

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203568Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 203568
Product Name: Kynamro (mipomersen sodium) Injection

PMR/PMC Description: Development and validation of a sensitive assay to assess for the presence of antibodies to double stranded (ds) DNA to allow for testing of patients treated with Kynamro (mipomersen sodium).

PMR/PMC Schedule Milestones: _____

Final Report Submission: 12/31/2013

Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Homozygous familial hypercholesterolemia (HoFH) is a rare genetic disorder caused by mutations in the low-density lipoprotein (LDL) receptor gene and characterized by elevated plasma levels of LDL cholesterol (LDL-C) with normal triglycerides, tendon xanthomas, and premature coronary atherosclerosis. Kynamro (mipomersen sodium) was granted orphan drug designation for the treatment of HoFH. Known adverse events include proteinuria, arthralgia, skin rash, and elevations in hepatic transaminases, all of which can be associated with autoimmune disease. No evaluation was performed to determine whether the administration of Kynamro (mipomersen sodium) induced antibodies to endogenous native nucleic acids such as occurs in several autoimmune diseases. Given the age of the population affected by this disorder, reports in the literature that treatment with synthetic oligonucleotides may induce antibodies to dsDNA, the unexpected high incidence of anti-drug antibodies elicited by the treatment, and the increase in circulating antigen-antibody complexes, a post-marketing study is required to assess whether treatment with Kynamro (mipomersen sodium) places patients at increased risk of developing auto-antibodies.

This is suitable for a post-marketing requirement since the risk is theoretical at this time.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The absence of data regarding induction of antibodies to native nucleic acids is a concern. The clinical development program revealed a high incidence of antibodies to the product as well as evidence of adverse reactions associated with Kynamro (mipomersen sodium) including hepatic transaminase elevations, proteinuria, arthralgia, and skin rash. The goal of this PMR is to assess whether patients treated with Kynamro (mipomersen sodium), a synthetic oligonucleotide, develop antibodies that bind to endogenous native dsDNA and could be at increased risk of developing autoimmune disease.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Development and validation of a sensitive assay to assess for the presence of antibodies to double stranded (ds) DNA to allow for testing of patients treated with Kynamro (mipomersen sodium). The final report should include a summary of the validation exercise including supporting data, a summary of the development data supporting assay suitability for parameters not assessed in the validation exercise, and the assay standard operating procedure (SOP).

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

Homozygous familial hypercholesterolemia (HoFH) is a rare genetic disorder caused by mutations in the low-density lipoprotein (LDL) receptor gene and characterized by elevated plasma levels of LDL cholesterol (LDL-C) with normal triglycerides, tendon xanthomas, and premature coronary atherosclerosis. Kynamro (mipomersen sodium) was granted orphan drug designation for the treatment of HoFH. Known adverse events include proteinuria, arthralgia, skin rash, and elevations in hepatic transaminases, all of which can be associated with autoimmune disease. No evaluation was performed to determine whether the administration of synthetic oligonucleotides induced antibodies to endogenous native nucleic acids such as occurs in several autoimmune diseases. Given the age of the population affected by this disorder, reports in the literature that treatment with synthetic oligonucleotides may induce antibodies to dsDNA, the unexpected high incidence of anti-drug antibodies elicited by the treatment, and the increase in circulating antigen-antibody complexes, a post-marketing study is required to assess whether treatment with Kynamro (mipomersen sodium) places patients at increased risk of developing auto-antibodies. This is suitable for a post-marketing requirement since the risk is theoretical at this time.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The absence of data regarding induction of antibodies to nucleic acids is a concern. The clinical development program revealed a high incidence of antibodies to the product as well as evidence of adverse reactions associated with Kynamro (mipomersen sodium) including hepatic transaminase elevations, proteinuria, arthralgia, and skin rash. The goal of the PMR is to assess whether patients develop antibodies to endogenous native nucleic acids and could be at increased risk of developing autoimmune disease.

The study may be conducted with stored serum samples from patients treated with Kynamro (mipomersen sodium) in the clinical development program, but should include samples from patients who test negative as well as patients who test positive for antibodies to mipomersen. Among patients who develop anti-drug antibodies, samples should be included from patients shortly after seroconversion as well as from sustained responders.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The risk of developing antibodies to nucleic acids remains a concern in this population. Development of antibodies to mipomersen in treated patients was unexpectedly high reaching over 70% in the open label studies. The clinical development program revealed a high incidence of anti-drug antibodies, elevated levels of circulating antigen-antibody complexes, and adverse events associated with Kynamro (mipomersen sodium) including proteinuria, elevated transaminases, arthralgias, and skin rash.

The goal of this PMR is to assess whether patients treated with Kynamro (mipomersen sodium), a synthetic oligonucleotide, develop antibodies that bind to endogenous native dsDNA and could be at increased risk of developing autoimmune disease.

Required

Observational pharmacoepidemiologic study

Registry studies

Primary safety study or clinical trial

Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety

Thorough Q-T clinical trial

Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

Pharmacokinetic studies or clinical trials

Drug interaction or bioavailability studies or clinical trials

Dosing trials

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

- Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA # 203568
Product Name: Kynamro (mipomersen sodium) Injection

PMR/PMC Description: A long-term prospective observational study (product exposure registry) of patients with homozygous familial hypercholesterolemia (HoFH) treated with Kynamro (mipomersen sodium) to evaluate known and potential serious risks related to the use of Kynamro (mipomersen sodium), including hepatotoxicity (hepatic transaminase elevations, hepatic steatosis), malignancy (hepatocellular adenoma and carcinoma, and fibroma, fibrosarcoma, and fibrous histiocytoma of the skin and subcutis), and new diagnoses of autoimmune disorders (lupus erythematosus, antiphospholipid syndrome, rheumatoid arthritis, glomerulonephritis). The registry will include a sample of patients prescribed Kynamro (mipomersen sodium) and continue for 10 years from the date of last patient enrollment.

PMR/PMC Schedule Milestones: Final Protocol Submission: 10/29/2013
11/29/2014
11/29/2015
11/29/2016
11/29/2017
11/29/2018
11/29/2019
11/29/2020
11/29/2021
11/29/2022
11/29/2023
11/29/2024
11/29/2025
Study/Trial Completion: 11/29/2026
Final Report Submission: 05/29/2027
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Homozygous familial hypercholesterolemia (HoFH) is a rare genetic disorder caused by mutations in the low-density lipoprotein (LDL) receptor gene and characterized by elevated plasma levels of LDL cholesterol (LDL-C) with normal triglycerides, tendon xanthomas, and premature coronary atherosclerosis. Kynamro (mipomersen sodium) was granted orphan drug designation for the treatment of HoFH. Known and potential safety concerns include hepatic transaminase elevations, hepatic steatosis, and hepatic fibrosis, malignancy, including hepatocellular adenomas and carcinomas, fibroma/fibrosarcoma/fibrous histiocytoma of the skin/subcutis, and immune-mediated reactions, including the development of anti-drug antibodies elicited by treatment and an increase in circulating antigen-antibody complexes. Given the small population affected by this disorder (~1 in a million), the small number of patients and the short duration of clinical trials, a postmarketing registry is required to generate additional person-years to assess risks related to the long-term use of the drug.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The paucity of long-term safety data on Kynamro (mipomersen sodium) remains a concern. Because of the rarity of HoFH, the availability of patients and person-years of exposure that contribute to our current understanding of the safety of Kynamro (mipomersen sodium) is limited. The clinical development program revealed known and potential serious risks associated with Kynamro (mipomersen sodium) including hepatic transaminase elevations, hepatic steatosis, and hepatic fibrosis, malignancy, including hepatocellular adenomas and carcinomas, fibroma/fibrosarcoma/fibrous histiocytoma of the skin/subcutis, and immune-mediated reactions, including the development of anti-drug antibodies and an increase in circulating antigen-antibody complexes. The goal of the registry is to generate additional person-years of exposure to assess these and other serious risks related to Kynamro (mipomersen sodium) use.

The registry will include a sample of patients prescribed Kynamro (mipomersen sodium) and continue for 10 years from the date of last patient enrollment.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The paucity of long-term safety data on Kynamro (mipomersen sodium) remains a concern. Because of the rarity of HoFH, the availability of patients and person-years of exposure that contribute to our current understanding of the safety of Kynamro (mipomersen sodium) is limited. The clinical development program revealed known and potential serious risks associated with Kynamro (mipomersen sodium) including hepatic transaminase elevations, hepatic steatosis, and hepatic fibrosis, and malignancy, including hepatocellular adenomas and carcinomas, and fibroma/fibrosarcoma/fibrous histiocytoma of the skin/subcutis, and immune-mediated reactions. The goal of the registry is to generate additional person-years of exposure to assess these and other serious risks related to Kynamro (mipomersen sodium) use.

The registry will include a sample of patients prescribed Kynamro (mipomersen sodium) and followed for 10 years to describe the following:

- a. Patient age, sex, and race
- b. Country of treatment
- c. Cardiovascular history
- d. History of apheresis
- e. History of autoimmune disease
- f. Other medical history
- g. Concomitant medications, including start and stop dates
- h. Use of dietary and vitamin supplements
- i. Kynamro dose, duration of use, start date, discontinuation date, reasons for discontinuation, person-years of exposure
- j. Liver enzyme monitoring frequency
- k. Serum lipid levels

Data to be provided should include incidence rates for the following outcomes of interest:

- Malignancies, including hepatocellular adenomas and carcinomas, fibroma/fibrosarcoma/fibrous histiocytoma of the skin/subcutis
- Hepatic adverse events including hepatic transaminase elevations with and without bilirubin elevations, hepatic steatosis, non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH), hepatic fibrosis
- Autoimmune disorders including lupus erythematosus, antiphospholipid syndrome, rheumatoid arthritis, glomerulonephritis

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials

- Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA #	203568
Product Name:	Kynamro (mipomersen sodium) Injection
PMR/PMC Description:	An assessment and analysis of spontaneous reports of serious hepatic abnormalities, malignancy, and immune-mediated reactions in patients treated with Kynamro (mipomersen sodium) for a period of 10 years from the date of approval. Specialized follow-up should be obtained on these cases to collect additional information on the events.
PMR/PMC Schedule Milestones:	Final Protocol Submission: 10/29/2013
	Interim submissions: 02/28/2014
	08/29/2014
	02/28/2015
	08/29/2015
	02/28/2016
	08/29/2016
	02/28/2017
	02/28/2018
	02/28/2019
	02/28/2020
	02/28/2021
	02/28/2022
	02/28/2023
	02/28/2024
	Study/Trial Completion: 11/29/2024
	Final Report Submission: 05/29/2025
	Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Homozygous familial hypercholesterolemia (HoFH) is a rare genetic disorder caused by mutations in the low-density lipoprotein (LDL) receptor gene and characterized by elevated plasma levels of LDL cholesterol (LDL-C) with normal triglycerides, tendon xanthomas, and premature coronary atherosclerosis. Kynamro (mipomersen sodium) was granted orphan drug designation for the treatment of HoFH. Known and potential safety concerns for Kynamro (mipomersen sodium) include: hepatic abnormalities, malignancies, and immune-mediated reactions. Given the small population affected by this disorder (~1 in a million), the small number of patients and the short duration of clinical trials, enhanced pharmacovigilance is required to generate additional data to better assess risks related to the long-term use of the drug.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The paucity of long-term safety data on Kynamro (mipomersen sodium) remains a concern. Because of the rarity of HoFH, the availability of patients and person-years of exposure that contribute to our current understanding of the safety of Kynamro (mipomersen sodium) is limited. Kynamro (mipomersen sodium) pre-clinical and clinical development programs revealed known and potential serious risks associated with its use, including hepatic abnormalities (hepatic transaminase elevations (b) (4), hepatic steatosis, (b) (4), malignancies (hepatocellular adenomas or carcinomas, fibroma/fibrosarcoma/fibrous histiocytoma of the skin/subcutis), (b) (4) and autoimmune disorders).

The goal of the enhanced pharmacovigilance study is to gather additional data to better assess risks related to the long-term use of the drug. The study will continue for a period of 10 years from the date of approval.

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

(b) (4)
reports of hepatic abnormalities, malignancy, and immune-mediated reactions in patients with HoFH treated with Kynamro (mipomersen sodium) for a period of 10 years from the date of approval. The enhanced pharmacovigilance program will include the following:
a) Active query of reporters to obtain additional clinical information related to reports of hepatic abnormalities, malignancy, and immune-mediated reactions. The sponsor should actively query reporters for the following information:
(i) For reports of hepatic abnormalities: liver-related laboratory, imaging and pathology results, duration of Kynamro (mipomersen sodium) exposure, and other risk factors for hepatic abnormalities
(ii) For reports of malignancy: cancer site, timing and duration of Kynamro (mipomersen sodium) exposure in relation to diagnosis, and other risk factors for the specific cancer.
(iii) For reports of immune-mediated reactions (such as severe cutaneous reactions, anaphylaxis, vasculitis, acute onset renal failure, and autoimmune disorders): nature of the defect, timing and duration of Kynamro (mipomersen sodium) exposure, and other risk factors for the immunologic responses.
b) Expedited reporting to FDA of all initial and follow-up reports of hepatic abnormalities and malignancy. Interim analyses and summaries of new and cumulative safety information must be submitted annually, followed by the final report at the conclusion of the monitoring period.
c) Expedited reporting to FDA of all initial and follow-up reports of serious cases of potential immune-mediated adverse reactions. Interim analyses and summaries of new and cumulative safety information of reports of immune-mediated reactions with a serious outcome must be submitted semi-annually, followed by the final report at the conclusion of the monitoring period.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
Enhanced pharmacovigilance program
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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

/s/

AMY G EGAN
01/24/2013

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion
Division of Consumer Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: January 10, 2013

To: Kati Johnson, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Samuel Skariah, Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)
Office of Prescription Drug Promotion (OPDP)

Kendra Y. Jones, Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP)

Subject: NDA 203568 KYNAMRO™ (mipomersen sodium) Injection Solution
for Subcutaneous Injection

OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, and Instructions for Use for KYNAMRO™ (mipomersen sodium) Injection Solution for Subcutaneous Injection submitted for consult on December 11, 2012.

OPDP's comments on the proposed draft PI are based on the version sent via email from Kati Johnson (RPM) on January 4, 2013. OPDP's comments on the proposed draft Medication Guide and Instructions for Use are based on the marked versions sent via email from Sharon Williams (DMPP) on January 10, 2013, that is provided directly below. Comments on the proposed draft Prescribing Information, Medication Guide, and Instructions for Use are provided directly on the marked version of the labeling below.

Thank you for the opportunity to comment on this label. If you have any questions regarding this proposed draft PI, please contact Samuel Skariah at 301-796-2774 or Sam.skariah@fda.hhs.gov.

If you have any questions regarding this proposed draft Medication Guide or Instructions for Use, please contact Kendra Jones at 301-796-3917 or Kendra.jones@fda.hhs.gov.

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/s/

KENDRA Y JONES
01/10/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: January 9, 2013

To: Mary Parks, MD, Director
**Division of Metabolism and Endocrinology Products
(DMEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Robin Duer, RN, BSN, MBA
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Sharon W. Williams, MSN, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: DMPP Review of Patient Labeling (Medication Guide) and
Instructions for Use (IFUs)

Drug Name (established
name): KYNAMRO (mipomersen sodium)

Dosage Form and Route: subcutaneous injection

Application
Type/Number: NDA 203568

Applicant: Genzyme Corporation

1 INTRODUCTION

On May 23, 2006, KYNAMRO (mipomersen sodium) injection was granted orphan-designation by the Office of Orphan Products Development, FDA, for the treatment of homozygous familial hypercholesterolemia (HoFH).

On March 29, 2012, Genzyme Corporation submitted an original New Drug Application (NDA) indicated for the treatment of homozygous familial hypercholesterolemia (HoFH) when used as adjunct to a low-fat diet and other lipid-lowering therapies (LLT).

This review is written in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFUs) for KYNAMRO (mipomersen sodium).

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFUs was completed on December 17, 2012.

The Risk Mitigation and Evaluation Strategy (REMS) is being reviewed by the Division of Risk Management (DRISK) and will be provided to DMEP by DRISK under separate cover.

2 MATERIAL REVIEWED

- Draft KYNAMRO (mipomersen sodium) Medication Guide received on March 29, 2012, and received by DMPP on December 11, 2012
- Draft KYNAMRO (mipomersen sodium) Instructions for Use received on March 29, 2012, and received by DMPP on December 11, 2012
- Draft KYNAMRO (mipomersen sodium) Prescribing Information (PI) received on March 29, 2012, revised by the Review Division throughout the current review cycle, and received by DMPP on January 2, 2013
- Approved JUXTAPID (lomitapide mesylate) comparator labeling dated December 21, 2012

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB)

published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG and IFUs document using the Verdana font, size 11.

