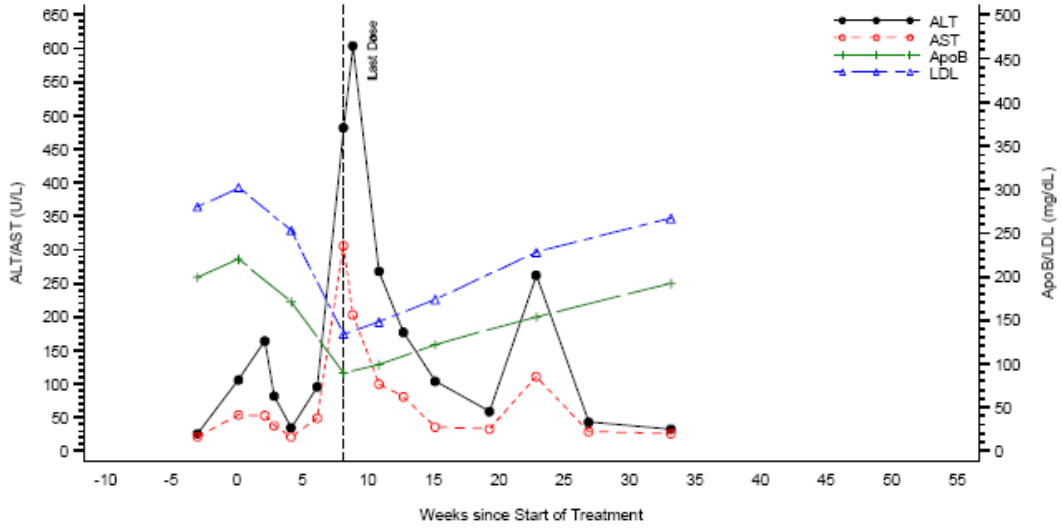
Figure 21. Select Laboratory Values for Patient 4000-1052



Source: NDA 203568 Figure 14.3.4.5-5, CSR MIPO108 Figure 12-9

Patient 5000-1049 in the mipomersen group had ALT/AST elevations ≥3 × ULN. The patient's baseline ALT value was 106 U/L. Elevations in ALT ≥3 × ULN were observed at Week 3 (164 U/L), Week 13 (268 U/L), and Week 32 (177 U/L). Elevations in ALT ≥10 × ULN were observed at Week 9 (482 U/L and 604 U/L). The patient's apo B values were 99.0 mg/dL at Week 13, 122.0 mg/dL at Week 32, and 89.0 mg/dL at Week 9, representing reductions from the patient's baseline of up to approximately 60%. At baseline, the patient's AST value was 54 U/L. The patient had AST elevations ≥5 × ULN at Week 9 (306 U/L and 203 U/L) and AST elevations ≥3 × ULN at Week 40 (111 U/L). Patient 5000-1049 met the liver chemistry stopping rule, ALT/AST ≥8 × ULN, which was confirmed by a retest, and dosing was stopped. The patient had a for-cause MRI assessment of liver fat content at Day 89 and Day 348. The patient's average fat fraction was -0.9% at baseline, 12.1% at Day 89, and 1.9% at Day 348. The liver imaging results showed an alteration in the appearance of the liver, which was a loss of signal on the out-of-phase imaging indicating an increase in generalized hepatic fatty infiltration since baseline. The patient had 2 liver-related AEs (Hepatic steatosis and Hepatic function abnormal). The patient's baseline medications included clopidogrel sulfate, fluvastatin, and cetirizine hydrochloride. The following figure shows the ALT, AST, apo B, and LDL-C levels for Patient 5000-1049 over time.

Figure 22. Select Laboratory Values for Patient 5000-1049



Source: NDA 203568 Figure 14.3.4.5-5, CSR MIPO108 Figure 12-10

Patient 6000-1032 in the mipomersen group had ALT elevations ≥3 × ULN. The patient's baseline ALT value was 44 U/L. The patient's ALT values were 124 U/L at Week 17, 141 U/L at Week 26, 169 U/L at Week 28, and 139 U/L at Week 32. Apo B values were 95.0 mg/dL at Week 17, 81.0 mg/dL at Week 26, 75.0 mg/dL at Week 28, and 119.0 mg/dL at Week 32, representing reductions from the patient's baseline of approximately 60%. Patient 6000-1032 met the liver chemistry safety monitoring rule, ALT/AST ≥3 × ULN; however, dosing was not stopped. The patient had a for-cause MRI assessment of liver fat content at Day 134 and Day 393. The patient's average fat fraction was 2.9% at baseline, 23.3% at Day 134, and 0.0% at Day 393. The patient's baseline medications included acetylsalicylic acid, clopidogrel sulfate, ezetimibe, fluvastatin, metoprolol succinate, molsidomine, pantoprazole, ramipril, and ranolazine.

9.4.5 Narratives for Those with ALT Levels ≥8 X ULN (Pooled Phase 3)

This table lists the individuals with ALT Levels ≥8 X ULN.

Trial No.	Patient ID	Peak ALT on-drug
MIPO3500108	5000-1049*	14.7
301012-CS07	1622-7323	11.9
301012-CS12	1535-2133	9.6; (12.9 off-drug)
301012-CS12	1553-1233	8.2
301012-CS12	1553-1297	10.1
301012-CS12	1646-1374	(8.1 and 10.7 off-drug)

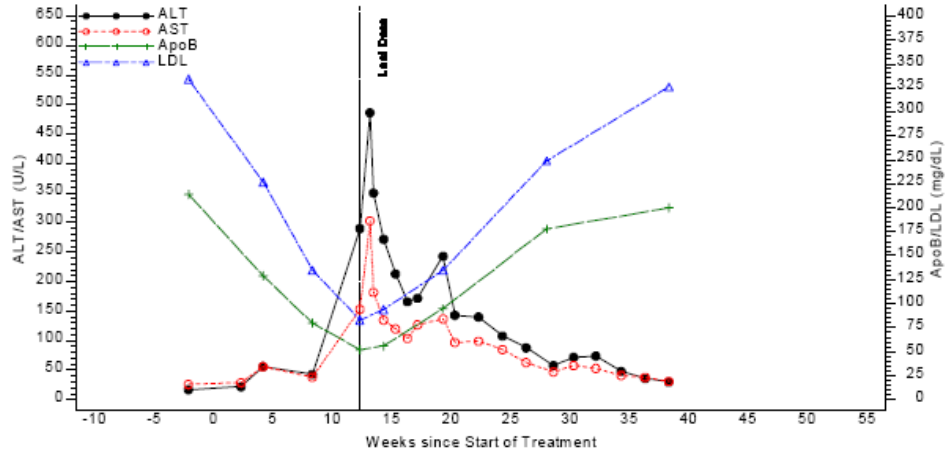
*Narrative appears in Section 9.4.4.

No mipomersen-treated patients in CS5 had ALT ≥8 x ULN, compared with 1 mipomersen-treated patient each in MIPO35 (2.6%) and CS7 (1.2%) and 4 (3.8%) mipomersen-treated patients in CS12.

Clinical Study Report ISIS 301012-CS7
(Patient 1622-7323) AST ≥5 × ULN and ALT ≥10 × ULN

Patient 1622-7323 had a pre-treatment ALT value of 17 U/L and a pre-treatment AST value of 26 U/L. During Week 13, the patient's ALT values were 290 U/L, 486 U/L (11.9xULN), and 350 U/L; the patient's AST values were 153 U/L, 303 U/L, and 182 U/L. Mipomersen was stopped at this point. At Week 17, the patient's ALT and AST were 272 U/L and 135 U/L, respectively. Corresponding apo B values were 52.0 mg/dL at Week 13 and 56.0 mg/dL at Week 17. The patient's ALT and AST values returned to pre-treatment levels by the last visit of the post-treatment follow-up period. Patient 1622-7323 met the liver chemistry-stopping rule and had an AE of mild Liver function test abnormal and thus discontinued study drug. An MRI was performed at Week 1 and on Day 98 (Week 14) after discontinuation of study drug. The patient's average liver fat fraction was -3.59% at Week 1 and 13.96% at the Day 98 MRI.

Figure 23. Selected Laboratory Values for Patient 1622-7323

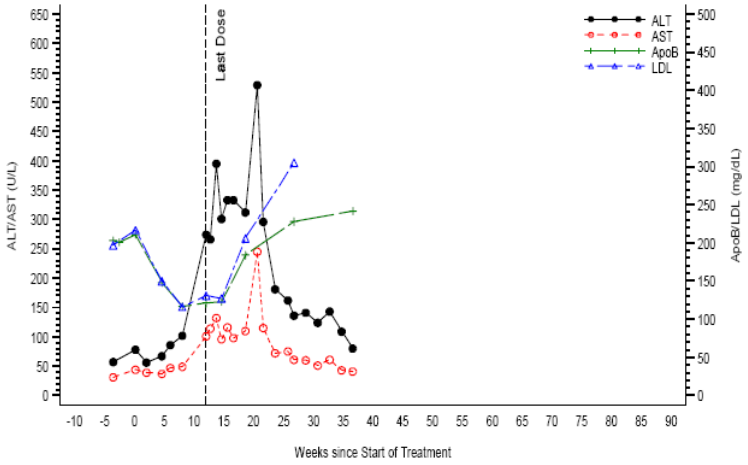


Source: CSR CS7 Figure 12-14, Figure 14.3.4.5-5

Clinical Study Report ISIS 301012-CS12
(Patient 1535-2133): ALT ≥5 × ULN and <10 × ULN and AST ≥3 × ULN and <5 × ULN during the treatment period and ALT ≥10 × ULN during the post-treatment follow-up period
The patient had a pre-treatment ALT of 78 U/L. At Week 13, the patient's ALT was 274 U/L. At a Week 13 follow-up visit, the patient's ALT was 395 U/L. Patient 1535-2133 had a pre-treatment AST of 44 U/L. At Week 13, the patient's AST was 114 U/L. At a Week 13 follow-up visit, the patient's AST was 132 U/L. The patient had 2 liver-related AEs of severe ALT increased and moderate AST increased. In addition to an AE of Myalgia,

the AEs of ALT and AST increased led to discontinuation of study drug. The last dose of study drug was at Week 13 (Day 84). Following the last dose of study drug, the patient's ALT values remained elevated from Week 17 to Week 50, reaching an elevation ≥10 × ULN at a Week 32 follow-up visit (529 U/L; highest value measured during the post-treatment follow-up period). The last values of ALT and AST measured at a Week 50 follow-up visit were 80 U/L and 41 U/L, respectively. Patient 1535-2133 had an MRI performed at Week 1, at the ET Visit (Day 104), and an unscheduled MRI during the post-treatment follow-up period on Day 252. The patient's average liver fat fraction was 17.6% at Week 1, 36.9% on Day 104, and 27.3% on Day 252.

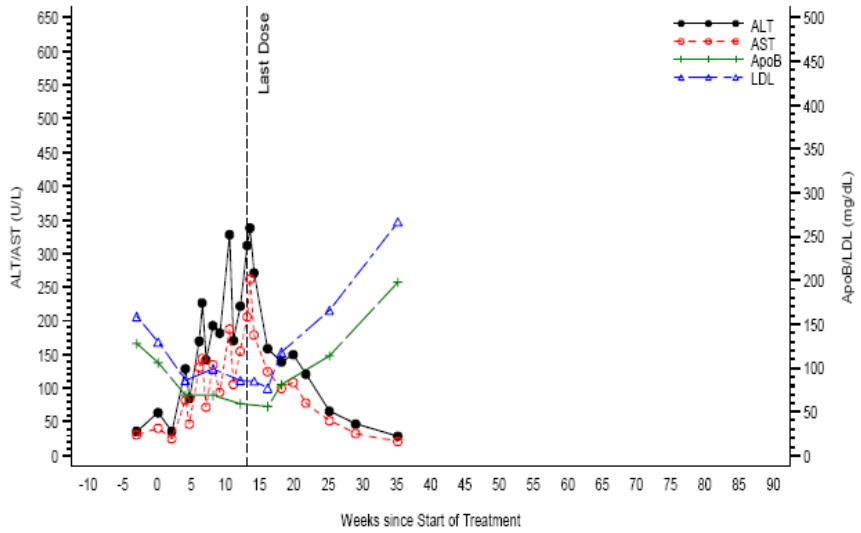
Figure 24. Selected Laboratory Values for Patient 1535-2133



Source: CSR CS12 Figures 12-12 and 14.3.4.5-5

(Patient 1553-1233) ALT and AST ≥5 × ULN and<10 × ULN
The patient had a pre-treatment ALT of 64 U/L. From Week 5 to Week 13, the patient's ALT ranged from 129 U/L to 338 U/L. The patient had a pre-treatment AST of 41 U/L. From Week 5 to Week 13, the patient's AST ranged from 106 U/L to 262 U/L. The patient had a liver-related AE (moderate Liver function test abnormal) and mipomersen was discontinued. The last dose of study drug was at Week 14 (Day 92). By Week 50, the patient's ALT and AST values had returned to 29 U/L and 21 U/L, respectively. Patient 1553-1233 only had an MRI performed at Week 1. The patient's average liver fat fraction was 33.9% at Week 1.

Figure 25. Selected Laboratory Values for Patient 1553-1233

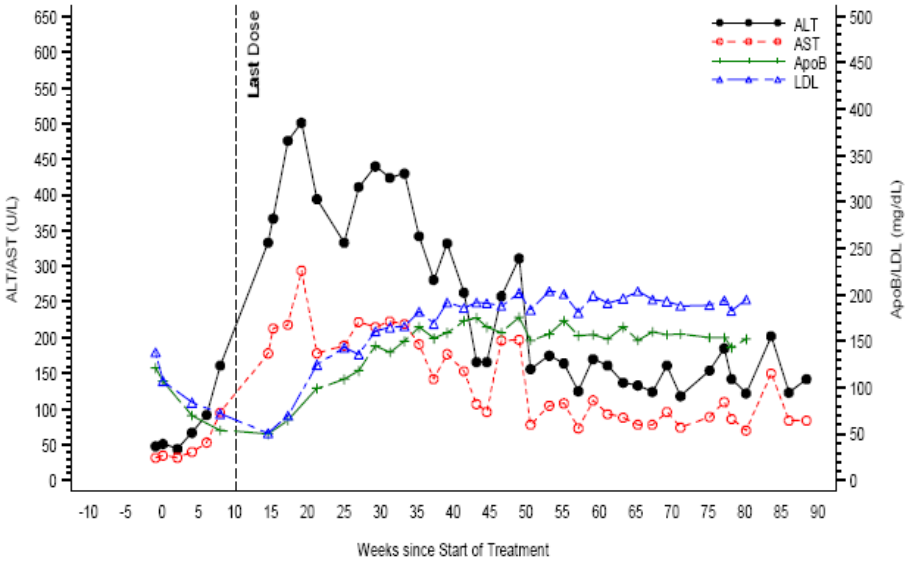


Source: CSR CS12: Figures 12-13 and 14.3.4.5-5

(Patient 1646-1374) ALT and AST ≥5 × ULN and <10 × ULN during the treatment period and ALT ≥10 × ULN during the post-treatment follow-up visit

The patient had a pre-treatment ALT of 51 U/L. At Week 9, the patient's ALT was 161 U/L and at Week 17, the patient's ALT was 333 U/L. Patient 1646-1374 had a pre-treatment AST of 35 U/L and at Week 17, an AST of 178 U/L. The patient had a severe liver-related AE (Hepatic enzyme increased), which led to discontinuation of study drug. The last dose of study drug was administered at Week 11 (Day 71). Following discontinuation of study drug, the patient's ALT and AST remained elevated. At a Week 40 follow-up visit (Day 189), Week 50, and Week 50 follow-up visits (Day 219 and Day 233), the patient's ALT elevation was ≥10 × ULN (411 U/L, 440 U/L, 424 U/L, and 430 U/L, respectively). At the last visit at Week 50, ALT was 118 U/L and AST was 74 U/L. Patient 1646-1374 had an MRI performed at Week 1, at the ET Visit (Day 106), and at an unscheduled visit on Day 277. The patient's average liver fat fraction was 5.0% at Week 1, 29.3% at Day 106, and 2.7% at Day 277.