In our review of the MG and IFUs we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFUs are consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFUs meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFUs are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG and IFUs are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated versions of the MG and IFUs are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
01/09/2013

ROBIN E DUER
01/09/2013

LASHAWN M GRIFFITHS
01/09/2013

January 9, 2013

To: NDA 203568

Consult and Review for Immunogenicity

Review approved by: Daniela Verthelyi, M.D./Ph.D, Chief, LIM/DTP/OBP/CDER
Michael Norcross, M.D., LIM/DTP/OBP/CDER

From: Jinhai Wang, M.D., Medical Officer, LIM/DTP/OBP/CDER
Bldg. 29B, Rm. 4E12, HFD-122
8800 Rockville Pike
Bethesda, MD20892
301-594-5223

Drug product: Mipomersen sodium

Indication: Reduce LDL-C, apo B, total cholesterol, non-HDL-C, and Lp(a) in patients with HoFH

Sponsor: Genzyme Corporation (500 Kendall Street, Cambridge, MA 02142. 617-252-75000)

Date received: March 29, 2012

Action date: Jan. 29, 2013

Immunogenicity Consult Recommendation:

There are no immune response induced issues that prevent Approval.

Antibody binding and confirmatory assays to measure ADA to mipomersen have been validated and are acceptable for testing patient samples. Frequency of antibody development in patients on long term therapy is high overall, reaching 71% in the open label follow-up study and 66% in HoFH patients. Of note, patients continued to develop ADA months after initial exposure. However, the presence of ADA did not correlate with reduced safety or efficacy but could do so long term. The presence of neutralizing antibodies was not evaluated. The impact of neutralizing antibodies on long term safety and efficacy was considered but it is not clear that it's assessment would be informative. The development of antibodies to nucleic acids was not evaluated by the sponsor during the clinical trials. PMRs to develop an assay to assess antibodies to dsDNA and to establish whether treatment is associated

with increased incidence of anti-dsDNA ab and /or autoimmune disease will be requested.

Summary

Background:

DNA therapeutics have broad therapeutic potential for many diseases due to the ability of antisense and RNAi to specifically reduce mRNA or the translation of a given target gene. However, the in vivo delivery has been difficult and delivery methods usually rely on chemical reagents that have off-target side effects.

Genzyme developed a 2-ME- modified PS backbone based 20 nucleotide DNA anti-sense therapeutic candidate targeting ApoB100, called Mipomersen. In human ApoB100 transgenic mice, Mipomersen was able to specifically knock down human ApoB100 as seen by reduction of mRNA levels in mouse liver and protein in blood. The reduction was specific as mouse Ap(a) gene levels were unchanged. The effect is sequence specific as a control ODN of the same chemical class, but different gene sequence failed to reduce ApoB100.

In human studies, a total 811 patients were enrolled. The drug reduced LDL-C levels in blood by 25%-30% in treated patients, which was stated to be comparable to effects of Statins. Therefore, Mipomersen could have therapeutic potential to reduce the incidence of cardiovascular diseases/adverse events in patients with high LDL-C.

Results:

Due to the presence of anti-DNA antibodies in patients with autoimmune diseases, the unusual modification of this DNA, and the high affinity of rabbit antibodies to this ODN, the sponsor was asked to perform immunogenicity testing for this ODN therapeutic in their clinical studies. The Sponsor was also asked to monitor antibodies to DNA.

Sponsor developed and validated a screening assay (ELISA) and confirmatory assay (IP). Both assays were used in testing patients samples. Validation of assays included cut point determination, precision, repeatability, inter-assay precision, sensitivity (125 ng/ml),

specificity, drug tolerance, and selectivity. Antibodies to the product are partly specific for the 2-ME modification, in that oligonucleotides carrying this modification with a different sequence can partially block ADA binding to mipomersen.

During index studies, 40 % patients (108/266) were positive for ADA in studies CS5/CS6, CS7, CS12, and 3500108. The incidence of antibodies increased over time of treatment and in the open label study CS6, the incidence of ADA reached 71% (102/142). This pattern of response is different from that of therapeutic proteins, in which patients most likely to become ADA positive develop antibodies between week 4 and 8. On December 15, 2012, the Sponsor sent in report in response to an FDA request detailing the AE of patients diagnosed with HoFH. The incidence of ADA among HoFH patients in the CS6 study was 66%.

The presence of ADA does not appear to prevent the reduction of LDL or ApoB100 in the blood during early phase of drug treatment, but did so at later times (though only a few patients). Antibody level or presence is not clearly related to occurrence or severity of adverse effects. Antibody to the product may lead to higher trough levels of the drug.

In terms of safety, serious adverse events were not correlated with ADA positivity, titer, or duration of ADA in CS6 study. The sponsor analyzed the immunogenicity related data for this study in 2 ways:

- 1) Patients were grouped by presence of circulating immune complex before and after drug therapy (Assay was not specified) and compared with appearance of AEs. Although more AEs per patient number were listed in patients who developed ICs, no clear correlation was evident that could be attributed to ADA.
- 2) Sponsor did a correlation analysis and found that there was a moderate correlation between trough levels and ADA levels. However, it was not clear that differences in AE frequency was evident between patients grouped into HHT (highest high trough), HT, and NT (normal trough) drug levels.

There were more cardiovascular AEs and SAEs in CS6 (30% and 20% patients, respectively) than in CS5 (6%) but no definite relationship between ADA and SAEs was evident.

Among the HoFH patients, there were 7 patient that developed 22 cardiovascular SAEs in the CS6 study. Of these patients 4 had ADA, 2 had transient ADA and 1 was negative.

No neoplasm cases were reported for the 38 HoFH patients in CS6 study, but there were multiple bacterial infections.

Review

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The product

The product is an unusually modified anti-sense ODN intended to target mRNA of Apo100 gene to reduce blood LDL-C level.

The ODN is a 20 base-long oligonucleotides with PS backbone (as most anti-sense ODNs, to reduce degradation) and multiple 2-ME modifications.

The mipomersen sodium sequence can be written in shorthand as follows:



The underlined residues are 2'-MOE nucleosides. It should be noted that 2'-O-(2-methoxyethyl)-5-methyluridine (2'-MOE ^{Me}U) nucleosides are also sometimes designated as 2'-O-(2-methoxyethyl)ribothymidine (2'-MOE T). Mipomersen is a 2'- methoxyethyl (MOE) phosphorothioate ASO. The 2'-MOE

modification has increased the potency of antisense activity and improved the tolerability properties relative to first-generation ASOs (Henry, 2001, *Curr Opin Investig Drugs*).

Mipomersen is a phosphorothiolated oligonucleotide and therefore differs from naturally occurring oligonucleotides by substitution of the phosphate diester internucleotide linkage by a phosphorothioate diester. Other modifications are methylation of the cytosine bases at the 5-position and substitution in the 2'-position with a 2-methoxyethyl moiety for 10 of 20 nucleotides. These modifications result in a compound that is more stable *in vivo* and could be more active than unmodified oligonucleotides.

Mechanism of Action

The MOA is proposed as the following: Mipomersen inhibits expression of the apo B-100 gene by sequence-specific hybridisation, or binding, to a complementary sequence on the messenger ribonucleic acid (mRNA) through Watson-Crick base-pair interactions. This results ultimately in selective degradation of the mRNA through one of several possible enzyme-mediated pathway (b) (4)

*In a paper published on Circulation, 2008, hApoB100 protein from **human ApoB100 transgenic mice** was significantly reduced by the drug, but not by a control ODN of the same chemical class with different sequence.*

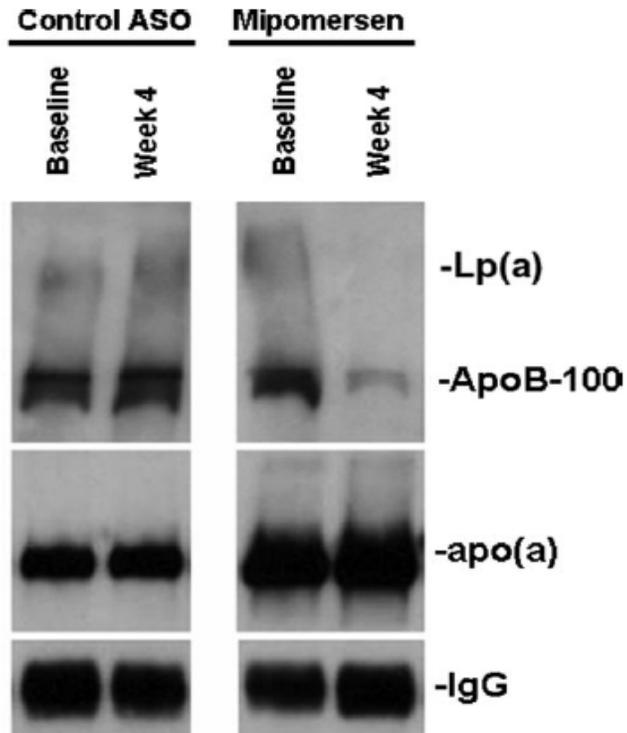


Figure 2. Western blot analysis of h-apoB-100, Lp(a), apo(a), and mouse IgG. Shown are the findings from plasma in mice from study 2 at the baseline and 4-week time points after administration of mipomersen or control ASO. Lp(a) and h-apoB immunoblots were performed in nondenaturing conditions, whereas apo(a) and IgG blots were done under denaturing conditions.

Specifications, release, and stability of drug substance and product

Table 1: Specification for Mipomersen Sodium Drug Substance

Test	Method	Acceptance Criterion
Sequence Determination, Melting Temperature	Melting Temperature (AM-00223)	(b) (4)
Sequence Determination, Failure Sequence Analysis ^a	IP-HPLC-TOF-MS (AM 00221)	
Identification	IP-HPLC-UV-MS (AM 00184/TM003-142)	
Assay		
Purity		
Impurity Profile		

GC – Gas Chromatography; ICP-MS – inductively coupled plasma-mass spectrometry; ICP-OES – inductively coupled plasma-optical emission spectroscopy; IP-HPLC-TOF-MS – Ion pair-high performance liquid chromatography-time of flight-mass spectrometry; IP-HPLC-UV-MS – Ion pair- high performance liquid chromatography-ultraviolet detection-mass spectrometry; KF – Karl Fisher; LOD – limit of detection; NLT – Not less than; NMT – Not

more than; PhEur – European Pharmacopoeia; USP – United States Pharmacopoeia; UV - ultraviolet

^a This test is conducted as an intermediate test on Crude ISIS 301012.

^b Defined (b) (4)

Table 3: Release Data for Mipomersen Sodium Injection Pre-filled Syringe Registration Batches

Test	Method	Acceptance Criterion	CL10002	CL10004	CL10006
Appearance	TM014-19				(b) (4)
Identification (IP-HPLC-UV-MS ^a)	TM003-136				
Assay (% Label Claim)	TM003-136				
Purity (%)	TM003-136				
Degradation Products (%)	TM003-136				
Volume of Injection in Container (mL)	TM015-66				
pH	TM007-17				
Osmolality (mOsm/kg)	TM013-08				
Particulate Matter	MTM063				

Doc ID: m2-3-p-5-contr-drug-prod-mipomersen-sodium-injection-pfs-v02 doc

Table 3: Release Data for Mipomersen Sodium Injection Pre-filled Syringe Registration Batches

Test	Method	Acceptance Criterion	CL10002	CL10004
Bacterial Endotoxins (EU/mL)	BXMB1004			(b) (4)
Sterility	BXMB1009			

^a Ion Pair-High Performance Liquid Chromatography with Ultraviolet and Mass Spectrometry detection

^b Not Less Than

^c Not More Than

^d Not detected. The limit of detection for all degradation products is (b) (4).

^e Defined as the (b) (4)

Table 4: Stability Data for Mipomersen Sodium Injection Batch CL10002 Stored at 5°C ± 3°C

Product: Mipomersen Sodium Injection, 200 mg/mL PFS		Batch#/Trial #/Protocol#: CL10002/ 981/ SB128
Date Manufactured: 28 Jun 2010		Manufacturing Site: Genzyme Ridgefield (Ridgefield, NJ, USA)
Stability Start Date: 11 Aug 2010		Container Closure: (b) (4) 1 mL, long, clear glass syringes with (b) (4)
Storage Condition: 5°C ± 3°C		staked needles and a needle shield stoppered with (b) (4) rubber plunger stoppers (b) (4)
Test	Method	(b) (4)
Appearance	TM014-19	
Assay ^a	TM003-136	
Purity ^b	TM003-136	
ISIS 301012 (b) (4)		
Degradation Products ^a	TM003-136	
(b) (4)		
Total degradation products ^d		
pH	TM007-18	
Particulate Matter	MTM063	
Particles/ Container, (b) (4)		
Particles/ Container, (b) (4)		
Bacterial Endotoxins	MTM064	
Sterility	USP<71> / PhEur 2.6.1	

Doc ID: m2-3-p-8-stab-mipomersen-sodium-injection-pfs-v02 doc

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The product is sterile with endotoxin levels (b) (4). Therefore, immunogenicity of the product is unlikely to be affected by these impurities.

Drug formulation

Mipomersen sodium at 200 mg/mL in water, with pH adjustment as required to 7.5-8.5. Currently available stability data allow for a 30 month expiry for vials and 18 month expiry for pre-filled syringes when stored at (b) (4) protected from light.

The formulation itself is unlikely to affect the immunogenicity of the product.

Route of Administration

The proposed dose is 200 mg once weekly as a subcutaneous injection.

Immunogenicity Review and Consult

The testing of Phase III serum samples employed three second generation assays as described below:

These 3 second-generation assays for the detection, confirmation, and titration of antibodies to mipomersen in human serum were developed and validated by Genzyme.

These assays comprise the following, performed in this order:

1. An ELISA assay was used to detect antibody responses to mipomersen in patient serum (ITR 559-0911).
2. For samples found to be reactive in the ELISA, an immunoprecipitation polyacrylamide gel electrophoresis assay was used to confirm the specificity of the antibody response to mipomersen (ITR 560-1011).
3. For antibody-positive samples that were found to be specific to mipomersen by the confirmatory assay, the ELISA assay described above was used to determine the end point titer of a positive sample as an estimate of the magnitude of the response (ITR 559-0911).

(2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods)

I. Anti-ADA binding assay

Procedure Summary

Streptavidin coated 96-well ELISA plates are used to capture biotin-Mipomersen using 0.5 ug/mL of Mipomersen diluted in 1xPBS (nuclease free). Plates are allowed to coat for one hour at 36-38 °C and any unbound sites are subsequently blocked for 1-2 hours at 36-38 °C using 3% nonfat dry milk in PBS containing 1M NaCl (assay diluent). Samples are diluted 1/100 (minimum dilution) in sample diluent. Following a wash step, 100 µL of diluted sample is added to duplicate wells of the plate and incubated for two hours at 36-38 °C to allow for antibody binding to Mipomersen. Following incubation, plates are washed and Protein-A/G-HRP diluted in plate wash buffer is added and incubated for one hour at 36-38 °C. The presence of antibodies bound to Mipomersen is detected by adding TMB substrate and measuring absorbance at 450 nm with 650 nm reference. The intensity of the signal is proportional to the quantity of specific antibody present in the sample. Values are reported as OD after rounding to two digits after the decimal. Sample results will be evaluated as Negative or Reactive relative to the assay screening cut point. The specificity of any reactive samples will be confirmed in the non-radioactive immunoprecipitation assay. Confirmed samples will be titered in this assay and an end point titer, defined as the reciprocal of the last dilution above the titration cut point OD value, will be assigned and reported.

Review of ADA Binding Assay and its Validation

Sponsor provided validation protocols and data. Both the screening ELISA assay and the IP confirmation assay were validated for specificity, sensitivity, precision, and multiple other parameters. The assays specifically detect the drug, but not ODNs without 2-ME modifications. Another 2-ME modified ODN with different sequence moderately inhibited the binding of the drug.

The assay specifically detects anti-drug antibodies, but not other antibodies.

(b) (4)

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III. Clinical Binding ADA data

The product is very immunogenic in humans. Current available data show that 71 % patients (102/142, reported by Sponsor) were positive for ADA in the open label study CS6. The ADA response occurred later than for most therapeutic proteins, which are usually detected between 4-8 weeks. The number of patients positive for ADA went upward from 4% at 13 weeks, to 20% at 28 weeks and 33% at week 50 in treated arms while none of the patients in placebo groups were positive for ADA during the controlled Phase III studies. Many patients turned to ADA positive after 50 weeks in CS6 study. Most positive patients (89 patients in the 98 ADA+ in CS6 that had 138 individual ADA data reported) had increased titer or remain positive till the last test, and 45 patients (32%) had titers at or above 1:3200. The ADA response appears to be long lasting (some patients had been tested positive for more than 2 years already).