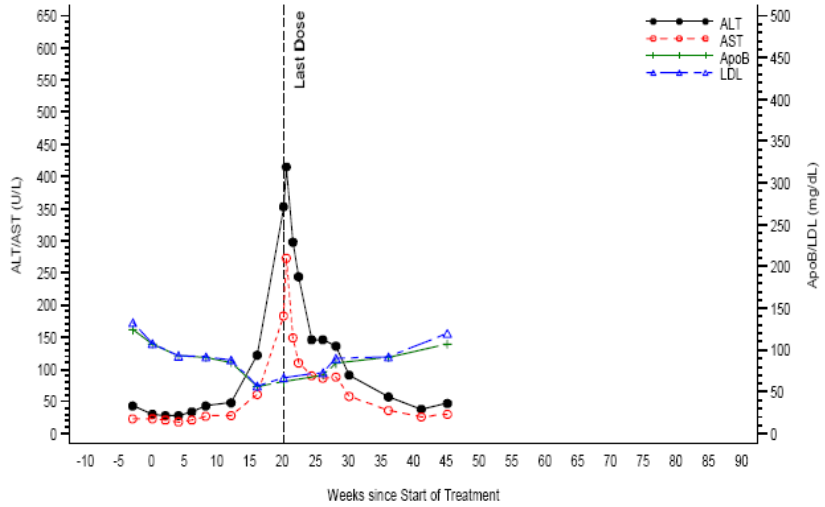
Figure 26. Selected Laboratory Values for Patient 1646-1374



Source: CSR CS12: Figures 12-15 and 14.3.4.5-5

(Patient 1553-1297) ALT ≥10 × ULN and AST ≥5 × ULN and <10 × ULN
The patient had a pre-treatment ALT of 30 U/L. At Week 21, the patient's ALT was 353 U/L. At a Week 21 follow-up visit, the patient's ALT was 415 U/L (10.1xULN). Patient 1553-1297 had a pre-treatment AST of 23 U/L. The highest value of AST measured at Week 21 was 273 U/L. The patient had 2 liver-related AEs (mild Hepatic steatosis and moderate Liver function test abnormal). Study drug was withdrawn and the last dose was administered at Week 21 (Day 141). By Week 50, the patient's ALT and AST values had returned to 38 U/L and 26 U/L, respectively. Patient 1553-1297 had an MRI performed at Week 1 and at the ET Visit (Day 152, Week 22). The patient's average liver fat fraction was 7.8% at Week 1 and 31.1% at Day 152.

Figure 27. Selected Laboratory Values for Patient 1553-1297



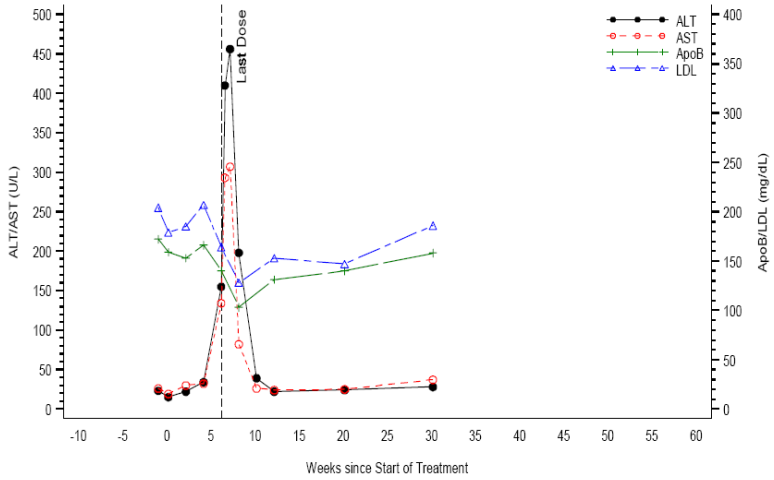
Source: CSR CS12 Figure 14.3.4.5-5

9.4.6 Narratives for the Individuals with an ALT ≥10 × ULN and ALTs ≥5 × ULN and <10 × ULN in Trial ISIS 301012-CS19

The narrative for Patient 1497-1073, who had an ALT ≥10 × ULN, is below:

- Patient 1497-1073, a 63-year-old White female, began mipomersen in December 2009. She had a baseline ALT level of 15 U/L (normal range [NR] 6-41 U/L), an AST level of 19 U/L (NR 9-34 U/L), an alkaline phosphatase level of 61 U/L (NR 37-116 U/L), and a total bilirubin of 0.49 mg/dL (NR 0.10-1.0 mg/dL). On Study Day 43, she had an ALT of 155 U/L (3.8xULN), an AST of 134 U/L (3.9xULN), an alkaline phosphatase of 82 U/L, and a total bilirubin of 0.42 mg/dL. On Study Day 50, she has an ALT of 456 U/L (11.1xULN), AST of 307 U/L (9.0xULN), alkaline phosphatase of 194 U/L, and a total bilirubin of 0.51 mg/dL. On Study Day 50, mipomersen was permanently discontinued due to the events and no further doses were given. On Study Day 71, the ALT decreased to 39 U/L, AST of 26 U/L, alkaline phosphatase of 112 U/L, and a total bilirubin of 0.49 mg/dL. The patient's medical history includes HeFH, MI, hypertension percutaneous transluminal coronary angioplasties, percutaneous transluminal coronary angioplasties with stents, stomach complaints, muscle pain after statin intake, common cold, Cesarean sections, adnexa of the uterus extirpation, excision benign tumor mammae right, and laparoscopic cholecystectomy. Concomitant medications included bisoprolol, nifedipine, carbasalate calcium, omeprazole, quinapril, and ezetimibe.

Figure 28. Selected Laboratory Values for Patient 1497-1073

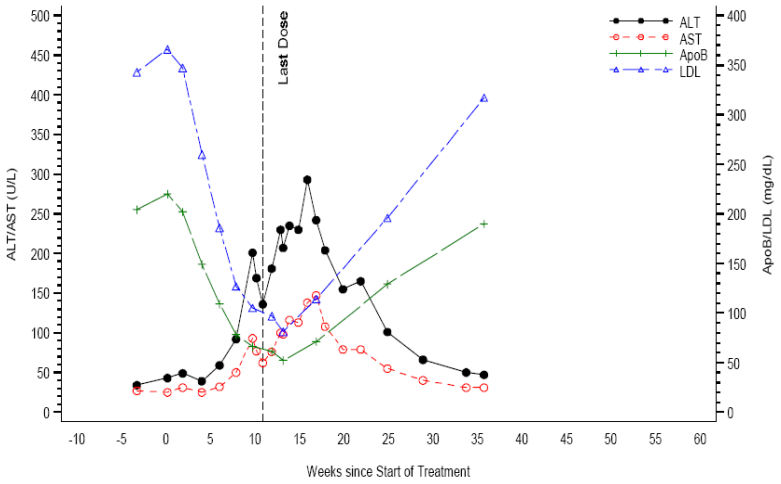


Source : NDA 203568; CSR CS19: Figure 12-7

Patient 1497-1071

- Patient 1497-1071 had a pre-treatment ALT value of 43 U/L. At Weeks 11, 13, 32, and 40, the patient had ALT increases ≥3 × ULN and <5 × ULN ranging from 136 U/L to 204 U/L. At Weeks 13 (Days 90 and 92) and 32 (Days 97, 104, 111, and 118), the patient had ALT increases ≥5 × ULN and <10 × ULN ranging from 207 U/L to 293 U/L. After Week 40, the patient had elevations in ALT, all <3 × ULN. The patient's corresponding apo B levels ranged from 52 mg/dL to 129 mg/dL. The patient met the liver chemistry stopping rule on Day 90; however, that patient had already been discontinued from the study due to the on-treatment AEs of Bone disorder and Myalgia. The patient had for-cause MRS assessments of liver fat content at Days 68, 95, and 250. The patient's average fat fraction was 25.6% at Day 68, 37.0% at Day 95, and 18.3% at Day 250. The patient had liver-related AEs of ALT increased, AST increased, and Hepatic steatosis. The AEs of ALT increased and AST increased resolved by the end of the study and the AE of Hepatic steatosis was ongoing.