Binding ADA data from Controlled Phase III studies

Development of ADA in Mipomersen treated patients in controlled Phase III study

Controlled Phase III Studies (# of patients in Mipomersen groups)	Wk1 (Newly/Total)	Wks 13 (Newly/Total)	Wks 28 (Newly/Total)	Wks50 (Newly/Total)
CS5 (n= 34)	0/0	0/0	7/7	0/7
CS7 (n= 83)	1/1	7/8	18/26	14/40

CS12 (n= 105)	1/1	1/2	6/8	18/26
3500108 (n= 39)	0/0	0/0	9/9	5/14
ADA positive (%)	1 (1%)	3 (4%)	16 (20%)	14 (33%)

Based on ADA data from the following tables (Table 5-1):

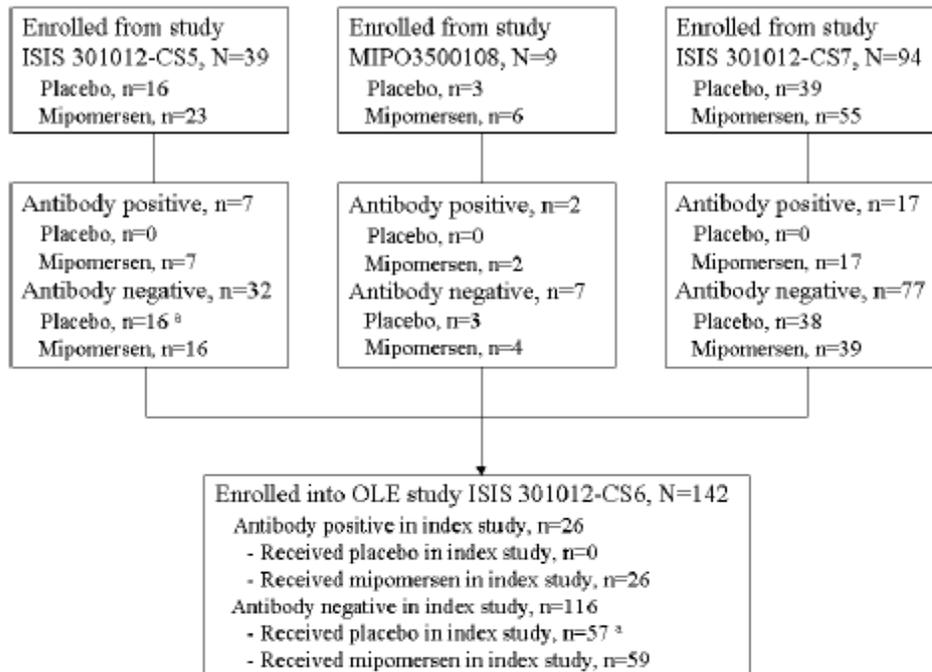
Table 5-1 Antibody Titers for Patients Who Tested Positive for Anti- Mipomersen Antibodies in Study ISIS 301012-CS7 – All Randomized Patients

Binding ADA data from Phase III Open Label study CS6

Based on the validated ADA binding ELISA, the following ADA data were provided for patients in the controlled CS5, then in Open –Label Study CS6 (Table 8-20 and Table 8-21) and summarized in table 1 after Figure 4-1.

Patient enrolment for Open-label study CS6 is provided as below:

Figure 4-1 Overview of Patient Enrolment from Index Studies into Open-Label Extension Study ISIS 301012-CS6



OLE, open-label extension

Antibody status determined by second generation assays for anti-mipomersen antibodies.

Patient 1506-7447 from study ISIS 301012-CS7 initially declined enrolment into the OLE study but subsequently enrolled after completing the follow-up period. Enrolment occurred after the database was locked for study ISIS 301012-CS7; therefore, this is not reflected in the final ISIS 301012-CS7 CSR.

Patient 1501-6035 from study ISIS 301012-CS5 enrolled into the OLE study but was never dosed in the OLE study; this patient tested positive for anti-mipomersen antibodies during the index study (ISIS 301012-CS5 Patient Number 1501-8377).

a. Patient 1536-6025, who received placebo during study ISIS 301012-CS5, did not have any post-treatment samples available. Since no other patients who received placebo during their index study developed anti-mipomersen antibodies during the course of their index study, this patient was presumed to be negative for anti-mipomersen antibodies upon entry into the OLE study.

Source: ISIS 301012-CS5 CSR Addendum (23 Feb 2012), MIPO3500108 CSR Addendum 2, and ISIS 301012-CS7 CSR Addendum 2

Table 1. ADA Binding Data of Patients enrolled in CS5, then CS6 open-label study.

Controlled Phase III study CS5	ADA status	# of Patients	ADA in CS6	ADA Positive in CS6 (% of Index Groups)	ADA Positive in CS6 (all patients)
Mipomersen	Positive	7	16	47%	50% (26/51)
	Negative	27	18	(16/34)	
Placebo	Positive	0	10	59%	

	Negative	17	7	(10/17)	
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Binding ADA Data of Open-label Study CS6 from Second Generation Assay

Controlled Phase III studies	ADA status	# of Patients	ADA in CS6	ADA Positive in CS6 (% of Index Groups)	ADA Positive in CS6 (all patients)
Mipomersen	Positive	26	65	76%	71% (98/138)
	Negative	59	20	(65/85)	
Placebo	Positive	0	33	60%	
	Negative	53	20	(33/53)	

IV. Impact of ADA on Efficacy and Safety

The impact of the ADA on efficacy and safety has been evaluated on the following aspects:

1. LDL-C, the primary efficacy endpoint

Sponsor presented data suggest that Mipomersen reduced LDL-C by 25-30% on average (Table 6) and ADA has no impact on the 25-30% reduction of LDL-C and ApoB levels during controlled study CS5 (Table 22) and Open-label study CS6 (Table 23). However, there was high drop-out in the analysis with fewer than 10 patients per arm left after 52 weeks. The level of attrition is uncommon.

Table 6: Summary of Efficacy Findings in Pivotal and Supportive Studies (Gravimetric Units) – Full Analysis Set

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

Table 22: Comparison of Efficacy Between Patients Who Tested Positive for Anti- Mipomersen Antibodies and Those Who Remained Negative for Anti-Mipomersen Antibodies in ISIS 301012-CS5 (Gravimetric Units) – Safety Set

Parameter Time Point	Antibody Positive Patients			Antibody Negative Patients		
	n	Level Mean (SD)	% Change from Baseline Mean (95% CI)	n	Level Mean (SD)	% Change from Baseline Mean (95% CI)
Low-Density Lipoprotein Cholesterol (mg/dL)						
Baseline	11	440.64 (139.84)	--	22	437.32 (144.35)	--
Week 28	11	294.09 (118.63)	-36.4 (-47.3, -14.3)	17	326.65 (129.53)	-24.24 (-33.5, -14.9)

Apolipoprotein B (mg/dL)						
Baseline	11	292.23 (65.93)	--	22	278.77 (86.80)	--
Week 28	11	195.91 (72.21)	-33.27 (-46.9, -19.6)	17	202.53 (74.23)	-26.22 (-34.1, -18.3)

CI, confidence interval; SD, standard deviation

Source: [TE-LDL-APOB-OT-ABNEG-GR-CS5](#) and [TE-LDL-APOB-OT-ABPOS-GR-CS5](#)

No difference in ApoB reduction was evident in ADA+ patients

Table 23: Comparison of Efficacy Between Patients Who Tested Positive for Anti-Mipomersen Antibodies and Those Who Remained Negative for Anti-Mipomersen Antibodies in ISIS 301012-CS6 (Gravimetric Units) – Safety Set

Parameter Time Point	Antibody Positive Patients			Antibody Negative Patients		
	n	Level Mean (SD)	% Change from Baseline Mean (95% CI)	n	Level Mean (SD)	% Change from Baseline Mean (95% CI)
Low-Density Lipoprotein Cholesterol (mg/dL)						
Baseline	26	443.7 (139.9)	--	12	369.1 (151.2)	--
Week 26	23	346.5 (110.1)	-24.91 (-32.4, -17.5)	9	310.8 (110.4)	-25.48 (-34.2, -13.9)
Week 52	22	345.4 (118.0)	-25.82 (-34.5, -17.1)	5	321.8 (175.4)	-19.80 (-41.3, 1.7)
Week 76	7	345.9 (174.9)	-29.53 (-57.0, -2.1)	4	237.8 (132.4)	-31.56 (-64.5, 1.4)
Week 104	2	308.5 (81.3)	-31.89 (-390.3, 326.5)	1	147.0	-51.64
Week 130	2	417.5 (143.5)	-14.59 (-43.2, 14.1)	1	204.0	-32.89
Apolipoprotein B (mg/dL)						
Baseline	26	290.5 (81.2)	--	12	235.7 (81.3)	--
Week 26	23	220.2 (67.7)	-27.17 (-34.2, -20.1)	9	191.8 (53.9)	-25.23 (-32.5, -17.9)
Week 52	22	222.8 (78.2)	-26.11 (-35.8, -16.5)	5	194.7 (88.4)	-20.73 (-34.8, -6.7)
Week 76	7	215.3 (93.5)	-34.43 (-56.9, -12.0)	4	151.3 (68.1)	-28.83 (-53.3, -4.4)
Week 104	2	182.5 (47.4)	-38.89 (-360.2, 282.5)	1	91.0	-49.16
Week 130	3	271.7 (65.4)	-25.84 (-44.3, -7.4)	1	107.0	-40.22

CI, confidence interval; SD, standard deviation

Data are from patients who enrolled from index study ISIS 301012-CS5.

Source: [TE-LDL-APOB-OT-ABNEG-GR-CS6](#) and [TE-LDL-APOB-OT-ABPOS-GR-CS6](#)

At Week 130, no reduction of LDL-C (443 vs 417) and ApoB (290 vs 271) were showed in ADA positive group when compared to baseline.

2. Cardiovascular events that the drug intended to reduce or prevent

The potential benefit of the drug is to reduce cardiovascular events in indicated patient population as the drug reduced LDL-C levels in treated patients. However, this health benefit may not be materialized in a short term due to the cardiovascular events occur in patients over the observed term at current dose.

Table 6-4 showed that there were many SAEs of the cardiovascular system during Open-label study CS6. The question is whether they were more than that of the indicated

patient population. Since it was an open-label study, the best available data for comparison is the data of patients in the placebo groups of the controlled phase III studies. Table 16 listed SAEs of patients in placebo group and Mipomersen group. These SAEs were far less than that of the open label study CS6 (Figure 1).

Table 6-4 Listing of Treatment-Emergent Serious Adverse Events in the Open-label Treatment Extension Study (ISIS 301012-CS6)

Patient Number	Adverse Event Preferred Term	Relationship to Study Drug	Severity	Led to Treatment Discontinuation
Treatment Assignment in Index Study: Mipomersen 200 mg				
1501-6022	Aortic valve stenosis	Not related	Severe	No
	Femoral artery occlusion	Not related	Severe	No
1501-6033	Aortic valve stenosis	Not related	Severe	No
1501-6037 [a]	Ankle fracture	Not related	Moderate	No
1503-6039 [b]	Basal cell carcinoma	Not related	Moderate	No
1505-6082	Rectal cancer	Not related	Moderate	No
	Gastrointestinal anastomotic leak	Not related	Severe	No
	Ileostomy	Not related	Moderate	No
1506-6130	Non-cardiac chest pain	Unlikely	Mild	No
	Glomerulonephritis membranous	Possible	Moderate	Yes
	Partial seizures	Possible	Moderate	No
1520-6097	Supraventricular tachycardia	Not related	Severe	No
1525-6001	Aortic stenosis	Not related	Severe	No
	Contrast media allergy	Not related	Severe	No
	Aortic stenosis	Not related	Severe	No
	Peripheral artery dissection	Not related	Severe	No
	Myocardial infarction	Not related	Severe	No
1534-6062	Angina pectoris	Not related	Moderate	No
	Non-cardiac chest pain	Not related	Mild	No
	Pyrexia	Not related	Moderate	No
	Cardiac failure congestive	Not related	Mild	No
1571-6098	Syncope	Not related	Severe	No
1574-6077	Influenza	Unlikely	Severe	No
	Atrial fibrillation	Possible	Moderate	No

Patient Number	Adverse Event Preferred Term	Relationship to Study Drug	Severity	Led to Treatment Discontinuation
1574-6112	Arachnoid cyst	Unlikely	Severe	No
	Extradural haematoma	Not related	Severe	No
1585-6107	Dehydration	Not related	Moderate	No
1587-6111	Neck pain	Not related	Mild	No

1589-6128 [c]	Acute myocardial infarction	Unlikely	Severe	No
1589-6134	Breast cancer	Unlikely	Moderate	No
1590-6121	Atrial fibrillation	Not related	Severe	No
1597-6029	Coronary artery restenosis	Not related	Moderate	No
	Dyspnoea	Not related	Moderate	No
	Coronary artery disease	Not related	Moderate	No
	Angina unstable	Not related	Severe	No
1597-6057	Angina pectoris	Not related	Moderate	No
1664-6123	Syncope	Not related	Mild	No
1689-6141 [d]	Cardiac discomfort	Not related	Severe	No

Patient Number	Adverse Event Preferred Term	Relationship to Study Drug	Severity	Led to Treatment Discontinuation
Treatment Assignment in Index Study: Placebo				
1501-6012	Angina unstable	Not related	Severe	No
	Chest pain	Not related	Moderate	No
1503-6038	Amnesia	Not related	Mild	No
1503-6040	Coronary artery disease	Not related	Severe	No
1506-6056	Aortic aneurysm	Unlikely	Moderate	No
1506-6146	Atrial fibrillation	Not related	Moderate	No
1523-6053	Angina pectoris	Not related	Mild	No
	Biliary colic	Possible	Moderate	Yes
	Angina pectoris	Not related	Severe	Yes
1574-6101	Diverticulum intestinal	Not related	Moderate	No
1575-6073	Dementia Alzheimer's type	Not related	Severe	Yes
1578-6117	Alcoholism	Not related	Moderate	Yes
	Non-cardiac chest pain	Not related	Severe	No
1578-6142	Acute myocardial infarction	Not related	Severe	No
	Non-cardiac chest pain	Not related	Severe	No
	Coronary artery disease	Not related	Severe	No
1589-6115	Splenic haemorrhage	Not related	Severe	No
1610-6043	Appendicitis	Possible	Severe	No

Source: [ISIS 301012-CS6 CSR Statistical Listing 16.2.7.5 Spring 2012 Analysis](#)

Note: data are presented as of database cut-off of 30 March 2012.

[a] This event occurred in study ISIS 301012-CS5 and was included in this extension study due to the patient's treatment gap (<6 months).

[b] This event occurred in study ISIS 301012-CS7 and was included in this extension study due to the patient's treatment gap (<6 months).

[c] This event occurred in study ISIS 301012-CS7 and was included in this extension study due to the patient's treatment gap (<6 months).

[d] This event occurred in study MIPO3500108 and was included in this extension study due to the patient's treatment gap (<6 months).