Figure 29. Selected Laboratory Values for Patient 1497-1071

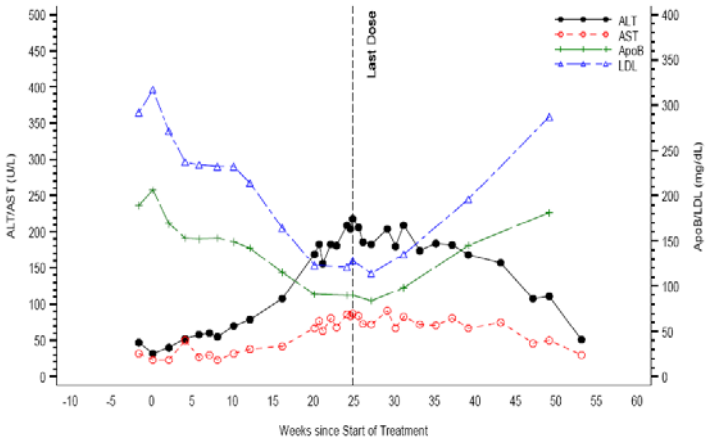


Source : NDA 203568; CSR CS19: Figure 12-6

Patient 1497-1047

- Patient 1497-1047 had a pre-treatment ALT value of 32 U/L. At Weeks 21, 25, 28, 32, and 40, the patient had ALT increases ≥3 × ULN and <5 × ULN ranging from 156 U/L to 204 U/L. At Weeks 25 (Days 169, 174, and 179) and 32 (Day 218), the patient had ALT increases ≥5 × ULN and <10 × ULN ranging from 206 U/L to 218 U/L. After Week 40, the patient had elevations in ALT, all <3 × ULN. The patient's corresponding apo B levels ranged from 84 mg/dL to 98 mg/dL. The patient had for-cause MRS assessments of liver fat content. The patient's average fat fraction was 22.6% at Day 141, 33.0% at Day 190, and 21.9% at Day 344.

Figure 30. Selected Laboratory Values for Patient 1497-1047



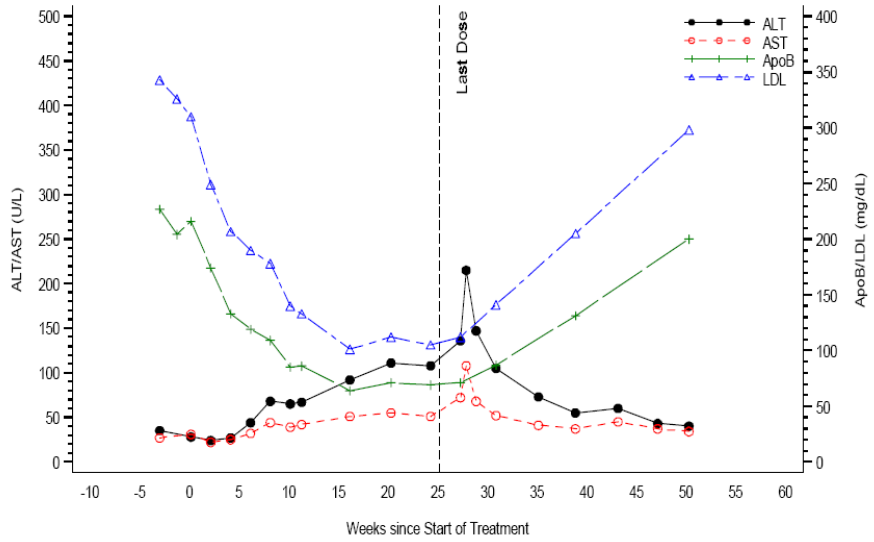
Source : NDA 203568; CSR CS19: Figure 12-3

Patient 1497-1088

- Patient 1497-1088 had a pre-treatment ALT value of 28 U/L. The patient's ALT values were 136 U/L at Week 28, 215 U/L at Week 32, and 147 U/L at Week 32. The patient's

ALT value returned to within normal range by Week 50. The patient's corresponding apo B values were 71 mg/dL at Week 28 and 87 mg/dL at Week 32. The patient had for-cause MRS assessments of liver fat content. The patient's average fat fraction was 16.7% at Day 142, 22.2% at Day 191, and 7.2% at Day 352.

Figure 31. Selected Laboratory Values for Patient 1497-1088



Source : NDA 203568; CSR CS19: Figure 12-8

9.4.7 Other Patient Narratives

Glomerulonephritis Membranous

Patient 1506-6130 is a 48-year-old male patient who was enrolled in ISIS 301012-CS6 (An open-label extension study to assess the long term safety and efficacy of ISIS-301012 in subjects with Familial Hypercholesterolemia). Prior to this study the patient was enrolled, with Patient ID 1506-7456, in clinical study ISIS 301012-CS7 (A randomized, double-blind, placebo controlled study to assess safety and efficacy of ISIS-301012 as add on therapy in Heterozygous Familial Hypercholesterolemia subjects with Coronary Artery Disease) and received 26 mipomersen injections from June 2009 to November 2009. The patient initiated mipomersen under trial ISIS 301012-CS6 in December 2009.

The patient's medical history is significant for heterozygous familial hypercholesterolemia, myocardial infarction, coronary artery disease, extrasystole, chest pain, hematuria with intermittent proteinuria since 2009, pancreatitis (age 12), right orchiectomy (childhood), hypogonadism, prostate hypertrophy, andropause, left hand Dupuytren's disease, and Raynaud's phenomenon. During the CS7 and CS6 trials, the patient experienced pruritus and a recall injection site reaction of erythema in the left upper abdominal quadrant following mipomersen administration. There is no

history of renal disease in the patient's family. The patient has no history of illicit drug use. Concomitant medications include acetylsalicylic acid, Cipralex (escitalopram oxalate), and Plavix (clopidogrel sulfate), Crestor (rosuvastatin), Ezetrol (zetimibe), Xatral (alfuzosin hydrochloride), nitroglycerin, Androgel (testosterone), oxazepam, Rivotril (clonazepam), Pantoloc (pantoprazole sodium), Avelox (moxifloxacin hydrochloride), and Pulmicort (budesonide).

Table 54. Baseline Urinalysis Results for ISIS 301012-CS6 Patient 1506-6130

Parameter	Result in Gravimetric Units	Normal Range in Gravimetric Units
Albumin (Urine)	1.03 mg/dL	0.00-2.99
Albumin/Creatinine Ratio	2.89 mg/g	
Amorphous (Urine) Crystals*	Present (H)	Absent
Beta-2-Microglobulin (Urine)	0.23 mg/L (H)	0.00-0.20
Bilirubin (Urine)	Negative	Negative
Blood (Urine)	Negative	Negative
Creatinine (Urine)	356.8 mg/dL	
Erythrocytes (Urine)	None (per HPF)	0-2
Glucose (Urine)	Negative (mg/dL)	Negative
Ketone (Urine)	Negative (mg/dL)	Negative
Leukocytes (Urine) -dipstick	Negative	Negative
Leukocytes (Urine) - microscopy	None (per HPF)	0-5
Nitrite (Urine)	Negative	Negative
Protein (Urine)	Trace (mg/dL) (H)	Negative
Protein, Quantitative (Urine)	17 mg/dL	0-29
Protein/Creatinine Ratio	47.65 mg/g	
Specific Gravity (Urine)	1.033	1.002-1.035
Urine Appearance	Clear	Clear
Urine Color	Amber	Yellow, Amber
Urobilinogen	0.2 mg/dL	0.0-0.9

Parameter	Result in Gravimetric Units	Normal Range in Gravimetric Units
pH (Urine)	5.5	5.0-8.0

* For Amorphous (Urine) Crystals – Urine Microscopy* the baseline value is from the lab sample collected on May 22, 2009. No result was available on June 3, 2009.
Sample collection June 3, 2009 except as noted

In May 2011, the patient experienced chest pain with radiation to his throat and lip numbness. By the time he arrived at the hospital, his symptoms were gone. All laboratory tests and diagnostic procedures (including an exercise electrocardiogram [ECG; stress test]) were normal. The patient was not hospitalized, but stayed in the emergency department for greater than 24 hours. Specific tests stated by the investigator include troponin of <0.02 µg/L and creatine kinase (CK) of 44 U/L. The event of chest pain was considered resolved. There were no actions taken regarding study treatment.

In December 2010, the patient experienced gross hematuria and was referred to a urologist. He was seen in February 2011. Prior to the urology visit, the patient had a normal renal ultrasound and normal urine cytology. His cystoscopy was normal in June 2011. The urologist determined that the patient's hematuria was consistent with a glomerular process and referred him to a nephrologist.

His pre-visit nephrology workup included the following tests performed in April 2011: positive cytoplasmic anti-neutrophil cytoplasmic antibody (ANCA) at 1:640, negative perinuclear ANCA, negative atypical ANCA, anti-protein-3 was positive at 81 units (normal range <20), anti-MPO was positive at 1 unit (normal range <20), normal anti-DNA at 16 IU/cc, normal serum protein electrophoresis, glomerular basal anti-membrane of <5, negative serologies for hepatitis B and C, and negative for anti-nuclear factor. A subsequent C-ANCA test (date not specified) was positive with titers of 1:1280. On this subsequent testing the anti-MPO was negative, anti-proteinase-3 was positive at 43 units, anti-nuclear factor was positive at 1/40, hemoglobin was of 128, platelets of 163 x 10^9/L, C-reactive protein of 1 mg/L, creatinine of 93, urea of 6.8, and rheumatoid factor of 5 units.

A 24-hour urine collection on revealed the following: creatinine clearance of 117 cc/min, serum creatinine of 87 mcmol/L, and total proteinuria of 0.18 g/d. Additional labs include HbA1c of 0.063, urea of 9.6, creatinine of 90 mmol/L, total protein of 69, albumin of 45, HDL cholesterol of 1.26 mmol/L, LDL cholesterol of 2.09 mmol/L, and cholesterol/HDL cholesterol ratio of 2.88. His urinalysis revealed blood of 3+, protein of 1+, red blood cells of 0 to 3/field, granular cylinders of 0 to 1/field, microalbumin/creatinine ratio of 5.3, protein/creatinine ratio of 0.021 (normal range <0.015).

The patient was evaluated by the nephrologist in June 2011. In addition to his history of hematuria and proteinuria, the patient was noted to have been experiencing nocturia for

about two years with symptoms of decreasing urinary stream and urinary hesitation. His urine had been "frothy" for about a year and he had had lower bilateral lumbar pain that was increased by movement. A subsequent cytoplasmic ANCA test performed in July 2011 was positive with titers of 1:1280. Rheumatoid factor was negative. Imaging studies of his lungs and sinuses were normal. The nephrologist's initial impressions were that the patient's hematuria was of glomerular origin, probably attributable to glomerulitis combined with positive cytoplasmic ANCA (microscopic polyangitis that may be related to the end of a clinical syndrome whose paroxysm manifested two or three years ago when the patient had his heart attack). The nephrologist stated that the event could be medication-induced and listed Plavix (clopidogrel sulfate), acetylsalicylic acid, Cipralex (escitalopram oxalate), and mipomersen as possible medications. In July 2011, mipomersen was stopped (after 25 total months of treatment). Due to the microscopic hematuria, proteinuria, and positive ANCA results, a renal biopsy was arranged to assess or rule out possible glomerular disease. The nephrologist concluded "concerning the explanation for C-ANCA and anti-PR3, for the time being there is no index of vasculitis nor other systemic disease requiring a specific therapeutic approach for this problem. Concerning the membranous glomerulopathy, the prognosis is globally good. There is no indication for corticotherapy nor immunosuppressive therapy as a part of stage 1 membranous without clinical repercussions on the renal function or liver condition." Clinically, the patient is stable. The patient still feels some muscular pain when he exercises. He takes Crestor (rosuvastatin) 40 mg daily with Ezetrol (ezetimibe). The patient restarted Plavix and Aspirin one week after the renal biopsy as planned, and was to continue with his current medications and return after follow-up visits.

A renal biopsy was performed in August 2011. According to the pathologist, the diagnosis for the renal biopsy is "glomerulopathy with peripheral storage of IgG, C1q complex, kappa chain, and lambda chain with immunofluorescence for which a membranous glomerulonephritis was fostered. There was slight acute tubular damage focuses with fine microvacuolation of the cytoplasm of certain tubules, minimal tubular atrophy, slight interstitial fibrosis, and moderate atherosclerosis."

Electron microscopy confirmed small deposits of sub-epithelia immune complexes, compatible with a diagnosis of stage 1 membranous glomerulonephritis. In her comments, the pathologist noted, "The sub-epithelial deposits found are very small and relatively small in number but are compatible with an early stage membranous glomerulonephritis or even on the way to being resolved. There were also some rare and small mesangial deposits for which a secondary form should be excluded."

Detailed electron microscopy results are as follows: "examination showed a glomerulus. There are some dense deposits with sub-epithelial electrons, often barely visible. They are distributed sparsely, of small size, of weak density, and with contours that flow, without a secondary effect with a strong enlargement. They are at times edged with small projections of basal membranes without a marked thickening of the basal

membrane. In some places there is no clearly visible deposit, but irregularities of the external contours of the basal membranes were found, suspected sites of the old resorbed deposits. Also some rare and small mesangial densities were found. There was a slight increase of the mesangial matrix. The glomerular basal membranes were of a normal thickness (measurements: 316, 353, 421 nanometers). There was a slight erasure of the pedicles and presence of microvilous transformation of podocytes. There is no tubuloreticular inclusion in the endothelial cells. There was interstitial fibrosis. There is a certain ballooning of the cytoplasm of the proximal tubular cells making a protrusion in the light. Small dense granules and vacuole organelles in the distal tubular cytoplasm were found, with a nonspecific appearance."

Circulating immune complex (CIC) test results were received in October 2011 and showed that for the samples drawn in September 2011, the patient was negative for both solid phase C1 q CIC and Raji-equivalent CIC.

The patient's nephrologist interpreted these findings as being consistent with a stage 1 membranous glomerulonephritis.

On (b) (6), the patient had a third ANCA test and also was tested for circulating immune complexes (CIC). This ANCA test was performed at (b) (6) (b) (6) Hospital, whereas the previous 2 tests were performed at the patient's local lab. This third ANCA test was positive at 105 units, with ELISA confirming the presence of antibodies to proteinase 3. The CIC test was negative. According to the immunologist's interpretation, "the presence of antibodies to proteinase 3 found in this patient's serum is virtually diagnostic of Wegener's granulomatosis, microscopic polyarteritis nodosa, related forms of vasculitis or idiopathic necrotizing and crescentic glomerulonephritis."

The patient was tested retrospectively for CIC at 7 additional time points (June 2009 (baseline), November 2009, December 2009, July 2010, December 2010, April 2011, July 2011) and tested negative for CIC at all of these time points. In October 2011, the patient was tested for ANCA again at his local lab and was positive at 1:80.

In September 2011, the patient started on two new drugs, Elavil (amitriptyline hydrochloride) and cyclobenzaprine, for suspected fibromyalgia. Additional labs taken in October 2011 showed a creatinine level of 84 mcmol/L, a creatine kinase level of 68 U/L, and abnormal, high urinalysis values of trace ketone, 0.3 g/L protein, trace leukocyte esterase, 1 + bacteria, and occasional hyaline cast and squamous epithelial cells. All other urinalysis values were within normal limits.

In November 2011, the patient again saw his nephrologist, who felt he was stable without clinical signs or symptoms of Wegener's granulomatosis or other vasculitides. The patient was noted to be normotensive, without polyarthralgia, difficulty breathing, retrosternal pain, abdominal pain, or oedema of the lower limbs. According to the

nephrologist, the membranous glomerulonephritis stage 1 caused a minimal non-nephrotic proteinuria, for which the patient has been treated conservatively. The patient stopped mipommersen treatment in July 2011 and has not resumed.

This patient was tested for anti-mipomersen antibodies utilizing the second-generation assay. He tested positive at a single time point, Week 90 with a titer of 100 while participating in ISIS 301012-CS6. At all other times, including one later time point (Week 104), the patient tested negative. This patient was CIC negative at all time points in trials CS7 and CS6.

Reviewer comment: This event of glomerulonephritis may be medication-induced and one cannot exclude mipomersen as a causative or precipitating factor.

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/s/

EILEEN M CRAIG
11/26/2012

ERIC C COLMAN
11/26/2012

CLINICAL FILING CHECKLIST FOR NDA 203568

NDA/BLA Number: 203568	**Applicant: Genzyme**	**Stamp Date: 3/29/2012**
Drug Name: Kynamro (mipomersen sodium) Vials/Prefilled Syringes	**NDA/BLA Type:1 NME 505 (b)(1)**	**PDUFA Date: 29 January 2013**

Filing Meeting:	Monday, 14 May 2012
Filing Date:	28 May 2012
Mid-cycle Review Meeting:	Monday, 27 August 27 2012
Wrap-up Meeting	3 December 2012
Reviews signed-off in DARRTS:	3 December 2012
Action Goal Date:	29 January 2013
PDUFA Date:	29 January 2013

Labeling:

11/14/2012-Labeling Edits in E-Room

11/19/2012-Substantially Complete Labeling to DDMAC

11/19/2012-Substantially Complete Labeling to Patient Labeling Group

12/3/2012-Proposed labeling to sponsor (to be returned 12/7/2012)

12/10/2012-Labeling Discussion with Sponsor begins

The network location is: \\CDSESUB1\EVSPROD\NDA203568\0000

Indication: The proposed indication for mipomersen sodium, an apolipoprotein B synthesis inhibitor, is 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.