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The numbers of patients with on-treatment SAEs in the 6-month treatment period for the pooled Phase 3 studies are displayed in Table 16. 8% (21/261) of mipomersen-treated patients and 5.4% (7/129) of placebo-treated patients experienced at least one SAE. Similar to results across the mipomersen programs, the most frequently reported SAEs reported were classified as cardiac disorder by the Sponsor, but actually was cardiovascular disorders, occurring in 5.3% (14/261) of mipomersen-treated patients and 3.9% (5/129) of placebo-treated patients. With the exception of acute Myocardial infarction (2 mipomersen-treated patients, 1 placebo-treated patient), Angina pectoris (3 mipomersen-treated patients, 0 placebo-treated patients), Angina unstable (2 mipomersen-treated patients; 0 placebo-treated patients), and Non-cardiac chest pain (2 mipomersen-treated patients; 1 placebo-treated patient), all other SAEs were single events experienced by 1 patient each in one or both groups. *Although these types of SAEs were not unexpected given the medical history of the patient populations, there was a slight increase of cardiovascular SAEs in Mipomersen group in the index study. In comparing to the data of the index studies listed in Table 16, the incidence of cardiovascular SAEs in the open-label study CS6 was higher*

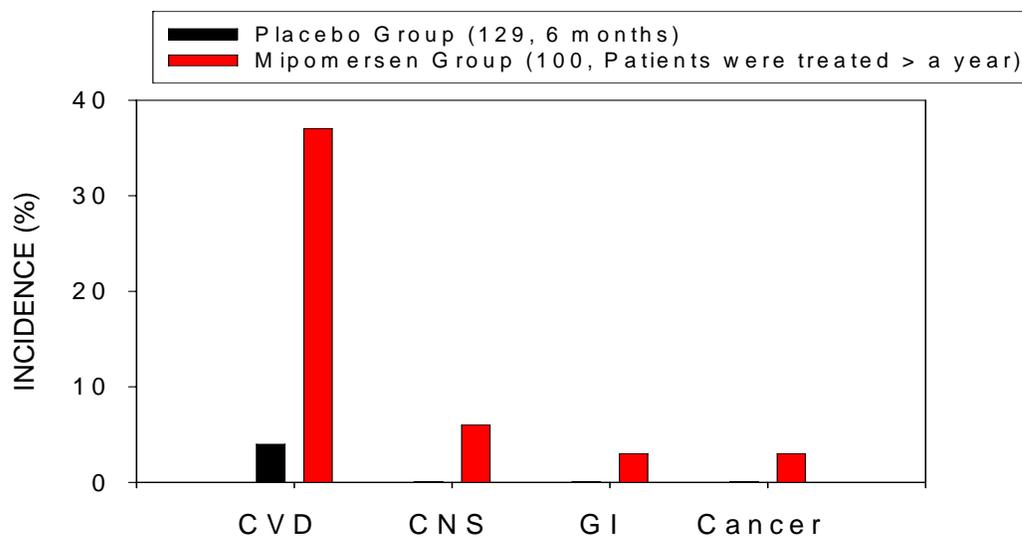
Table 16: On-Treatment Serious Adverse Events by System Organ Class and Preferred Term for Pooled Phase 3 Placebo-Controlled Studies

System Organ Class Preferred Term	Placebo (N=129)	Mipomersen (N=261)
Any AE, n (%)	7 (5.4)	21 (8.0)
Cardiac disorders	4 (3.1)	10 (3.8)
Acute myocardial infarction	1 (0.8)	2 (0.8)
Angina pectoris	0 (0.0)	3 (1.1)
Acute coronary syndrome	1 (0.8)	1 (0.4)
Angina unstable	0 (0.0)	2 (0.8)
Coronary artery disease	1 (0.8)	1 (0.4)

System Organ Class Preferred Term	Placebo (N=129)	Mipomersen (N=261)
Cardiac failure	0 (0.0)	1 (0.4)
Cardiogenic shock	1 (0.8)	0 (0.0)
Prinzmetal angina	0 (0.0)	1 (0.4)
Supraventricular tachycardia	1 (0.8)	0 (0.0)
General disorders and administration site conditions	1 (0.8)	4 (1.5)
Non-cardiac chest pain	1 (0.8)	2 (0.8)
Chest pain	0 (0.0)	1 (0.4)
Device malfunction	0 (0.0)	1 (0.4)
Hepatobiliary disorders	0 (0.0)	1 (0.4)
Hepatic steatosis	0 (0.0)	1 (0.4)
Injury, poisoning and procedural complications	0 (0.0)	1 (0.4)

Ankle fracture	0 (0.0)	1 (0.4)
Investigations	1 (0.8)	1 (0.4)
Alanine aminotransferase increased	0 (0.0)	1 (0.4)
Aspartate aminotransferase increased	0 (0.0)	1 (0.4)
Electrocardiogram abnormal	1 (0.8)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	2 (0.8)
Basal cell carcinoma	0 (0.0)	1 (0.4)
Non-small cell lung cancer	0 (0.0)	1 (0.4)
Nervous system disorders	0 (0.0)	1 (0.4)
Hypoaesthesia	0 (0.0)	1 (0.4)
Renal and urinary disorders	1 (0.8)	0 (0.0)
Nephrolithiasis	1 (0.8)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	1 (0.8)	1 (0.4)
Dyspnoea exertional	1 (0.8)	0 (0.0)
Pulmonary embolism	0 (0.0)	1 (0.4)
Vascular disorders	0 (0.0)	1 (0.4)
Hypertension	0 (0.0)	1 (0.4)

Figure 1. SAEs in Placebo group (Index Study) and Mipomersen treated group (CS6)



Some patients had 2-3 SAEs.

3 patients in CNS group were also included in CVD (cardiovascular disease) group due to both CNS and CVD SAEs.

44 patients in CS6 were treated less than a year and were removed from the data presented.

The figure indicates that there were increased cardiovascular SAEs in the open label study CS6 comparing to that of placebo treated patients in controlled phase III studies .

Trough and ADA titer relationship

Sponsor proposed that there was a correlation between on-board drug levels and ADA. However, the correlation was not very strong. 71% patients were positive for ADA.

Anti-Mipomersen Antibody (ADA) Status in Highest Trough (HHT), High Trough (HT), and Normal Trough (NT) Patients in the Pooled Phase 3 and ISIS 301012-CS6 Studies

In the pooled Phase 3 studies, there were 7 HHT patients and 22 of 35 HT patients that were reported as antibody-positive for anti-mipomersen antibodies. The majority of NT patients were ADA negative.

There were more ADA positive patients in the OLE study ISIS-301012-CS6. All of the HHT and the majority of HT patients are antibody positive although there were a few antibody negative HT patients. 38% NT patients were negative for ADA. A summary of HT patients (including HHT patients) and their anti-mipomersen antibody status is provided by Sponsor in Table 9-11.

Although the Sponsor suggested that there were a weak correlation between the titer of ADA and the trough levels, it was not linear.

Table 9-11 Summary of Number of Highest Trough (HHT), High Trough (HT), and Normal Trough Patients and their Anti-mipomersen-antibody (ADA) Status in the Pooled Phase 3 and ISIS 301012-CS6 Studies

Study	ADA Status	Trough Status		
		HHT (n=7)	HT (n=35)	NT (n=152)
Pooled Phase 3 Population	Positive (n, %)	7 (100.0)	22 (62.9)	54 (35.5)
	Negative (n, %)	0	13 (37.1)	98 (64.5)
ISIS 301012-CS6		HHT (n=24)	HT (n=57)	NT (n=65)
	Positive (n, %)	24 (100.0)	51 (89.5)	40 (61.5)

Treatment-Emergent Adverse Events as Grouped by Trough levels in Open-label Study CS6

Table 9-6 showed that there were more treatment emergent adverse events in HHT and HT groups in comparison to that of NT group. *Although there were 62% NT patients positive for ADA, all HHT and 90% HT were positive for ADA, it is yet clear whether those increased events were due to ADA, or more likely due to the higher levels in drug in the circulation.*

Table 9-6 Treatment-Emergent Adverse Events in $\geq 5\%$ of Highest Trough (HHT), High Trough (HT), and Normal Trough (NT) Patients in Study ISIS 301012-CS6

System Organ Class Preferred Term	HHT Patients (N=24)	HT Patients (N=57)	NT Patients (N=65)
Upper respiratory tract infection	5 (20.8)	11 (19.3)	12 (18.5)
Urinary tract infection	3 (12.5)	9 (15.8)	11 (16.9)
Influenza	6 (25.0)	8 (14.0)	7 (10.8)
Sinusitis	3 (12.5)	8 (14.0)	8 (12.3)
Bronchitis	1 (4.2)	3 (5.3)	2 (3.1)
Gastrointestinal disorders	15 (62.5)	32 (56.1)	36 (55.4)
Nausea	6 (25.0)	17 (29.8)	17 (26.2)
Abdominal pain	4 (16.7)	8 (14.0)	5 (7.7)
Diarrhoea	3 (12.5)	7 (12.3)	10 (15.4)
Abdominal pain upper	2 (8.3)	5 (8.8)	1 (1.5)
Constipation	2 (8.3)	4 (7.0)	2 (3.1)
Vomiting	0 (0.0)	4 (7.0)	8 (12.3)
Diverticulum intestinal	2 (8.3)	3 (5.3)	0 (0.0)
Haemorrhoids	2 (8.3)	2 (3.5)	0 (0.0)
Musculoskeletal and connective tissue disorders	15 (62.5)	32 (56.1)	31 (47.7)
Myalgia	8 (33.3)	14 (24.6)	11 (16.9)
Back pain	2 (8.3)	10 (17.5)	9 (13.8)
Arthralgia	2 (8.3)	7 (12.3)	8 (12.3)
Muscle spasms	3 (12.5)	5 (8.8)	2 (3.1)
Pain in extremity	1 (4.2)	4 (7.0)	7 (10.8)
Arthritis	0 (0.0)	3 (5.3)	1 (1.5)
Musculoskeletal pain	2 (8.3)	3 (5.3)	4 (6.2)
Musculoskeletal stiffness	2 (8.3)	3 (5.3)	2 (3.1)
Neck pain	1 (4.2)	3 (5.3)	2 (3.1)
Investigations	12 (50.0)	30 (52.6)	26 (40.0)
Alanine aminotransferase increased	3 (12.5)	10 (17.5)	11 (16.9)
Aspartate aminotransferase increased	3 (12.5)	9 (15.8)	10 (15.4)
Carotid bruit	1 (4.2)	4 (7.0)	0 (0.0)
Hepatic enzyme increased	2 (8.3)	4 (7.0)	2 (3.1)
Blood creatinine increased	2 (8.3)	3 (5.3)	2 (3.1)
Cardiac murmur	1 (4.2)	3 (5.3)	0 (0.0)

Platelet count decreased	2 (8.3)	3 (5.3)	1 (1.5)
Red blood cells urine positive	2 (8.3)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	7 (29.2)	26 (45.6)	18 (27.7)
Procedural pain	3 (12.5)	6 (10.5)	3 (4.6)
Laceration	1 (4.2)	5 (8.8)	0 (0.0)

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Table 9-6 Treatment-Emergent Adverse Events in $\geq 5\%$ of Highest Trough (HHT), High Trough (HT), and Normal Trough (NT) Patients in Study ISIS 301012-CS6

System Organ Class Preferred Term	HHT Patients (N=24)	HT Patients (N=57)	NT Patients (N=65)
Contusion	1 (4.2)	4 (7.0)	3 (4.6)
Post-traumatic pain	1 (4.2)	3 (5.3)	0 (0.0)
Thermal burn	0 (0.0)	3 (5.3)	1 (1.5)
Nervous system disorders	11 (45.8)	26 (45.6)	28 (43.1)
Headache	4 (16.7)	14 (24.6)	16 (24.6)
Dizziness	4 (16.7)	6 (10.5)	3 (4.6)
Tremor	3 (12.5)	5 (8.8)	3 (4.6)
Syncope	2 (8.3)	4 (7.0)	1 (1.5)
Hypoaesthesia	1 (4.2)	1 (1.8)	4 (6.2)
Respiratory, thoracic and mediastinal disorders	12 (50.0)	25 (43.9)	22 (33.8)
Dyspnoea	3 (12.5)	8 (14.0)	2 (3.1)
Cough	3 (12.5)	6 (10.5)	6 (9.2)
Oropharyngeal pain	3 (12.5)	6 (10.5)	5 (7.7)
Epistaxis	2 (8.3)	3 (5.3)	1 (1.5)
Rhinorrhoea	1 (4.2)	3 (5.3)	4 (6.2)
Upper respiratory tract congestion	0 (0.0)	3 (5.3)	1 (1.5)
Sinus congestion	1 (4.2)	2 (3.5)	4 (6.2)
Skin and subcutaneous tissue disorders	9 (37.5)	19 (33.3)	14 (21.5)
Urticaria	2 (8.3)	4 (7.0)	1 (1.5)
Ecchymosis	1 (4.2)	3 (5.3)	0 (0.0)
Pruritus	3 (12.5)	3 (5.3)	2 (3.1)
Skin lesion	2 (8.3)	3 (5.3)	1 (1.5)
Skin plaque	2 (8.3)	2 (3.5)	0 (0.0)
Vascular disorders	9 (37.5)	17 (29.8)	7 (10.8)
Hypertension	5 (20.8)	6 (10.5)	0 (0.0)
Hot flush	2 (8.3)	4 (7.0)	0 (0.0)
Flushing	2 (8.3)	3 (5.3)	0 (0.0)
Aortic aneurysm	2 (8.3)	2 (3.5)	0 (0.0)
Cardiac disorders	5 (20.8)	16 (28.1)	18 (27.7)
Atrial fibrillation	2 (8.3)	4 (7.0)	3 (4.6)
Coronary artery disease	1 (4.2)	4 (7.0)	1 (1.5)

Angina pectoris	0 (0.0)	2 (3.5)	11 (16.9)
Blood and lymphatic system disorders	6 (25.0)	11 (19.3)	2 (3.1)
Anaemia	4 (16.7)	6 (10.5)	1 (1.5)
Thrombocytopenia	2 (8.3)	4 (7.0)	0 (0.0)

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Table 9-6 Treatment-Emergent Adverse Events in $\geq 5\%$ of Highest Trough (HHT), High Trough (HT), and Normal Trough (NT) Patients in Study ISIS 301012-CS6

System Organ Class Preferred Term	HHT Patients (N=24)	HT Patients (N=57)	NT Patients (N=65)
Eye disorders	2 (8.3)	10 (17.5)	7 (10.8)
Cataract	0 (0.0)	3 (5.3)	1 (1.5)
Hepatobiliary disorders	3 (12.5)	10 (17.5)	6 (9.2)
Hepatic steatosis	2 (8.3)	8 (14.0)	5 (7.7)
Hepatomegaly	2 (8.3)	4 (7.0)	2 (3.1)
Metabolism and nutrition disorders	4 (16.7)	10 (17.5)	4 (6.2)
Dehydration	1 (4.2)	3 (5.3)	0 (0.0)
Decreased appetite	2 (8.3)	2 (3.5)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (12.5)	8 (14.0)	5 (7.7)
Seborrhoeic keratosis	0 (0.0)	3 (5.3)	0 (0.0)
Psychiatric disorders	4 (16.7)	8 (14.0)	12 (18.5)
Depression	1 (4.2)	4 (7.0)	3 (4.6)
Anxiety	2 (8.3)	3 (5.3)	2 (3.1)
Insomnia	1 (4.2)	2 (3.5)	4 (6.2)
Renal and urinary disorders	3 (12.5)	8 (14.0)	8 (12.3)
Dysuria	1 (4.2)	3 (5.3)	1 (1.5)
Pollakiuria	2 (8.3)	3 (5.3)	1 (1.5)
Proteinuria	1 (4.2)	3 (5.3)	2 (3.1)

Source: [IMPk-TS-TEAE-HHT-6S12](#); [IMPk-TS-TEAE-HT-6S12](#); [IMPk-TS-TEAE-NT-6S12](#)

Note 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.

Note 2: To obtain the number of patients, 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.

Note 3: Patient percentages are based on the total number of treated patients in the particular treatment group.

	Negative (n, %)	0	6 (10.5)	25 (38.5)
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Note: Patients with either unknown ADA status or trough status are not presented in this table. HHT=highest trough; HT=high trough; NT=normal trough; ADA=anti-mipomersen-antibody

Source: [IMPK-TS-CROSSTAB-AB-TROUGH-FSPDAP3](#); [IMPK-TS-CROSSTAB-AB-TROUGH-6S12](#)

Several AE were more frequent among HHT patients including vascular events, anemia, and neoplasms.

Treatment-Emergent Adverse Events as Grouped by Trough levels in Phase III Controlled Studies

There were hardly any cardiovascular AEs in the controlled studies listed in Table 9-1, which is in contrast with the data presented in Table 9-6 of the open label study CS6. Comparing data of Table 9-1 and data of Table 9-6, the logic seems that it was a progressive process for those cardiovascular SAEs. This concept is inline with the cardiovascular finding of monkeys.

Table 9-1 On-Treatment Adverse Events in $\geq 5\%$ of Highest Trough (HHT), High Trough (HT), and Normal Trough (NT) Patients in the Pooled Phase 3 Placebo- Controlled Studies

System Organ Class Preferred Term	HHT Patients (N=7)	HT Patients (N=35)	NT Patients (N=153)
Dyspepsia	1 (14.3)	1 (2.9)	4 (2.6)
Musculoskeletal and connective tissue disorders	6 (85.7)	14 (40.0)	37 (24.2)
Myalgia	2 (28.6)	4 (11.4)	8 (5.2)
Pain in extremity	2 (28.6)	4 (11.4)	10 (6.5)
Arthralgia	0 (0.0)	3 (8.6)	4 (2.6)
Muscle spasms	1 (14.3)	3 (8.6)	1 (0.7)
Musculoskeletal pain	2 (28.6)	3 (8.6)	4 (2.6)
Back pain	0 (0.0)	1 (2.9)	8 (5.2)
Bursitis	1 (14.3)	1 (2.9)	0 (0.0)
Fibromyalgia	1 (14.3)	1 (2.9)	0 (0.0)
Infections and infestations	3 (42.9)	12 (34.3)	52 (34.0)
Nasopharyngitis	1 (14.3)	4 (11.4)	12 (7.8)
Sinusitis	1 (14.3)	2 (5.7)	1 (0.7)
Upper respiratory tract infection	1 (14.3)	2 (5.7)	11 (7.2)
Urinary tract infection	2 (28.6)	2 (5.7)	13 (8.5)
Influenza	0 (0.0)	1 (2.9)	10 (6.5)
Investigations	1 (14.3)	10 (28.6)	42 (27.5)
Alanine aminotransferase increased	0 (0.0)	3 (8.6)	11 (7.2)
Aspartate aminotransferase increased	0 (0.0)	3 (8.6)	5 (3.3)
Hepatic enzyme increased	1 (14.3)	2 (5.7)	4 (2.6)
Liver function test abnormal	0 (0.0)	0 (0.0)	8 (5.2)
Nervous system disorders	4 (57.1)	8 (22.9)	39 (25.5)
Headache	2 (28.6)	5 (14.3)	18 (11.8)
Dizziness	1 (14.3)	2 (5.7)	8 (5.2)
Syncope	2 (28.6)	2 (5.7)	2 (1.3)

Paraesthesia	1 (14.3)	1 (2.9)	3 (2.0)
Respiratory, thoracic and mediastinal disorders	4 (57.1)	7 (20.0)	25 (16.3)
Oropharyngeal pain	2 (28.6)	2 (5.7)	7 (4.6)
Increased upper airway secretion	1 (14.3)	1 (2.9)	0 (0.0)
Rhinorrhoea	1 (14.3)	1 (2.9)	2 (1.3)
Cough	0 (0.0)	0 (0.0)	10 (6.5)
Injury, poisoning and procedural complications	3 (42.9)	6 (17.1)	22 (14.4)
Fall	1 (14.3)	3 (8.6)	0 (0.0)
Fibula fracture	1 (14.3)	1 (2.9)	0 (0.0)

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Table 9-1 On-Treatment Adverse Events in $\geq 5\%$ of Highest Trough (HHT), High Trough (HT), and Normal Trough (NT) Patients in the Pooled Phase 3 Placebo- Controlled Studies

System Organ Class Preferred Term	HHT Patients (N=7)	HT Patients (N=35)	NT Patients (N=153)
Muscle strain	1 (14.3)	1 (2.9)	1 (0.7)
Wound	1 (14.3)	1 (2.9)	0 (0.0)
Cardiac disorders	1 (14.3)	5 (14.3)	15 (9.8)
Palpitations	1 (14.3)	1 (2.9)	5 (3.3)
Hepatobiliary disorders	0 (0.0)	4 (11.4)	13 (8.5)
Hepatic steatosis	0 (0.0)	3 (8.6)	11 (7.2)
Psychiatric disorders	1 (14.3)	4 (11.4)	14 (9.2)
Insomnia	1 (14.3)	2 (5.7)	2 (1.3)
Immune system disorders	1 (14.3)	3 (8.6)	3 (2.0)
Seasonal allergy	1 (14.3)	1 (2.9)	2 (1.3)
Vascular disorders	1 (14.3)	3 (8.6)	20 (13.1)
Hypertension	0 (0.0)	1 (2.9)	12 (7.8)
Hypotension	1 (14.3)	1 (2.9)	2 (1.3)
Blood and lymphatic system disorders	1 (14.3)	2 (5.7)	9 (5.9)
Anaemia	1 (14.3)	2 (5.7)	5 (3.3)

Source: [IMPk-TS-OTAE-HHT-FSPDAP3](#); [IMPk-TS-OTAE-HT-FSPDAP3](#); and [IMPk-TS-OTAE-NT-FSPDAP3](#)

Note 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.

Note 2: To obtain the number of patients, 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.

Note 3: Patient percentages are based on the total number of treated patients in the particular treatment group.

Circulating Immune Complex and AEs in Phase III Open-label Study CS6

Sponsor provided another line of supportive data (Table 11-11 and Table 4) showing that by forming immune complex (No assay information was provided), potentially ADA-drug in group -/+ may associate with more AEs. In fact, there were more cardiovascular AEs in circulating immune complex -/+ group in comparison to the CIC -/- group.

Table 11-11 Results of Circulating Immune Complex Assays for Patients in Study ISIS 301012-CS6

Patient Subgroup	Number of Patients (N=116)
CIC negative in all samples prior to the start of treatment and tested negative in all samples after the start of treatment (Neg/Neg)	90 (77.6 %)
CIC negative in all samples prior to the start of treatment and tested positive at any sample after the start of treatment (Neg/Pos)	15 (12.9 %)
CIC positive at any sample prior to the start of treatment and tested negative in all samples after the start of treatment (Pos/Neg)	2 (1.7 %)
CIC positive at any sample prior to the start of treatment and tested positive at any sample after the start of treatment (Pos/Pos)	9 (7.8 %)

Source: [Results of Circulating Immune Complex Testing in Patients Enrolled in the Open-label Treatment Extension Study ISIS 301012-CS6 and in ISIS 301012-CS5, ISIS 301012-CS7, MIPO3500108 Patients Who Enrolled in ISIS 301012-CS6 \(Appendix](#)

B). Neg=negative; Pos=positive

Circulating Immune Complex and Adverse Events in CS6 Open-label Study

Sponsor proposed a way of data analysis based on circulating Immune Complex results (no detailed method was provided for the testing).

Table 4. Cardiovascular adverse events

	CIC +/+ (n=9)	CIC -/+ (n=15)	CIC -/- (n=90)
Carotid bruit	0	2	2
Cardiac murmur	0	1	2
Acute Myocardial infarction	0	1	1
Atrial fibrillation	0	0	5
Coronary artery disease	1	1	3
Aortic valve stenosis	0	1	1
Aortic valve disease	0	1	0
Angina pectoris	1	0	9
Aortic valve incompetence	0	0	1
Cardiac failure congestive	0	0	1
Myocardial ischaemia	0	0	1
Aortic aneurysm	0	2	2
Aortic dilatation	0	1	1

Hypertension	0	3	1
Hypertension crisis	0	0	1
Aortic stenosis	0	1	0
Aortic calcification	0	1	0
Femoral artery occlusion	0	1	0
Vascular infarction	0	1	0
Subclavian artery stenosis	0	0	1
Peripheral vascular disorder	0	0	1
Total events	2 (/9)	17 (/15)	33 (/90)

There may be a higher incidence of cardiovascular events in CIC -/+ group, although its not clear that this is related to ADA or immune complexes

Antibody Responses and SAEs in Open-label Study CS6

ADA peak titer was entered by the Reviewer and not the sponsor.

Open-label Treatment Extension Study (ISIS 301012-CS6)

Patient Number	Adverse Event Preferred Term	ADA (peak titer, duration)	Severity	Led to Treatment Discontinuation
Treatment Assignment in Index Study: Mipomersen 200 mg				
1501-6022	Aortic valve stenosis	6400, 15 months	Severe	No
	Femoral artery occlusion		Severe	No
1501-6033	Aortic valve stenosis	100, 1 Time	Severe	No
1501-6037 [a]	Ankle fracture	800, 6months	Moderate	No
1503-6039 [b]	Basal cell carcinoma	-, Treated for 16months	Moderate	No
1505-6082	Rectal cancer	-, treated for 3yrs	Moderate	No
	Gastrointestinal anastomotic leak		Severe	No
	Ileostomy		Moderate	No
1506-6130	Non-cardiac chest pain	100. 1 Time	Mild	No
	Glomerulonephritis membranous		Moderate	Yes
	Partial seizures		Moderate	No
1520-6097	Supraventricular tachycardia	200, 1 Time	Severe	No
1525-6001	Aortic stenosis	200, 1 Time	Severe	No
	Contrast media allergy		Severe	No
	Aortic stenosis		Severe	No
	Peripheral artery dissection		Severe	No
	Myocardial infarction		Severe	No

1534-6062	Angina pectoris	-, treated for 3Yrs	Moderate	No
	Non-cardiac chest pain		Mild	No
	Pyrexia		Moderate	No
	Cardiac failure congestive		Mild	No
1571-6098	Syncope	1600, lasted for 2yrs	Severe	No
1574-6077	Influenza	3200, lasted for 32m	Severe	No

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Table 6-4 Listing of Treatment-Emergent Serious Adverse Events in the Open-label Treatment Extension Study (ISIS 301012-CS6)

Patient Number	Adverse Event Preferred Term	ADA (peak titer, duration)	Severity	Led to Treatment Discontinuation
1574-6112	Arachnoid cyst	-, treated for 27m	Severe	No
	Extradural haematoma		Severe	No
1585-6107	Dehydration	Not related	Moderate	No
1587-6111	Neck pain	Not related	Mild	No
1589-6128 [e]	Acute myocardial infarction	6400, lasted 6m	Severe	No
1589-6134	Breast cancer	400, lasted 7m	Moderate	No
1590-6121	Atrial fibrillation	1638400, lasted 26m	Severe	No
1597-6029	Coronary artery restenosis	12800, lasted 2yrs	Moderate	No
	Dyspnoea		Moderate	No
	Coronary artery disease		Moderate	No
	Angina unstable		Severe	No
1597-6057	Angina pectoris	200, lasted 6m	Moderate	No
1664-6123	Syncope	6400, lasted 11m	Mild	No
1689-6141 [d]	Cardiac discomfort	-, treated for 2Yrs	Severe	No

Table 6-4 Listing of Treatment-Emergent Serious Adverse Events in the Open-label Treatment Extension Study (ISIS 301012-CS6)

Patient Number	Adverse Event Preferred Term	ADA (peak titer, duration)	Severity	Led to Treatment Discontinuation
Treatment Assignment in Index Study: Placebo				
1501-6012	Angina unstable	200, lasted 15m	Severe	No
	Chest pain		Moderate	No
1503-6038	Amnesia	-, treated 2yrs	Mild	No
1503-6040	Coronary artery disease	3200, lasted 17m	Severe	No
1506-6056	Aortic aneurysm	6400, lasted 6M	Moderate	No
1506-6146	Atrial fibrillation	100, 1 Time	Moderate	No
1523-6053	Angina pectoris	-, treated 1Yr	Mild	No

	Biliary colic		Moderate	Yes
	Angina pectoris		Severe	Yes
1574-6101	Diverticulum intestinal	800, lasted 1 yr	Moderate	No
1575-6073	Dementia Alzheimer's type	-, 2 Times only	Severe	Yes
1578-6117	Alcoholism	-, 2 Times	Moderate	Yes
	Non-cardiac chest pain		Severe	No
1578-6142	Acute myocardial infarction	-, 3 Times	Severe	No
	Non-cardiac chest pain		Severe	No
	Coronary artery disease		Severe	No
1589-6115	Splenic haemorrhage	-, 2 Times, treated 6M	Severe	No
1610-6043	Appendicitis	102400, lasted 13M	Severe	No

The data show on this table indicate that although ADA were found in most patients, their presence was not closely tied to the incidence of SAEs.

For non-Ig protein therapeutics, ADA could usually increase the t1/2 of the product in circulation from hours to 20 days. The T1/2 of this product is less than 20 hours for single injection, but in repeated dose studies, the proposed T1/2 were from 15-40 days due to a persistent low levels of the drug in the circulation. Since the T1/2 is likely to be long in humans as well, and there were levels of drug in blood even at times of predose. Therefore, the vascular system was exposed to the drug 24/7, in the presence or absence of ADA.

3. Neoplasm

The clinical data indicate that all the ten patients reported to have neoplastic lesions were in the treated groups (4%, 10/251), but not in the placebo groups (0%, 0/120). *No data showed these lesions were related to ADA.*

In July 2012 updates, Sponsor reported that 16 patients (out of 142 patient enrolled) had found to have Neoplasms benign, malignant and unspecified (incl cysts and polyps), with 3 ADA positive (HHT group), 8 most likely to be ADA positive (HT group), and 5 in NT group that could be ADA positive. *Sponsor should report the types of neoplasms for each one and their ADA status.*

Carcinogenicity was evaluated in mice and rats for two years. Benign hepatocellular adenoma was increased in female mice at 60mg/kg/wk. Increased malignant fibrous histocytoma in both males and females at 10 and 20 mg/kg/wk, and malignant fibrosarcoma in females at 10 and 20 mg/kg/wk in rats were reported. No ADA data were available.

4. Hepatic Pathology/Function

Some patients developed hepatic steatosis (10%, 15/142) and hepatomegaly (5%, 8/142) in the Open-label study CS6. None was reported for placebo group (Table 16, page 18). CIC may or may not contribute to it.

	HHT	HT	NT
Hepatobiliary disorders	3 (12.5)	10 (17.5)	6 (9.2)
Hepatic steatosis	2 (8.3)	8 (14.0)	5 (7.7)
Hepatomegaly	2 (8.3)	4 (7.0)	2 (3.1)

ALT increased in 6/15 (40%) CIC +/-, 15/90 (17%) CIC -/-, and 1/9 CIC +/+ patients in CS6 study.

AST increased in 6/15 (40%) CIC +/-, 13/90 (14%) CIC -/-, and 1/9 CIC +/+ patients in CS6 study.

These data suggest that CIC or the drug itself may contribute to hepatic malfunction.

5. The relationship between ADA and SAE/Drop-out

The following analysis was provided for ADA and SAE/drop-out for Phase III Studies.

Patient disposition and demographics for antibody positive and negative mipomersen-treated patients in the pooled Phase 3 placebo-controlled studies are summarized in Table 6-9. The majority of antibody positive and antibody negative patients in the pooled Phase 3 studies completed treatment with mipomersen (81.7% and 71.6%, respectively). The most common reason for treatment discontinuation among antibody positive and negative patients was due to AEs or SAEs (16.1% and 19.4%, respectively).

Therefore, there were no differences between ADA positive and ADA negative patients as regard to completion of treatment and drop out in the controlled phase III studies.

Table 6-9 Patient Disposition for Antibody Positive and Negative Mipomersen-Treated Patients in the Pooled Phase 3 Placebo-Controlled Studies – Mipomersen-treated Patients in Safety Set

	Antibody Positive (N=93)	Antibody Negative (N=155)
Randomized, n	93	155
Treated, n (% of randomized)	93 (100.0)	155 (100.0)
Completed treatment, n (% of randomized)	76 (81.7)	111 (71.6)
Discontinued treatment, n (% of randomized)	17 (18.3)	44 (28.4)
Adverse Event or SAE	15 (16.1)	30 (19.4)
Withdrawal By Subject	2 (2.2)	8 (5.2)
Protocol Non-Compliance	0 (0.0)	2 (1.3)
Physician Decision	0 (0.0)	1 (0.6)
Other	0 (0.0)	3 (1.9)

Source [IMPK-TS-DISPOS-ABNEG-FSPDAP3](#); [IMPK-TS-DISPOS-ABPOS-FSPDAP3](#)

Really high drop-out rate, only 42% patients completed first 2 years study.

Table 4-1 Disposition of Patients as of 30 March 2012 – All Enrolled Patients

Patient Status	Total N=142 n (%)
Enrolled, n	142
Never treated, n (% of enrolled) ^a	1 (0.7)
Treated, n (% of enrolled)	141 (99.3)
Completed up to 2 years of initial treatment, n (% of treated)	60 (42.6)
Completed follow-up, n (% of treated)	23 (16.3)
Discontinued follow-up, n (% of treated)	20 (14.2)
AE or SAE	1 (0.7)
Other	19 (13.5)
Continuing follow-up, n (% of treated)	17 (12.1)
Discontinued prior to completing up to 2 years of initial treatment, n (% of treated)	79 (56.0)
AE or SAE	62 (44.0)
Lack of efficacy	2 (1.4)
Physician decision	2 (1.4)
Pregnancy	1 (0.7)
Withdrawal by patient	12 (8.5)
Completed follow-up, n (% of treated)	60 (42.6)
Discontinued follow-up, n (% of treated)	15 (10.6)
AE or SAE	3 (2.1)
Physician decision	2 (1.4)
Withdrawal by patient	7 (5.0)
Other	3 (2.1)
Continuing follow-up, n (% of treated)	4 (2.8)
Continuing up to 2 years of initial treatment, n (% of treated)	2 (1.4)
Consented to 2 years of additional treatment, n (% of treated)	41 (29.1)
Has not started 2 years of additional treatment, n (% of treated)	4 (2.8)
Completed up to 2 years of additional treatment, n (% of treated)	0 (0.0)
Completed follow-up, n (% of treated)	0 (0.0)

Discontinued follow-up, n (% of treated)	0 (0.0)
Continuing follow-up, n (% of treated)	0 (0.0)
Discontinued prior to completing up to 2 years of additional treatment, n (% of treated)	4 (2.8)
AE or SAE	3 (2.1)
Other	1 (0.7)
Completed follow-up, n (% of treated)	0 (0.0)
Discontinued follow-up, n (% of treated)	1 (0.7)
Other	1 (0.7)
Continuing follow-up, n (% of treated)	3 (2.1)
Continuing up to 2 years of additional treatment, n (% of treated)	33 (23.4)

AE, adverse event; SAE, serious adverse event

“Initial” treatment refers to the initial 2-year treatment period for the study. “Additional” treatment refers to the additional 2 years of treatment that were allowed as a result of Protocol Amendment 7 (18 May 2011) which resulted in a potential for 4 years of treatment in the study. Details regarding patient disposition prior to this addendum are available in the [ISIS 301012-CS6 CSR, Section 10.1](#) and [ISIS 301012-CS6 CSR Addendum \(29 February 2012\)](#).

- a One patient (Patient 1501-6035) enrolled in this study but was never dosed. Two patients (Patient 1534-6147 and Patient 1534-6148) who completed 3 years of dosing in study ISIS 301012-CS17 subsequently enrolled into ISIS 301012-CS6; these data are not included in the summary counts.

Source: [Table 14.1.2.1](#)

Patient Disposition and Demographics by Antibody Status in the Open Label Extension Study

Patient disposition and demographics for antibody positive and negative mipomersen-treated patients in the open-label extension study ISIS 301012-CS6 are summarized in Table 6-11.