The proposed dose is 200 mg once weekly as a subcutaneous injection.

Primary Reviewers

Clinical:	Eileen Craig
Nonclinical (Pharm-tox):	Ron Wange
Clin Pharm:	Immo Zdrojewski
Biometrics:	Japo Choudhury
CMC/Micro:	Joe Leginus/Bob Mello
OSE: DMEPA (tradename)	Reasol Agustin
OSE: DRISK (Health Risk Comm)	Joyce Weaver
OSI:	Susan Leibenhaut
Project Manager:	Kati Johnson

CLINICAL FILING CHECKLIST FOR NDA 203568

Background:
Homozygous familial hypercholesterolemia (HoFH) is a rare genetic disorder with a prevalence of about 1 in 1,000,000 persons[1,2] in which both LDL-receptor alleles are defective. Untreated HoFH patients have very high concentrations of LDL-C, in the range of 650 to 1000 mg/dL[3], cutaneous and tendinous xanthomata, corneal arcus and premature coronary artery disease.

Lipid-lowering drugs such as statins, which act mainly by up-regulating hepatic LDL receptors, are not particularly effective in reducing LDL-C levels in these individuals because their LDL receptors are dysfunctional. For example, in a study of HoFH individuals (n=40, 8-63 years) with rosuvastatin 20 to 40 mg[4], the mean LDL-C reduction from baseline was 22%. About one-third of the patients benefited from increasing their dose from 20 mg to 40 mg with further LDL lowering of greater than 6%. In the 27 patients with at least a 15% reduction in LDL-C, the mean LDL-C reduction was 30% (median 28% reduction). Among 13 patients with an LDL-C reduction of <15%, 3 had no change or an increase in LDL-C. Reductions in LDL-C of 15% or greater were observed in 3 of 5 patients with known receptor negative status. In a study with atorvastatin (20 to 80 mg) without a concurrent control group[5], 29 patients (ages 6 to 37 years) achieved a mean LDL-C reduction of 18%. Twenty-five patients with a reduction in LDL-C had a mean response of 20% (range of 7% to 53%, median of 24%); the remaining 4 patients had 7% to 24% increases in LDL-C. Other therapies used to treat HoFH include LDL apheresis, portocaval shunting and liver transplantation. All of these therapies are limited by expense, availability, and the potential for significant morbidity.

Mipomersen is an antisense oligonucleotide (ASO) inhibitor targeted to human apolipoprotein B-100 (apoB-100), the principal apolipoprotein of low density lipoprotein (LDL-C) and its metabolic precursor, VLDL. Mipomersen is complementary to a 20-nucleotide segment of the coding region of the messenger RNA for apoB-100 and binds to the mRNA by Watson and Crick base-pairing. The hybridization (binding) of mipomersen to the cognate mRNA results in RNase H-mediated degradation of the cognate mRNA thus inhibiting translation of the apoB-100 protein. This leads to a reduction in synthesis and transport of apo-B containing lipoprotein and a reduction in circulating LDL-C. Mipomersen is a first-in-class compound for apoB-100 inhibition and LDL reduction. Unlike the statins, mipomersen is not dependent on LDL receptor upregulation for its beneficial effects.

---

[1] Beigel R, Beigel Y. Homozygous familial hypercholesterolemia: Long term clinical course and plasma exchange therapy for two individual patients and review of the literature. Journal of Clinical Apheresis. 2009;24(6):219-24.
[2] Vella A, Pineda AA, O'Brien T. Low-density lipoprotein apheresis for the treatment of refractory hyperlipidemia. Mayo Clinic Proceedings. 2001;76(10):1039-46.
[3] Goldstein, AL, Brown MS. Molecular Medicine. The cholesterol quartet. Science. 2001;292(5520):1310-2.
[4] NDA 21366 Crestor PI, 2/28/2012
[5] NDA 20702 Lipitor PI, 2/28/2012

CLINICAL FILING CHECKLIST FOR NDA 203568

Regulatory History:

Date	Event/Notes
01 Sep 2005	Pre-IND responses to firm's questions • Firm proposed single 12-week Phase 3 study with single dose (200 mg/wk SQ) for NDA with Fast Track designation • Firm was told that there was insufficient information to proceed to a pivotal Phase 3 study. No safety margin from animal data to support 200 mg human dose. A more thorough dose-exploration was needed to establish a minimally effective dose prior to initiating the pivotal study. More rigorous renal monitoring and an assessment of immunotoxicity was required. Firm was told to submit the IND and request an End-of-Phase 2 meeting 30 days following FDA receipt.
18 Nov 2005	IND 70969 submitted by ISIS Pharmaceuticals • Preclinical toxicity concerns included an increase in aPTT, renal effects (nephrotic syndrome, glomerulonephritis, declines in renal function), liver effects (increase in liver transaminases, hepatic steatosis), and proinflammatory changes. • Potential safety concerns from clinical studies included systemic symptoms (fever, chills, arthralgias, nausea, vomiting, and flu-like symptoms), inhibition of the intrinsic coagulation pathway (prolongations of aPTT), thrombocytopenia, renal effects, liver effects (increase in liver transaminases, hepatic steatosis), proinflammatory effects (lymphadenpoathy), and injection site reactions. Recommended additional tests for Study CS9 were spot or 24-hour urine collection for total protein, microalbumin, β2-microglobulin and creatinine to determine urinary protein and glomerular filtration rate. To obtain information on the effect on complement and coagulation pathways, measurement of aPTT/PT and complement (factor Bb) was recommended.
12 Apr 2006	Fast-track designation request submitted
23 May 2006	Orphan Drug Designation (No. 06-2214) for treatment of HoFH was granted.
30 May 2006	Fast Track denied as the development program was not designed to address whether treatment with mipomersen in HoFH patients (or lower risk populations) reduces cardiovascular morbidity and mortality.
4 Jan 2007	The firm submitted a draft 6-month interim report of a one-year cynomolgus monkey toxicity study (Study ISIS301012-AS15).
8 Jun 2007	The final interim report (through Week 52) of the one year toxicity study was submitted. The new finding after one year of dosing was that animals treated with drug (3, 10 and 30 mg/kg/week) developed arterial (peri)vasculitis and intimal hyperplasia (N=5 total affected). The vasculitis was observed in the GI tract in 3 monkeys (3, 10 or 30 mg/kg) and in multiple organs in another 2 monkeys (30 mg/kg). Coronary artery vasculitis and intimal thickening was present in 1 out of 4 monkeys treated with 10 mg/kg and euthanized on Day 185 of the study. Additional new findings in the 30 mg/kg group included renal tubule epithelial cell degeneration, thrombocytopenia and decreases in complement protein C3.
11 Sep 2007	The firm requested an EOP2 meeting on May 4, 2007, which was granted. An internal meeting was held on September 5, 2007. It was determined that the clinical questions could not be addressed until some preclinical findings were resolved. The focus of the meeting was changed to a discussion of the preclinical