As shown in Table 6-11, the percentages of antibody positive and antibody negative patients who completed 2 years of initial treatment with mipomersen were similar (44.6% and 37.5%, respectively). The most common reason for treatment discontinuation was due to AEs or SAEs that was 45.5% in the antibody positive group and was 40.0% in the antibody negative group.

Therefore, there are no statistically significant differences between ADA positive and ADA negative patients as to completion of first 2 years study and discontinuation of treatment in open label extension study.

Table 6-11 Patient Disposition for Antibody Positive and Negative Patients in the Open-label Treatment Extension Study (ISIS 301012-CS6) – Safety Set

	Antibody Positive (N=101)	Antibody Negative (N=40)
Enrolled, n	101	40

Treated, n (% of randomized)	101 (100.0)	40 (100.0)
Completed up to 2 years of initial treatment, n (% of randomized)	45 (44.6)	15 (37.5)
Completed follow-up, n (% of treated)	20 (19.8)	3 (7.5)
Discontinued follow-up, n (% of treated)	14 (13.9)	6 (15.0)
Adverse Event or SAE	0 (0.0)	1 (2.5)
Other	14 (13.9)	5 (12.5)
Continuing follow-up, n (% of treated)	11 (10.9)	6 (15.0)
Discontinued treatment, n (% of randomized)	55 (54.5)	24 (60.0)
Adverse Event or SAE	46 (45.5)	16 (40.0)
Lack of efficacy	1 (1.0)	1 (2.5)
Physician decision	1 (1.0)	1 (2.5)
Pregnancy	1 (1.0)	0 (0.0)
Withdrawal By Subject	6 (5.9)	6 (15.0)
Completed follow-up, n (% of treated)	45 (44.6)	15 (37.5)
Discontinued follow-up, n (% of treated)	6 (5.9)	9 (22.5)
Adverse Event or SAE	0 (0.0)	3 (7.5)
Physician decision	1 (1.0)	1 (2.5)
Withdrawal By Subject	2 (2.0)	5 (12.5)
Other	3 (3.0)	0 (0.0)
Continuing follow-up, n (% of treated)	4 (4.0)	0 (0.0)
Continuing up to 2 years of initial treatment, n (% of treated)	1 (1.0)	1 (2.5)
Consented to 2 years of additional treatment, n (% of treated)	29 (28.7)	12 (30.0)
Hasn't started 2 years of additional treatment, n (% of treated)	3 (3.0)	1 (2.5)

ADA status and patient drop-out in HoFH patients

Out of the 22 dropped out patients, 14 had a positive ADA response. The ratio of 14/22, or 64% is not more than the ADA response in CS6 open label study. Therefore, there was no clear correlation between ADA response and patient drop out in this patient population. Sponsor should report SAE and ADA data for other HoFH patients enrolled in CS6 study.

Mipomersen (ISIS 301012)

Clinical Study Report ISIS 301012-CS6 (HoFH Patients From CS5)

14.3.3 Narratives of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Patient Number	Reason for Narrative		
	ADA		Discontinuation Due to Adverse Event
1500-6031	+		X
1501-6010	+		X
1501-6012	+		X
1501-6013	+		X
1501-6015	+		X
1501-6016	+		X
1501-6017	+		X
1501-6018	+		X
1501-6020	+		X
1501-6021	+		X
1501-6022	+		X
1501-6033	+		X
1501-6036	+		X
1501-6037	+		X ^[a]
1505-6002	+		X
1505-6006	+		X
1523-6053	?	Death	X
1525-6001	?	Death	X
1530-6027	+		X
1535-6004	+		X
1535-6005	+		X
1536-6024	+		X

[a] The SAE of Ankle fracture occurred in study ISIS 301012-CS5. Therefore, the narrative for this event is presented in the ISIS 301012-CS5 CSR ([Patient 1501-8193](#)).

CSR = Clinical Study Report; SAE = serious adverse event.

Sources: [Data Listings 16.2.7.4](#), [16.2.7.5](#), and [16.2.7.6](#)

In summary, based on the current analysis of the impact of immunogenicity on efficacy and safety in CS6 study, the reviewer believes that a similar analysis should be done for all available HoFH patients in index studies and open label study for assessing approvability of the product for HoFH indication.

6. Impact of ADA on Flu-like syndrome, liver enzymes, and LDL-C

In a lately update, sponsor provided the impact of ADA on several parameters in the index studies and CS6 open label study. There were more flu-like illness in ADA positive patients, especially in the open-label study (CS6), whereas the data of liver enzymes were not different between groups. Although LDL-C value reduced in both ADA positive group and ADA negative group when comparing to that of baseline, but the percent reductions of LDL-C in ADA positive group at different times were less than that of ADA negative patients. The data of HoFH patients, the indicated patient population were not provided.

Table 21-5: Incidence of Flu-Like Symptoms by Antibody Status in the Pooled Phase 3 Studies and Open-Label Extension Study

Flu-Like Symptom Event	Pooled Phase 3 Studies				Open-Label Extension Study			
	Antibody-Positive (N=93)		Antibody-Negative (N=155)		Antibody-Positive (N=101)		Antibody-Negative (N=40)	
	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)
Patients with events	97	36 (38.7)	116	39 (25.2)	379	72 (71.3)	64	21 (52.5)
Influenza like illness	26	15 (16.1)	44	15 (9.7)	158	47 (46.5)	38	10 (25.0)
Fatigue	25	14 (15.1)	35	14 (9.0)	75	29 (28.7)	3	3 (7.5)
Chills	15	8 (8.6)	11	7 (4.5)	87	20 (19.8)	2	2 (5.0)
Pyrexia	10	6 (6.5)	13	8 (5.2)	18	13 (12.9)	13	7 (17.5)
Malaise	0	0 (0.0)	1	1 (0.6)	2	2 (2.0)	0	0 (0.0)
Myalgia	15	8 (8.6)	7	6 (3.9)	34	21 (20.8)	6	4 (10.0)
Arthralgia	6	2 (2.2)	5	2 (1.3)	5	5 (5.0)	2	2 (5.0)

Data cutoff dates for the OLE study were 02 March 2012 for antibody data and 30 March 2012 for safety data.

On-treatment adverse events (pooled Phase 3 studies) were defined as adverse events that started during the treatment period. The treatment period spanned the time during which the study treatment was 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.

Treatment-emergent adverse events (OLE study) were those adverse events with start dates/times on or after the date/time of the first study drug dose.

To obtain the number of patients, if a patient had more than one event within a particular adverse event category or preferred term, he/she was counted only once for an adverse event category or preferred term.

Patient percentages were based on the total number of mipomersen-treated patients who had post-baseline antibody data.

Patients were classified as 'Antibody-negative' if all samples post-baseline were negative. Patients were classified as 'Antibody-positive' if at least one sample post-baseline was positive.

Source: [IMPK-TS-OTAE-FLU-ABTITER-FSPDAP3.rtf](#) and [IMPK-TS-TEAE-FLU-ABTITER-6S12.rtf](#)

Table 21-6: Incidence of Adverse Events Associated with Elevations in Liver Enzymes by Antibody Status in the Pooled Phase 3 Studies and Open-Label Extension Study

Elevated Liver Enzyme Event	Pooled Phase 3 Studies				Open-Label Extension Study			
	Antibody-Positive (N=93)		Antibody-Negative (N=155)		Antibody-Positive (N=101)		Antibody-Negative (N=40)	
	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)
Patients with events	34	20 (21.5)	38	30 (19.4)	49	28 (27.7)	15	10 (25.0)
Alanine aminotransferase increased	16	12 (12.9)	13	13 (8.4)	22	18 (17.8)	8	8 (20.0)
Aspartate aminotransferase increased	11	7 (7.5)	10	9 (5.8)	20	18 (17.8)	4	4 (10.0)
Liver function test abnormal	4	4 (4.3)	9	9 (5.8)	3	3 (3.0)	3	0 (0.0)
Hepatic enzyme increased	3	3 (3.2)	6	6 (3.9)	4	4 (4.0)	0	2 (5.0)

Data cutoff dates for the OLE study were 02 March 2012 for antibody data and 30 March 2012 for safety data.

On-treatment adverse events (pooled Phase 3 studies) were defined as adverse events that started during the treatment period. The treatment period spanned the time during which the study treatment was 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.

Treatment-emergent adverse events (OLE study) were those adverse events with start dates/times on or after the date/time of the first study drug dose.

To obtain the number of patients, if a patient had more than one event within a particular adverse event category or preferred term, he/she was counted only once for an adverse event category or preferred term.

Patient percentages were based on the total number of mipomersen-treated patients who had post-baseline antibody data.

Patients were classified as 'Antibody-negative' if all samples post-baseline were negative. Patients were classified as 'Antibody-positive' if at least one sample post-baseline was positive.

Source: [IMPK-TS-OTAE-LEE-ABTITER-FSPDAP3.rtf](#) and [IMPK-TS-TEAE-LEE-ABTITER-6S12.rtf](#)

Table 21-7: Incidence of Abnormal Transaminase Values by Antibody Status in the Pooled Phase 3 Studies and Open-Label Extension Study

Parameter	Pooled Phase 3 Studies		Open-Label Extension Study	
	Antibody-Positive (N=93) n (%)	Antibody-Negative (N=155) n (%)	Antibody-Positive (N=101) n (%)	Antibody-Negative (N=40) n (%)
Alanine Aminotransferase Maximum				
>ULN and <2 x ULN	38 (40.9)	54 (34.8)	39 (38.6)	14 (35.0)
≥2 x ULN and <3 x ULN	25 (26.9)	36 (23.2)	32 (31.7)	7 (17.5)
≥3 x ULN and <5 x ULN	13 (14.0)	18 (11.6)	15 (14.9)	6 (15.0)
≥5 x ULN and <8 x ULN	4 (4.3)	2 (1.3)	4 (4.0)	4 (10.0)
≥8 x ULN	1 (1.1)	5 (3.2)	1 (1.0)	1 (2.5)
Alanine Aminotransferase				
≥3 x ULN, two consecutive results (at least 7 days apart)	11 (11.8)	11 (7.1)	11 (10.9)	7 (17.5)
≥3 x ULN in presence of bilirubin >ULN	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Aspartate Aminotransferase Maximum				
>ULN and <2 x ULN	47 (50.5)	75 (48.4)	55 (54.5)	14 (35.0)
≥2 x ULN and <3 x ULN	11 (11.8)	16 (10.3)	20 (19.8)	9 (22.5)
≥3 x ULN and <5 x ULN	9 (9.7)	10 (6.5)	12 (11.9)	6 (15.0)
≥5 x ULN and <8 x ULN	2 (2.2)	2 (1.3)	1 (1.0)	1 (2.5)
≥8 x ULN	1 (1.1)	2 (1.3)	0 (0.0)	0 (0.0)

Table 21-9: Summary of Complement C3 Levels at Over Time in Open-Label Extension Study ISIS 301012-CS6 by Antibody Status

Parameter Time Point	Statistic	Antibody-Positive (N=101)	Antibody-Negative (N=40)
Baseline	n	85	34
	Mean (SD)	131.0 (23.8)	134.6 (27.5)
	Median (P25, P75)	132 (119, 142)	133 (113, 147)
Week 26	n	93	31
	Mean (SD)	122.5 (21.6)	128.5 (25.0)
	Median (P25, P75)	119 (107, 136)	132 (111, 142)
Week 52	n	87	24
	Mean (SD)	117.4 (23.5)	126.6 (19.7)
	Median (P25, P75)	117 (102, 125)	124 (113, 145)
Week 76	n	65	19
	Mean (SD)	116.9 (24.9)	128.5 (28.3)
	Median (P25, P75)	116 (105, 128)	120 (109, 146)
Week 104	n	47	11
	Mean (SD)	109.3 (23.5)	125.3 (20.2)
	Median (P25, P75)	111 (101, 128)	132 (107, 143)
End of Treatment	n	101	39
	Mean (SD)	113.3 (25.8)	125.2 (25.6)
	Median (P25, P75)	115 (99, 127)	125 (109, 145)

P25, 25th percentile; P75, 75th percentile; SD, standard deviation

Data cutoff dates were 02 March 2012 for antibody data and 30 March 2012 for safety data.

Source: [IMP-K-TS-LBSUM-OT-ABTITER-GR-6S12.rtf](#)

Table 21-13: Efficacy Results in Antibody-Positive and Antibody-Negative Patients in the Open-Label Extension Study ISIS 301012-CS6 (Gravimetric Units) - Safety Set

Parameter Time Point	Antibody-Positive Patients			Antibody-Negative Patients		
	n	Level Mean (SD)	% Change from Baseline Mean (95% CI)	n	Level Mean (SD)	% Change from Baseline Mean (95% CI)
Low-Density Lipoprotein Cholesterol (mg/dL)						
Baseline	101	236.7 (153.8)	--	40	222.8 (131.1)	--
Week 26	96	168.6 (120.3)	-27.34 (-31.3, -23.4)	34	154.4 (112.1)	-31.69 (-38.7, -24.7)
Week 52	88	173.0 (122.1)	-26.42 (-31.1, -21.7)	23	150.4 (121.9)	-29.34 (-39.5, -19.1)
Week 76	49	149.0 (111.5)	-25.45 (-31.8, -19.1)	17	130.5 (89.1)	-32.72 (-46.3, -19.1)
Week 104	44	119.4 (58.4)	-26.38 (-33.1, -19.6)	13	107.2 (40.1)	-32.85 (-48.3, -17.4)
Apolipoprotein B (mg/dL)						
Baseline	101	177.8 (86.4)	--	40	169.3 (66.0)	--
Week 26	96	126.1 (68.1)	-28.22 (-31.8, -24.7)	34	116.9 (57.5)	-30.94 (-37.4, -24.5)
Week 52	88	129.3 (72.3)	-27.23 (-31.6, -22.9)	23	111.7 (64.8)	-31.42 (-40.8, -22.0)
Week 76	49	112.9 (60.5)	-28.79 (-33.8, -23.8)	17	101.5 (49.1)	-34.77 (-44.3, -25.2)
Week 104	44	94.9 (32.5)	-29.19 (-35.1, -23.3)	13	86.3 (30.6)	-37.97 (-50.5, -25.5)

CI, confidence interval; SD, standard deviation

Data cutoff dates were 02 March 2012 for antibody data and 30 March 2012 for efficacy data.

Source: [IMPk-TE-LDL-APOB-OT-ABTITER-GR-6S12.rtf](#)

V. ADA and Non-clinical Studies

Table 11: Surviving Mice at Week 78 and Week 105

Dose Level	Male		Female	
	Week 78	Week 105	Week 78	Week 105
0	50 (71%)	24 (34%)	42 (71%)	24 (34%)
5 mg/kg/week ISIS 301012	51 (73%)	25 (37%)	43 (73%)	20 (33%)
20 mg/kg/week ISIS 301012	51 (73%)	22 (31%)	47 (67%)	0 (0%)
60 mg/kg/week ISIS 301012	41 (59%)	0 (0%)	26 (37%)	0 (0%)
80 mg/kg/month ISIS 301012	50 (71%)	24 (34%)	51 (73%)	19 (29%)
60 mg/kg/week ISIS 147764	57 (81%)	22 (33%)	56 (80%)	28 (43%)

DA data were

VI. Neutralizing antibodies

No assay protocol and validation report were provided for uptake neutralizing assay and no Nab data were reported.

Based on the MOA, either antisense oligos or RNAi products should enter cytoplasm and target specific mRNAs. Although in combination with various delivery methods, eg, transfection reagents, electroporation, micro-injection, RNAi is very effective in reducing

specified mRNAs in vitro, the specific targeting of anti-sense and RNAi products into desired cell or tissue targets in vivo has not been developed for clinical therapy.

Due to the existence of anti-DNA antibodies in many autoimmune disease (indicating that under certain situations, human DNA can be immunogenic in humans. Mipomeren is structurally different from human native DNA and can induce high affinity antibodies in rabbits, therefore it is possible that this product can induce antibodies in humans. If indeed the observed effect on the levels of lipids in patients is because of intracellular targeting of the Apo100 mRNAs, it is a concern whether uptake neutralizing antibodies could be generated and affect the efficacy of the product. Therefore, the sponsor should develop an uptake neutralization assay when ADA is found in patients. It was stated in Merki, et al. Circulation 2008 that a significant reduction in h-apoB-100 mRNA was noted (26.0_2.6% versus 87.5_7.1%; P_0.0033) in the mipomersen-treated group compared with the control ASO in hApoB100 transgenic mice).

Since the majority of treated patients developed binding antibodies, the sponsor should have assessed whether these antibodies are uptake Nabs and affect the reduction of ApoB100 mRNA and protein in an in vitro assay (no potency assay was listed in DS and DP lot release and stability testing), or affect the entry of the drug candidate into target cells.