Date	Event/Notes
	findings in the chronic monkey study (Study ISIS 301012-AS15) and the implications for future clinical development.
29 Jan 2008	IND placed on partial clinical hold. It was the firm's position that the vasculitis in the monkeys was due to complement activation and this activation does not occur in humans at the proposed dose levels. Complement and inflammatory markers will be monitored in the proposed Phase 3 studies. However, the division was not convinced that the firm's explanations are valid and remains concerned because, among other things, monitoring for vasculitis in clinical trials is not feasible. Because of the preclinical safety concerns and the lack of a validated biomarker for vasculitis, it was determined that, at this time, studies should be limited to patients at high risk for cardiovascular disease. Risk-benefit profile only supports treatment of patients at high risk for cardiovascular events defined as 10-year risk for CVD > 20%, on maximum statin dose and not at LDL goal.
15 Feb 2008	FDA Regulatory Briefing: Preclinical toxicity concerns included an increase in aPTT, complement activation and proinflammatory changes/vasculitis, liver effects (increase in liver transaminases, hepatic steatosis) and renal effects (glomerulonephritis, declines in renal function). In clinical studies, the four most relevant safety signals observed to date were: (1) transient prolongations of aPTT following intravenous dosing; (2) constitutional symptoms such fever and chills following initial administrations; (3) dermatological responses such as erythema at subcutaneous injection sites; and (4) serum transaminase elevations. Panel discussion included the following issues: (1) whether the available preclinical data on the immunostimulatory effects (pro-inflammatory tissue changes, complement activation, vasculitis) of this compound are concerning; (2) would additional preclinical studies clarify the potential clinical significance of ISIS 301012's immunostimulatory effects; (3) can the immunostimulatory effects of ISIS 301012 and the potential for vasculitis be adequately monitored (e.g., measurement of proinflammatory biomarkers) in clinical studies; and (4) if the currently available preclinical data support the use of ISIS 301012 in: a) patients at high-risk for cardiovascular disease; and b) in patients at low-to-moderate risk for cardiovascular.
23 Jul 2008	Change of IND sponsorship from ISIS Pharmaceuticals to Genzyme Corporation
27 Feb 2009	FDA provided feedback on statistical analysis plan (SAP) for protocol ISIS 301012-CS5 entitled *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.*
14 Jul 2009	FDA responded to the applicant's questions on CMC issues.
31 Aug 2009	FDA provided comments on applicant's proposed QT/QTc study entitled "*A Randomized Double-Blind Crossover Trial to Define the ECG Effects of Mipomersen (ISIS 301012) using a Therapeutic and a Supra-Therapeutic Dose compared to Placebo and Maxifloxacin (a Positive Control) in Healthy Men and Women: A Thorough ECG Trial"* (MIP02800209).
25 Jan 2010	FDA provided comments on applicant's revised QT/QTc study
27 Jan 2010	FDA provided comments on applicant's proposed carcinogenicity study statistical analysis plan (SAP).
02 Feb 2010	FDA provided comments on applicant's protocol entitled *A Drug-Drug Interaction Study to Assess the Effects of a Single Dose of Mipomersen (200 mg SC) on Single-Dose Warfarin Pharmacodynamics and Pharmacokinetics in Healthy Adult Subjects* (MIPO2900509).

Date	Event/Notes
	• Mipomersen has an elimination half-life of 31 days following a 200 mg subcutaneous dose. The effect of multiple doses of mipomersen on the pharmacodynamics of warfarin may be different compared to that seen following single-dose administration. We recommend that you use a multiple-dose regimen of mipomersen when evaluating the effect on warfarin pharmacodynamics and pharmacokinetics.
23 Feb 2010	FDA responded to the applicant's questions on CMC issues.
30 Mar 2010	FDA responded to the applicant's revisions to Protocol ISIS 301012-CS6, entitled, *An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 301012 in Subjects with Familial Hypercholesterolemia*. The primary purpose of this amendment is to include MRI assessments of liver fat fraction at approximately 6-month intervals during the study.
12 Apr 2010	FDA provided comments on applicant's revised protocol MIPO2900509 and confirmed that Protocol MIPO2900509 could proceed under the partial clinical hold, since it is a multiple-dose study to be conducted in healthy volunteers.
13 Dec 2010	Pre-NDA face-to-face meeting: Non-clinical: (1) There remains uncertainty about the clinical significance, monitorability and mechanism of action by which mipomersen induced vascular lesions in monkeys (characterized as multi-focal intimal hyperplasia with mixed inflammatory infiltrates). (2) Please provide the validation report for detection of anti-mipomersen antibodies in human serum/plasma. This should be submitted and found acceptable by the Agency prior to submission of the NDA. Clin-Pharm: Clinical pharmacology program appears to be sufficient for an NDA submission. Clinical: Whether the Phase 3 study ISIS 301012-CS5, along with the open-label extension study CS6, supports an indication for the treatment of patients with HoFH will be determined after a full review of the relevant data and, most likely, input from an FDA advisory committee. The database is inadequate (b) (4) .
16 Dec 2010	Email sent to applicant stating that after additional internal discussions, FDA has concluded that (b) (4) Examinations of the study sample sizes used to support NDAs for orphan conditions with prevalence rates similar to severe HeFH support a request for one-year placebo-controlled data in a minimum of 300 severe HeFH patients (e.g., 200 on active drug vs. 100 on placebo). Additional safety concerns which will require further investigation include differentiating "benign" vs. clinically significant transaminase elevations during mipomersen treatment and the nature of the relationship between the transaminase elevations and steatotic changes in the liver after mipomersen administration. Since hepatic steatosis may progress to steatohepatitis and cirrhosis, additional information is needed on the long-term use of mipomersen on intrahepatic triglyceride content and hepatic lipid changes particularly in patients with varying degrees of hepatic steatosis at baseline (e.g., patients with diabetes, obesity, hypertriglyceridemia, heavy alcohol use). Careful monitoring of antibodies, renal function (quantitative urine protein measurement, measurement of glomerular filtration rates etc), blood pressure changes and adverse events will also be necessary in ongoing and future studies of mipomersen.
04 Apr 2011	The proposed proprietary name for mipomersen sodium is Kynamro which was designated conditionally acceptable in correspondence from the Division of

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Date	Event/Notes
	Medication Error Prevention.
13 June 2011	Special Protocol Assessment (SPA) request for Protocol MIPO3801011: *A Phase 3, Randomized, Double-Blind, Placebo- Controlled, Parallel-Group Study to Assess the Safety and Efficacy of Two Different Regimens of Mipomersen in Patients with Familial Hypercholesterolemia and Uncontrolled Low-Density Lipoprotein Cholesterol*
22 Jul 2011	No agreement to SPA for Protocol MIPO3801011. FDA requested the firm to extend the duration of the trial in order to provide 52 weeks at the fully titrated dose. Provide which hepatic biomarkers will be utilized and the supporting evidence for choosing these biomarkers. The hepatic biomarkers should be determined prior to starting the protocol.
29 Jul 2011	Modification of the partial clinical hold to permit studies of less than six months' duration in patients who are not at high risk for CVD. Over the clinical development of mipomersen, several studies have been conducted, with FDA approval, in patients who are not at high risk for CVD. These studies include MIP02800209, a TQT study involving 60 healthy subjects each receiving a single injection of mipomersen; MIP02900509, a drug interaction study involving 18 healthy subjects each receiving four doses of mipomersen every other day; MIP03200309, a dose comparison study involving 84 healthy subjects each receiving one to three weekly doses of mipomersen for three weeks; and ISIS 301012-CS3, a Phase 2 study in 50 hypercholesterolemic subjects not on lipid-lowering therapy each receiving weekly doses of mipomersen for thirteen weeks. This accumulated clinical data have lessened our original concerns such that we are now allowing studies in low to moderate risk subjects for less than 6 months.
29 Aug 2011	Submission of SPA request for revised Protocol MIPO3801011
7 Sep 2011	The firm submitted a validation report for detection of anti-mipomersen antibodies in human serum/plasma, Study ISIS 301012-MV12 entitled Validation of an ELISA for the Detection of Anti-ISIS 301012 Antibodies in Human Serum.
27 Sep 2011	Agreement to SPA request for revised Protocol MIPO3801011 The revised protocol provides for a prospective, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 study with 60 weeks of blinded treatment which includes an 8-week adjusted dosing regimen phase and a 52-week full dose regimen phase.
1 Dec 2011	The deficiencies determined by the Office of Biotechnology Products (OBP), Division of Therapeutic Proteins (DTP) in the binding immune assay for detection of anti-mipomersen antibodies in human serum/plasma was emailed to firm.
13 Dec 2011	Tcon: Initial first generation antibody assay is inadequate. Preferably, the NDA should not be submitted until the appropriate immunological data are generated using the new assay. The firm ultimately agreed that the NDA would include the validation report for the newly developed, second-generation assays for the detection of anti-mipomersen antibodies in the human serum as well as clinical data for patients with HoFH (Study ISIS 301012-CS5) and corresponding samples for these patients in the open-label extension study, ISIS 301012-CS6. The antibody data from the remaining Phase 3 studies and ISIS 301012-CS6 would be provided in the Day 120 safety update report.

Labeling:
In Module 1.14, the applicant submitted draft labeling text in SPL format. The proposed Package Insert was submitted in both Microsoft word and pdf format and includes an annotated version.

Risk Evaluation and Mitigation Strategy (REMS):
Module 1.16 contains the proposed risk management plan. The applicant is proposing the following REMS

- Medication Guide
- Healthcare Professional Risk Communication, consisting of:
  - Dear Healthcare Provider Letter
  - Healthcare Professional Information Brochure
  - Summary of Recommendations Tear-Off Pad
- Timetable for submission of assessments of the REMS Program

Elements to Assure Safe Use (ETASU) and the Implementation System are not proposed.