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/s/

JINHAI WANG
01/09/2013

DANIELA I VERTHELYI
01/09/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: December 17, 2012

Reviewer: Reasol S. Agustin, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Yelena Maslov, PharmD
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Kynamro (Mipomersen Sodium) Injection, 200 mg/mL

Application Type/Number: NDA 203568

Applicant/Sponsor: Genzyme

OSE RCM #: 2012-927

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed container label, carton and insert labeling, and instructions for use for Kynamro (Mipomersen Sodium) Injection, NDA 203568, for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

The Applicant submitted a request for an assessment of the container label, carton, and insert labeling for the proposed product, Kynamro (Mipomersen Sodium) Injection, 200 mg/mL, in the NDA submission on March 29, 2012.

1.2 PRODUCT INFORMATION

The following product information is provided in the March 29, 2012 NDA submission.

- Active Ingredient: Mipomersen Sodium
- Indication of Use: an adjunct to maximally tolerated lipid-lowering medications and diet to reduce LDL-C, apo B, TC, non-HDL-C, and Lp(a) levels in patients with homozygous familial hypercholesterolemia (HoFH) (b) (4)
- Route of Administration: Subcutaneous
- Dosage Form: Injection solution
- Strength: 200 mg/mL
- Dose and Frequency: Once weekly
- How Supplied: Pre-filled syringe is packaged individually into trays. A single or four syringes in trays are placed in cartons with prescribing information. The cartons provide protection from light. Vials are packaged individually in cartons with prescribing information. The cartons provide protection from light
- Storage: Between 2°C to 8°C. Protect from light.
- Container and Closure Systems: *Vials:* (b) (4) 2 mL, clear glass vials with (b) (4) rubber stoppers (b) (4)
The vials are capped (b) (4) with flip-off caps.
Prefilled syringe: (b) (4) 1 mL, long, graduated, clear glass syringes (b) (4) needles and needle shields with 1 mL, long, (b) (4) rubber plunger stoppers (b) (4)
Syringes are assembled with a plunger rod and a needle shield safety device.

2 METHODS AND MATERIALS REVIEWED

DMEPA reviewed the Kynamro labels and package insert labeling submitted by the Applicant.

2.1 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted March 29, 2012 (Appendix A)
- Carton Labeling submitted March 29, 2012 (Appendix B)
- Insert Labeling submitted July 25, 2012 (no image)
- Instructions for Use (IFU) submitted March 29, 2012

3 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESMENT

Our label and labeling risk assessment identified areas of vulnerability to error such as:

- The use of all capitals to present the proprietary name on the carton and container label decreases readability
- The use of trailing zeros (i.e. 1.0) can be mistaken for the number 10 in the carton labeling and IFU.
- Lack of prominence of important information such as proprietary name and established name due to the use of distracting graphics or images.
- Overly cluttered labels due to excessive information on the principal display panel (PDP).
- Lack of important information on the carton labeling regarding leaving the drug at room temperature for at least 30 minutes prior to administration.
- Overly prominent information on the carton labeling that detracts from the most important information on the label (i.e. 1 Single-Use syringe)
- The Insert labeling contains inappropriate abbreviations (i.e. SC, IV) that are prone to errors².

Therefore, we provide recommendations for the Applicant in Section 4 below.

4 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

² ISMP's List of Error-Prone abbreviations, Symbols, and Dose Designations. ISMP 2012.
<http://www.ismp.org/tools/errorproneabbreviations.pdf>

4.1 COMMENTS TO THE APPLICANT

A. All Labels and Labeling: Vial Container Label, Prefilled Syringe Label, Prefilled Syringe Lid Label, Prefilled Syringe Carton Labeling and Vial Carton Labeling

1. We note that the established name is ½ the size of the proprietary name however, lacks prominence commensurate with the proprietary name. Thus, we request you decrease the font size of the proprietary name “Kynamro” and revise the established name in accordance with 21 CFR 201.10 (g)(2), taking into account all factors, including typography, layout, contrast and other printing features.
2. Revise the presentation of the proprietary name, KYNAMRO, from UPPERCASE to Title Case “Kynamro” to improve readability of the name.
3. Increase the prominence of the strength statement for improved readability.
4. Add the dosage form “Injection” immediately next to or immediately underneath the established name.

B. Prefilled Syringe Container Label

1. Relocate the NDC number to the top one-third of the PDP where the “Rx only” statement is currently located, as required by 21 CFR 207.35(3)(i).
2. Reduce the font size of the “Rx only” statement and relocate the statement to appear after the manufacturer’s information “Genzyme Corporation.” This will reduce clutter around the proprietary name, established name, and strength.

C. Prefilled Syringe Lid Label

1. On the prefilled syringe lid, increase the prominence of the statement “For subcutaneous injection only” so it is the same size as the “1 Single-use syringe” statement by increasing the font size of this statement since this is important information. This can be achieved by relocating the manufacturer’s information “Manufactured by:.. For:...Cambridge, MA 02142” to the white panel as this information clutters the principal display panel containing the most important information such as proprietary and established names of the product, strength, and route of administration.
2. Add the statement “Discard unused portion” immediately next to “1 Single-use syringe” statement to prevent the potential for multiple-use thus increasing the risk of contamination, since this is a single-use formulation.

D. Prefilled Syringe Carton Labeling

1. Reduce the prominence or color intensity of the (b) (4) background to provide adequate color contrast between the texts and the background color. In addition, ensure that the proprietary name, the established name, and strength are in the same color block in accordance with 21 CFR 201.10 (a) which states that these important information should not be separated by placement of intervening matter such as tagline or other graphics.

2. Add the statement “Discard unused portion” immediately following or underneath the net quantity statement. For example,

1 Single-use syringe
Discard unused portion
3. Ensure that the proprietary and established names of the product, strength, and NDC number are prominent on the principal display panel and all side panels, so that this information is visible regardless of the way the product is placed in the refrigerator.
4. Increase the prominence of the statement “For subcutaneous injection only” and relocate to the middle portion of the principle display panel underneath the statement, “Each prefilled syringe..,” similar to the vial carton labeling.
5. Decrease the prominence of the statements “1 Single-use syringe” and “4 Single-use syringes” in order to create room for the statement “For subcutaneous injection only.”
6. Add the statement “each containing 1 mL” immediately after the net quantity statement for the 4 Single-use syringes packaging to read “4 Single-use syringes each containing 1 mL”
7. If feasible, consider adding a statement to the side panel advising to leave the product at room temperature for 30 minutes prior to administration.

E. Vial Container Label

1. If feasible, increase the prominence of the route of administration by using bigger font size. This can be achieved by deleting the name of the firm “Genzyme” from the label as manufacturer information appears immediately underneath this name.
2. The “Rx only” statement is more prominent than the route of administration. Thus, decrease the prominence of the “Rx only” statement by decreasing font size and debolding.
3. Revise the statement (b) (4) to read “Discard unused portion” to prevent the potential for multiple-use thus increasing the risk of contamination since this is a single-use formulation. Additionally, relocate this statement to appear immediately underneath “Single-use vial” statement.

F. Vial Carton Labeling

1. See D.1. through D.3. and revise vial carton labeling accordingly.
2. Delete all trailing zeroes that appear throughout the insert labeling. Trailing zeroes (e.g. ‘1.0’) are considered dangerous abbreviations³. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve error prone trailing zeroes in the labeling of products.

³ <http://www.ismp.org/Tools/errorproneabbreviations.pdf>, Last accessed 01/03/2012.

3. Revise the net quantity statement (b) (4) to read “4 Single-use vials each containing 1 mL” so that it is consistent with the net quantity statement presentation of the prefilled syringe carton labeling.
4. Decrease prominence of the net quantity by debolding.
5. Relocate the statement “See package insert for dosage and administration” to the side panel to reduce clutter of the PDP and increase readability of other important information.
6. Decrease the prominence of the “Rx only” statement by debolding and relocating to the bottom portion of the PDP (i.e. lower right or left hand corner). As currently presented, it is centrally located on the PDP and is as prominent as the route of administration s taking central location and as prominent as route of administration.

G. Insert Labeling

1. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice’s List of Error-Prone Abbreviations, Symbols, and Dose Designations appear throughout the package insert.⁴ As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products. Thus, please revise the those abbreviations, symbols, and dose designations as follows:
 - i. Revise all instances of abbreviations “SC” to read “subcutaneous”. The abbreviation “SC” has been misinterpreted as SL (sublingual)
 - ii. Revise all instances of abbreviations “IV” to read “intravenously”. The abbreviation “IV” has been misinterpreted as IU (international unit), 10 (ten), IM (Intramuscular), or IN (intranasal)
2. Under Dosage and Administration, relocate Section 2.2 Instructions for Use to Section 17 (Patient Counseling Information) as this information is more appropriate in the patient counseling section (17) rather than Dosage and Administration (Section 2).

H. Instructions For Use

1. Delete all trailing zeroes that appear throughout the insert labeling. Trailing zeroes (e.g. ‘1.0’) are considered dangerous abbreviations⁵. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve error prone trailing zeroes in the labeling of products.
2. Revise the bullet points to read Step 1, 2, etc., so that it is easier for patients to follow the instructions.

⁴ <http://www.ismp.org/Tools/errorproneabbreviations.pdf>, Last accessed 10/28/2009.

⁵ <http://www.ismp.org/Tools/errorproneabbreviations.pdf>, Last accessed 01/03/2012.

3. The figures do not clearly illustrate the instructions. We recommend using actual photos of the product or more prominent illustrations in color to demonstrate the actual step being performed.
4. There are multiple steps represented by a single bullet point and only some steps contain figures or illustrations. Thus, the IFU should be revised to contain relevant information clearly expressed with illustrations in color for each step for the preparation and administration process.
5. In section (b) (4) revise the title to read “Supplies you will need before you inject Kynamro” so that patients are clear as to what supplies are needed prior to injection. In addition, consider adding illustration of the supplies or list the supplies in a bullet form so that it is easier to follow.
6. Under Section “How to prepare the syringe for injection,” patients are instructed to “Allow KYNAMRO to come to room temperature for at least 30 minutes. It is important that KYNAMRO be at room temperature prior to the injection” without stating the reason of importance. We recommend adding the reason for this instruction so that it emphasizes importance to patients.

If you have further questions or need clarifications, please contact Margarita Tossa, project manager, at 301-796-4053.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

REASOL AGUSTIN
12/17/2012

YELENA L MASLOV
12/17/2012

CAROL A HOLQUIST
12/17/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: November 30, 2012

TO: Kati Johnson, Regulatory Project Manager
Eileen Craig, M.D., Clinical Reviewer
Division of Metabolic and Endocrine Products (DMEP)

FROM: Susan Leibenhaut, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance

THROUGH: Janice K. Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Susan D. Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 203568

APPLICANT: Genzyme Corporation
DRUG: mipomersen sodium
NME: Yes

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: as an adjunct to a low-fat diet and other lipid-lowering drugs with or without LDL apheresis to reduce low-density lipoprotein cholesterol, total cholesterol, apolipoprotein B and triglycerides in patients with homozygous familial hypercholesterolemia.

CONSULTATION REQUEST DATE: May 14, 2012

CLINICAL INSPECTION SUMMARY DATE: November 30, 2012

DIVISION ACTION GOAL DATE: January 10, 2013

PDUFA DATE: January 29, 2013

I. BACKGROUND:

Genzyme Corporation has submitted an NDA for mipomersen sodium, a new molecular entity proposed to treat patients with homozygous familial hypercholesterolemia (HoFH), an orphan disease. It is proposed to be used as an adjunct to a low-fat diet and other lipid-lowering drugs with or without LDL apheresis to reduce low-density lipoprotein cholesterol, total cholesterol, apolipoprotein B, and triglycerides in patients with homozygous familial hypercholesterolemia. The pivotal Phase 3 study in the indicated population (ISIS 301012-CS5, in patients with HoFH) is supported by three other Phase 3 studies (MIPO3500108, in patients with severe heterozygous familial hypercholesterolemia (HeFH); ISIS 301012-CS7, in patients with HeFH and coronary artery disease; and ISIS 301012-CS12, in patients with high-risk hypercholesterolemia). The review division chose to inspect clinical investigator sites enrolling in the pivotal study, ISIS 301012-CS5, and clinical investigator sites enrolling in two of the three supportive studies based on feasibility of inspections and enrollment number of subjects at sites.

Lipoprotein Apo B-100 is essential for the assembly and secretion of VLDL from the liver. Lipids such as triglycerides and cholesterol are packaged with apo B-100 and other phospholipids into VLDL, which in turn is secreted into the plasma, where additional apolipoproteins are added. ISIS 301012 is a 20 base nucleotide that acts as an antisense drug targeted to human apo B-100, the principal apolipoprotein of atherogenic LDL and its metabolic precursor, VLDL. ISIS 301012 is complementary to the coding region of the mRNA for apo B-100, binding by Watson and Crick base pairing. The hybridization (binding) of ISIS 301012 to the cognate mRNA results in RNase H-mediated degradation of the cognate mRNA and inability to translate the apo B-100 protein. This inhibition of apo B-100 translation is postulated to impair VLDL synthesis and result in low levels of LDL-C.

A total of five clinical sites and the sponsor were inspected for this application. Clinical sites were chosen for inspection because the sites were among the highest enrollers in the studies or because of number of INDs in the OSI database. The sponsor was inspected because this is a new molecular entity. These inspections are considered routine because there were no specific concerns noted during the review of the application.

II. RESULTS (by Site):

Name of Clinical Investigator (CI) or Sponsor	Protocol #/Site #/ # Subjects Randomized	Inspection Date	Final Classification
Evan Stein, M.D., Ph.D. 5355 Medpace Way Cincinnati, OH 45227	ISIS 301012-CS7 Site 1503/ 12 subjects ISIS 301012-CS5 Site 1503/ 1 subject	June 9 to 12, 2012	NAI
Ralph Vicari, M.D. 1223 Gateway Drive, Suite 2H Melbourne, FL 32901-3142	ISIS 301012-CS7 Site 1622/ 4 subjects	July 30 to August 2, 2012	NAI
Richard Ceska, M.D. 3. Interní klinika 1LFUK a VFN Klinika endokrinologie a metabolismu U nemocnice 1, 128 08 Praha 2 Czech Republic	MIPO108 Site 4000/ 9 subjects	August 6 to 10, 2012	NAI
Frederick Raal, M.D. Carbohydrate and Lipid Metabolism Research Unit, Area 551, Department of Medicine, Johannesburg Hospital, 7 York Road, Parktown, South Africa 2193	ISIS 301012-CS5 Site 1501/ 26 subjects	August 6 to 13, 2012	Pending (Preliminary classification VAI)
Prashilla Soma, M.D. Clinical Research Unit, University of Pretoria Dr Savage Road Pretoria 0002 South Africa	MIPO108 Site 3002/ 5 subjects	August 14 to 17, 2012	Pending (Preliminary classification VAI)
Genzyme Corporation 500 Kendall Street Cambridge, MA 02142	ISIS 301012-CS5, ISIS 301012-CS7, and MIPO108	September 24 to October 5, 2012	Pending (Preliminary classification NAI)

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;
EIR has not been received from the field and complete review of EIR is pending.1. **Evan Stein, M.D., Ph.D.**

5355 Medpace Way, Cincinnati, OH 45227

- a. **What was inspected:** At this site, for ISIS 301012-CS5, two subjects were screened, and one subject was randomized and completed the study. At this site, for ISIS 301012-CS7, twenty subjects were screened, and twelve subjects were randomized and completed the study. An audit of all screened subjects' records for both protocols was conducted.