Genzyme plans to conduct a post-marketing safety surveillance study titled, "A Prospective Observational Study to Evaluate Long-Term Safety of Mipomersen in Clinical Practice". Genzyme states that the purpose of this registry study is to assess, in a post-approval clinical setting, the serious risks of mipomersen in patients who receive treatment under conditions of routine clinical practice. This registry will record safety information for the identified serious risks (e.g., increases in liver enzymes and hepatic fat). The protocol concept for this observational study is provided in Module 5.3.5.4 of the NDA.

Priority or Standard Review:
Genzyme requested a Priority review of this application but this application will likely be designated a Standard review.

Pediatric Waiver:
A pediatric waiver is not required since an Orphan Drug Designation (No. 06-2214) for treatment of homozygous familial hypercholesterolemia was granted on May 23, 2006.

Debarment Certification:
Genzyme Corporation certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal, Food, Drug and Cosmetic Act in connection with this application.

Financial Disclosures:
Genzyme submitted a completed Form FDA 3454 attesting to the absence of financial interests and arrangements for all investigators that submitted financial information.

Genzyme Corporation certifies that it has acted with due diligence to obtain the financial information described in 21 CFR 54.4(a)(3), but was unable to do so for five (5) principal investigators and thirty-one (31) sub-investigators involved in Study MIPO3500108.

Patent Exclusivity Request:
The applicant has not requested exclusivity. However, approval would typically trigger the 7-year orphan exclusivity provision.

Site Inspection:
The pivotal Phase 3 study in the indicated population (ISIS 301012-CS5, in patients with HoFH) is supported by three supportive Phase 3 studies (MIPO3500108, in patients with Severe HeFH; ISIS 301012-CS7, in patients with HeFH and coronary artery disease; and ISIS 301012-CS12, in patients with high-risk hypercholesterolemia).

Study CS5 randomized 51 patients from 9 study centers in 7 countries (Brazil, Canada, Singapore, South Africa, Taiwan, United Kingdom, and United States). The highest enrolling site for CS5 is in Parktown, South Africa with 26 subjects; this site also had the highest total risk score using the FDA Site Selection Tool (v2.2). The second highest enrolling site for CS5 is in Sao Paulo, Brazil with 6 subjects. Site 1503 (Evan Stein, Cincinnati, Ohio) had the greatest treatment efficacy but only enrolled one subject.

Study CS07: 26 sites in US and Canada, the 3 highest enrolling sites enrolled between 10 to 12 subjects. The two highest total risk scores were for site 1578 (John Guyton, Durham, NC, enrolled 5 subjects) and site 1503 (Evan Stein, Cincinnati, Ohio, enrolled 12 subjects).

Study 108: 23 sites, the highest enrolling sites were Site 4000 in Prague, Czech Republic with 9 subjects; Site 3000 in South Africa with 6 subjects and Site 3002 in South Africa with 5 subjects. The two highest total risk scores were for site 3000 (Lesley Burgess, Parow, South Africa, enrolled 6 subjects) and site 3002 (Prashilla Soma, Petoria, South Africa, enrolled 5 subjects).

Study CS12: 43 sites, all in the US, the highest enrolling sites had 16 and 10 subjects. The two highest total risk scores were for site 1681 (Natalie Doyle, Wilson, NC, enrolled 6 subjects, subject death occurred at this site [1861-2132]) and site 1682 (Richard Shultzaberger, Greenville, NC, enrolled 10 subjects).

In consultation with Susan Leibenhaut, two sites were identified for additional evaluation. The statistical team was asked to evaluate the following two sites to see if the removal of these sites would significantly affect the efficacy results. The trial and sites that we are interested in are:

1) Trial MIPO3500108; Site 4000; enrolled 9 out of a total of 58 subjects in trial.
2) Trial 301012-CS5: Site 1523; enrolled 6 out of a total of 51 subjects in trial.

The statistical analysis of Site 4000/MIPO108 and Site 1523/CS5 shows that the exclusion of sites 4000 and 1523 does not affect the efficacy result, which remains highly significant.

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The sites below are recommended for consideration primarily based on the number of subjects enrolled, total risk ranking, and efficacy results. Of note, for Trial MIPO3500108, site 3000 OR site 3002 should be selected. Both sites do not need to be evaluated.

Site # (Name, Address, Phone Number, email, fax #)	Protocol ID	# Subjects Enrolled	Indication
1501; Frederick Raal; Carbohydrate and Lipid Metabolism Research Unit, Area 551, Department of Medicine, Johannesburg Hospital, 7 York Road, Parktown, South Africa 2193 Telephone No: +27 11 4883538 cellphone (b) (6) Fax No: +27 11 6432935 E-Mail: Frederick.raal@wits.ac.za	CS5	26	HoFH
1503; Evan Stein, Metabolic and Atherosclerosis Research Center, 4685 Forest Avenue, Cincinnati, Ohio, 45212 Telephone No: 513-579-8811 Fax No: 513-579-8832 E-Mail: ESteinMRL@aol.com	CS5 CS7	1 12	HoFH (b) (4)
4000; Richard Ceska 3. Interní klinika 1LFUK a VFN Klinika endokrinologie a metabolismu U nemocnice 1 128 08 Praha 2 Czech Republic Phone: 420-6-0423-6637 Fax: 420-6-0496-6677 E-mail: rcesk@lf1.cuni.cz	MIPO108	9	(b) (4)
3000; Lesley Burgess TREAD Research cc Room 37, 8th Floor Department of Cardiology, Tygerberg Hospital Francie van Zijl Avenue, Parow, 7500 Cape Town, South Africa Phone No.: 27-21-931-7825 Fax: 27-21-933-3597 E-mail: Lesley@treadresearch.com	MIPO108	6	(b) (4)
3002; Soma Prashilla Clinical Research Unit, University of Pretoria Room 2-54 Pathology Building Prinshof Medical Campus	MIPO108	5	(b) (4)

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Site # (Name, Address, Phone Number, email, fax #)	Protocol ID	# Subjects Enrolled	Indication
Dr Savage Road Pretoria 0002 South Africa Phone No.:27-12-319-2166 Fax: 27-12-325-1695 E-mail: prashilla.soma@up.ac.za			

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?				As agreed in the pre-NDA meeting summary, the required components of the ISE are incorporated within Section 2.7.3.3, Comparison of Results Across Studies, rather than in a separate ISE in Module 5.
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)(1)

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	Content Parameter	Yes	No	NA	Comment
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? *Study Number: ISIS 301012-CS1* Study Title: A Double-Blind, Placebo-Controlled, Dose-Escalation, Phase 1 Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single and Multiple Doses of ISIS 301012 Administered Intravenously and Subcutaneously to Healthy Volunteers Sample Size: 36 Arms: 5 (Pl, 50, 100, 200, 400 mg) Location in submission: 5.3.3.1 *Study Number: ISIS 301012-CS3* Study Title: A Phase 2, Randomized, Double Blind, Placebo-Controlled Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Varying Loading and Maintenance Dosing Regimens of ISIS 301012 Administered to Hypercholesterolemic Subjects Sample Size: 50 Arms: 5 (50, 100, 200, 300, 400 mg) Location in submission: 5.3.3.2	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: CS-5 Indication: LDL-C lowering in HoFH Supporting Study #2: CS7 Indication: (b) (4) Supporting Study #3: MIPO-108 Indication: LDL-C lowering in severe hypercholesterolemia	X			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			Orphan indication
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			

	Content Parameter	Yes	No	NA	Comment
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[6]) been exposed at the dose (or dose range) believed to be efficacious?	X			Orphan indication; target US population=300 patients. Pivotal Trial (CS5) 51 subjects (17 PL; 34 Mipo studied. Six (11.8%) patients, all in the mipomersen group, discontinued from the study. In total, 45 (88.2% [100% PL: 82.4% Mipo]) patients completed the treatment period.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[7] used for mapping investigator verbatim terms to preferred terms?	X			Adverse events were classified using the standardized Medical Dictionary for Regulatory Activities (MedDRA) (Version 13.0). All AEs in the Phase 3 and Phase 2 studies in the pooled analyses were up-coded to this most current version.
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					

[6] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[7] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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	Content Parameter	Yes	No	NA	Comment
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	Orphan designation
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the Application is not fileable from the clinical 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.

Eileen Craig, MD — 14 May 2012

Reviewing Medical Officer — Date

Clinical Team Leader — Date

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

/s/

EILEEN M CRAIG
05/14/2012

ERIC C COLMAN
05/14/2012