- b. **General observations/commentary:** No significant regulatory violations were noted, and no Form FDA 483 was issued. For Protocol ISIS 301012-CS7, there was a single incident of failure to report the AE of itching at the injection site for Subject 7066 that occurred from January 31 to February 4, 2009. The primary endpoint data were verified.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. **Ralph Vicari, M.D.**

1223 Gateway Drive, Suite 2H, Melbourne, FL 32901-3142

- a. **What was inspected:** At this site, for ISIS 301012-CS7, five subjects were screened. Two subjects were considered screen failures and one of the initially screened subjects was rescreened and enrolled. This same subject was later terminated early due to elevated liver enzymes. Three subjects completed the study and were rolled over into the open label study. An audit of all screened subjects' records for the protocol was conducted.
- b. **General observations/commentary:** The protocol required that the sites be blinded to LDL values after screening, so only screening LDL values could be verified at the clinical site. There was no under reporting of adverse events. No significant regulatory violations were noted, and no Form FDA 483 was issued. Discussion items included instances when the site did not provide the subjects with the most recent version of the consent form in a timely manner. These instances were submitted by the sponsor as protocol violations to the NDA. The site has since instituted a Clinical Operating Procedure concerning the informed consent process. Another discussion item was the protocol violation concerning obtaining follow-up liver function tests (LFTs) in Subject 7323. This subject had a delay of 8 days in the protocol required follow-up for the elevated LFTs because she was on vacation and could not return in the protocol specified time period.
- c. **Assessment of data integrity:** The above findings are unlikely to impact data integrity or are isolated findings. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

3. **Richard Ceska, M.D.**

3. Interní klinika 1LFUK a VFN, Klinika endokrinologie a metabolismu
U nemocnice 1, 128 08 Praha 2, Czech Republic

- a. **What was inspected:** At this site, for MIP0108, 13 subjects were screened, nine subjects enrolled, and seven subjects completed the study. An audit of all screened subjects' records for the protocol was conducted.
 - b. **General observations/commentary:** The protocol required that the sites be blinded to LDL values after screening, so only screening LDL values could be verified at the clinical site. There was no under reporting of adverse events. No significant regulatory violations were noted and no Form FDA 483 was issued.
 - c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.
4. **Frederick Raal, M.D.**
Carbohydrate and Lipid Metabolism Research Unit, Area 551
Department of Medicine, Johannesburg Hospital,
7 York Road, Parktown, South Africa 2193

Note: Observations noted for this site are based on communications with the FDA investigator and draft review of the EIR. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

- a. **What was inspected:** At this site, for ISIS 301012-CS5, 28 subjects were screened. Two subjects were considered screen failures, and 26 subjects were enrolled. Twenty-three subjects completed the study through Visit 9. An audit of 16 subjects' records for the protocol was conducted.
- b. **General observations/commentary:** The protocol required that the sites be blinded to LDL-C values after screening, so only screening LDL-C values could be verified at the clinical site. There was no under reporting of adverse events. A Form FDA 483 was issued, and Dr. Raal adequately responded to the inspectional findings in a letter dated August 16, 2012. The regulatory violations noted and CI responses were the following:
 - i. Failure to conduct the study according to the investigational plan:
 - a. Subjects 8365 and 8101 met exclusion criteria because the dose of cyclical hormones was not stable for greater than 12 weeks.
CI response: The protocol was ambiguous with regard to contraceptive use. In the future, staff will be more diligent in ensuring that eligibility criteria are met.
 - b. Subject 8481 failed to meet eligibility requirements because he had ALT level greater than 1.5 ULN (an exclusion criterion) and had body weight less than 40 kg (inclusion criterion required body weight greater than 40 kg). He was rescreened the next day and met eligibility criteria.

CI response: In the future, the CI will request a waiver for re-screening.

ii. Failure to prepare and maintain adequate case histories as follows:

- a. In many instances, study nurses recorded dosing data directly into subject diaries without annotation as to who recorded the data. The Dose Administration Record template was not used at this site.

CI response: In the future, staff will not use subject diaries, but will use the appropriate forms for recording drug administration.

- b. Source data for kit dispensing was recorded directly into an Investigational Product (IP) Accountability Log, and the entries were not signed or initialed by the dispenser or any study personnel.

CI response: In the future, the appropriate forms will be used.

- c. Study records do not identify the date or time that incoming shipments of IP were placed into controlled temperature storage.

CI response: There was no place on the form to record the time of receipt of shipments. IP was placed into the refrigerator immediately upon receipt at the site. In the future, the time will be recorded.

Dr. Raal responded adequately to the observations in a letter dated August 16, 2012 and promised corrective actions.

- c. **Assessment of data integrity:** The above findings are unlikely to impact data integrity or are isolated findings. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

5. **Prashilla Soma, M.D.**
Clinical Research Unit, University of Pretoria
Dr Savage Road, Pretoria 0002, South Africa

Note: Observations noted for this site are based on communications with the FDA investigator and draft review of the EIR. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

- a. **What was inspected:** At this site, for MIP0108, eight subjects were screened and five subjects were enrolled. Four subjects completed the study and one subject died. An audit of eight subjects' records for the protocol was conducted.
- b. **General observations/commentary:** The protocol required that the sites be blinded to LDL-C values after screening, so only screening LDL-C values could be verified at the clinical site. There was no under reporting of adverse events. A Form FDA 483 was issued, and Dr. Soma adequately responded to the

inspectional findings in a letter dated August 29, 2012. The regulatory violations noted and CI responses included the following:

i. Failure to conduct the study according to the investigational plan:

- a. For Subjects 1027, 1029, and 1031, for clinic administration of test article, instead of administering test article from the 1-vial kit as noted in the Investigational Product Handling Manual (IPHM), medication was dispensed from the 6-vial kit intended for home use.

CI response: The IPHM was only a general guide. All vials within a kit are the same dose concentration, and the medication is stable at room temperature, so this finding is not a protocol violation.

- b. Study records do not include a copy of an angiogram reportedly used to support inclusion of Subject 1029/S002.

CI response: The subject had known coronary artery disease, and the site made multiple attempts to retrieve the files from the hospital. In the future a note to file will document these attempts.

ii. Failure to prepare and maintain adequate case histories as follows:

- a. In many instances, study nurses recorded dosing data directly into subject diaries without annotation as to who recorded the data. The Dose Administration Record template was not used at this site.

CI response: Subject diaries had no place for entry of who administered the injection. In the future this will be recorded.

- b. Study drug kits were removed from storage by the CI and dispensed to other study personnel. The PI recorded dispensing data directly into an Investigational Product (IP) Accountability Log but there was no record of the dispensee.

CI response: This site's practice conforms to local regulatory requirements. In the future, attention will be paid to other documentation requirements and the forms at the site have been updated.

- c. Temperature monitoring records for the refrigerator used to store study drug included periods of up to four days without recording storage temperature. This refrigerator had no alarm, no continuous temperature recorded, and no record of calibration of the thermometer.

CI response: The site has obtained new equipment with a continuous temperature recorder and calibration has been upgraded.

Reviewer note: Proposed labeling states, "When refrigeration is not available (product) may be stored at or below 30°C (86°F), away from heat sources, for up to (b) (4)

- c. **Assessment of data integrity:** The above findings are isolated and unlikely to impact data integrity. The study appears to have been conducted adequately,

and the data submitted by the sponsor may be used in support of the respective indication.

6. **Genzyme Corporation**
500 Kendall Street, Cambridge, MA 02142

Note: Observations noted for this site are based on communications with the FDA investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

- a. **What was inspected:** The inspection audited Protocol ISIS 301012-CS5, focusing on Drs. Raal and Stein; Protocol ISIS 301012-CS7, focusing on Drs. Stein and Vicari; and Protocol MIP0108, focusing on Drs. Prashilla and Ceska. The inspection reviewed monitoring procedures and activities, and the safety reporting as well as comparing the primary endpoint at the sponsor site with the data listings submitted to the NDA.
- b. **General observations/commentary:** The primary endpoint was verified. There was no evidence of under-reporting of adverse events. No violations were noted, and no Form FDA 483 was issued.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data submitted by the sponsor may be used in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Five clinical investigator sites and the sponsor were inspected in support of this NDA. For Drs. Stein's, Vicari's, and Ceska's sites, and the sponsor inspection, no violations were noted. For Drs. Raal's and Prashilla's sites minor violations were noted that do not impact data reliability. The classifications for the inspections of the sponsor and Drs. Raal's and Prashilla's sites are pending. An inspection summary addendum will be generated if conclusions change upon receipt and final review of the EIRs.

Based on results of these inspections it appears that data submitted by the Applicant in support of the requested indication are considered reliable.

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Good Clinical Practice Assessment Branch
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUSAN LEIBENHAUT
12/03/2012

JANICE K POHLMAN
12/03/2012

SUSAN D THOMPSON
12/03/2012

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY (OSE)
OFFICE OF PHARMACOVIGILANCE AND EPIDEMIOLOGY (OPE)

DATE: 24 July 2012

FROM: John R. Senior, M.D., Associate Director for Science, OPE
Leonard B. Seeff, M.D., Consultant to OPE/OSE/CDER

TO: Mary Parks, M.D., Director, Division of Metabolic and Endocrine Products
(DMEP), Office of New Drugs (OND)
Amy Egan, M.D., Deputy Director, DMEP
Eileen Craig, M.D., Medical Reviewer (mipomersin), DMEP
James Smith, M.D., Medical Reviewer (lomitapide), DMEP

VIA: Gerald Dal Pan, M.D., Director, OSE

RCM: 2012-1005 (lomitapide)
2012-1006 (mipomersin)

SUBJECT: Possible hepatic adverse effects of lomitapide and mipomersin, new agents for treatment of elevated serum low-density lipoprotein cholesterol in patients with the orphan disease homozygous familial hypercholesterolemia (HoFH).

Documents reviewed:

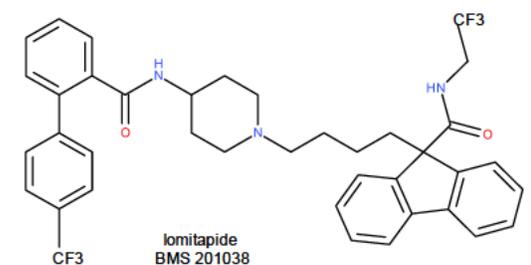
- 1) Consultation request dated 20 April 2012 for OSE hepatology review of two new drugs, lomitapide (BMS 201038) and mipomersin (ISIS 301012), both agents associated with elevations of serum aminotransferases and induction of fatty liver
 - 2) NDA 203858 (lomitapide) received 29 February 2012 from Aergerion Pharmaceuticals, and NDA 203568 (mipomersin) received 29 March 2012 from Genzyme Corporation.
 - 3) Selected medical literature articles on lomitapide, mipomersin, fatty liver disease, and erythropoietin for orphan indication of end-stage kidney disease requiring dialysis and repeated red blood cell transfusions.
-

In an earlier response dated 19 June 2012, we provided limited and only partial answers to the seven questions asked about both drugs, but focused attention on the single very serious, in fact fatal, case of death in fulminant liver failure of a 68-year-old man. He had been treated with 200 µg mipomersin weekly subcutaneous injections for six months, without notable liver injury other than modestly elevated and fluctuating serum aminotransferase elevations, but some 4.9 months after stopping it suffered catastrophic liver failure that appeared concurrent with myocardial infarction. We concluded that the case was unlikely to have been caused by a long-delayed adverse hepatic mipomersin-induced liver injury, dysfunction, and failure but much more likely

the consequence of severe and acute liver congestion and hypoxia caused by rapidly evolving acute myocardial infarction that was initially relatively silent. We did not address in detail the less serious but fairly frequent elevations of serum aminotransferase activities in other subjects treated, nor the questions posed for both drug products.

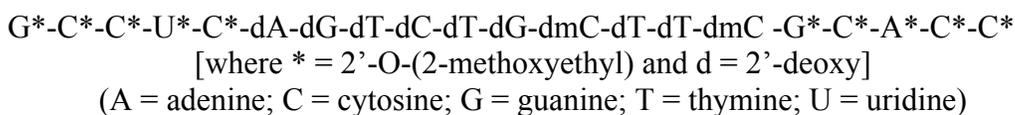
This review represents a single, formal response to the consultation request from the Division of Metabolic and Endocrine Products (DMEP) with interest in the hepatic safety of lomitapide (RCM 2012-1005) and mipomersen (RCM 2012-1006). These two new agents are being evaluated by DMEP for treatment of homozygous familial hypercholesterolemia (HoFH). HoFH is an inherited genetic disorder causes premature cholesterol deposits in arteries throughout the body and leads to a very high rate of premature death, often before reproductive age, mainly from coronary atherosclerosis. Before advent of effective lipid-lowering therapies, children and adolescents with HoFH were dying of acute myocardial infarction and had a median survival of 18 years. The worldwide incidence of this disorder is estimated at 1 per million, but in specific locales and subgroups, such as the white Afrikaners of South Africa, consanguinity has produced a much higher prevalence of about 1 per 30,000, some 30-35 times greater (Raal et al, 2011). Treating HoFH is a true orphan indication, but may provide valuable insights into the much more prevalent heterozygous form (HeFH), and other various types of hypercholesterolemia, where the future expanded market for such agents may lie. Study of the mechanism of HoFH effects led to elucidation of liver receptors for low-density lipoproteins of serum and a Nobel prize for Drs. Joseph Goldstein and Michael Brown in 1985. The two agents discussed here are quite different, but both are now under active review by the DMEP, both under suspicion of causing liver injury, at least transiently but possibly sometimes more severely.

Lomitapide has been under investigation for many years, was first discovered by Bristol-Myers Squibb as the orally administered compound BMS-201038, and now is sponsored by Aegerion Pharmaceuticals. It inhibits the microsomal triglyceride transfer protein needed for very-low-density lipoprotein (VLDL) assembly in the liver. Although it was found in a phase II trial to be probably causing elevated serum aminotransferase levels and increased liver fat in 2007, the sponsor nevertheless carried out phase III trials in 2007-2011 and has now submitted results as NDA 203858 for possible approval as treatment of HoFH.



The other agent, **mipomersen**, is quite different, a modified 20-nucleotide antisense sequence inhibiting the messenger ribonucleic acid (mRNA) production of apo-lipoprotein B, developed originally by ISIS as 301012 and now licensed to Genzyme Corporation and further developed as

mipomersin for weekly subcutaneous injection (Kynamro®). The sponsor has submitted results for possible approval for treating homozygous familial hypercholesterolemia (NDA 203568). It also has been associated with elevated serum aminotransferase activities, and possibly with a case of fatal fulminant hepatic failure concurrent with acute myocardial infarction (see above).



Rather troubling is the deception implicit in the manner in which these two agents have been investigated and the results reported for our review by the applicants, both of whom sought priority review and orphan drug status, and approval only for treatment of HoFH. The great majority of the patients and subjects studied (more than 90% for both agents), for whom data have been reported in these applications did not have HoFH, but instead a variety of disorders that cause elevated serum cholesterol levels, a vastly more common problem (and much greater potential market). From the subjects selected for study, and papers published recently, it appears obvious that the sponsors seek the larger market. It seems very likely that labeling restrictions will not be effective in limiting the use of these drugs, if approved, to patients with HoFH.

A parallel and similar situation is evident in the story of erythropoietin development for treating severe anemia in patients with renal failure requiring long-term, recurrent dialysis and repeated transfusions. Orphan disease status was granted in 1984, based on a prevalence of about 50,000 cases in the United States at that time. I had consulted to the Office of Orphan Drug Products 1984-1994 as an outside consultant before becoming employed at CDER in 1995, evaluating the data submitted by Chugai-Genetics Institute about 1986 for OOPD and recommending approval of their product MAROGEN about 1988 or so. But recombinant erythropoietin (epoetin alfa), as a competing Amgen product (given trade names EPOGEN and PROCRIT) was approved for the orphan indication in 1989 with seven-year exclusivity, and Chugai lost in a patent dispute. The indication was expanded in 1993 by Amgen to anemia in cancer patients on chemotherapy and HIV-infected patients on ziduvodine, and several times since. Although the OODP awarded orphan product grants to the developer to gather data on dialysis patients, expanded indications soon made the drug a non-orphan and the market exploded to billions of dollars annually, as described in the Washington Post front-page article by Peter Whoriskey (on Friday 20 July 2012). The effect of granting exclusivity to one orphan product and excluding competitors should be noted, especially when the “orphan” evolves into a blockbuster.

In preparation for the meeting later this week of the Risk Evaluation Management Strategy Oversight Committee, we submit these opinions now. The questions asked about both of these quite dissimilar these agents, both proposed for treatment of HoFH, were:

- 1) *Are the available data adequate to assess hepatic safety and potential monitoring mechanisms for these drug products in the HoFH population?*
- 2) *Do the hepatic biomarkers (e.g., CK18 and its fragments, ELF panel) performed by the sponsor provide any clinically useful information?*

- 3) *Are the labeled recommendations from the sponsor adequate to assess and monitor liver safety if these drugs were to be approved?*
- 4) *Are there subgroups of particular interest (e.g., demographic or baseline characteristics) that we should ensure we study with interest during the review with regard to liver safety?*
- 5) *Please provide recommendations for several GI/hepatologists who can sit on the AC panel.*
- 6) *Should these products be approved, what monitoring (enhanced pharmacovigilance, registry, etc.) would you propose to further assess liver safety post-approval?*
- 7) *Are there additional concerns unique to the pediatric population that would necessitate different monitoring of liver safety in pre-approval trials?*

Although the two agents are quite different in structure, mechanism of actions, and other ways, the questions are generic and can be responded to, at least provisionally as follows:

- 1) *Are the available data adequate to assess hepatic safety and potential monitoring mechanisms for these drug products in the HoFH population?*

In general, there are two problems that are unresolved: 1) the rather frequent incidence of serum aminotransferase elevations, albeit without much in functional disturbance as indicated by serum bilirubin and prothrombin times; and 2) the frequent induction of fatty liver in many or most of the patients receiving these drugs.

- 1) In review of transaminase elevations in patients with homozygous hypercholesterolemia, there do not appear yet to be any with elevated serum bilirubin or jaundice that are clearly or probably drug induced. However, it had been observed almost two decades ago by Bob Temple that when a drug causes more frequent serum aminotransferase elevations than placebo or control agents, then it may (but not always) be suspected that rarer but more serious cases of liver injury with dysfunction may occur, and should be looked for very carefully. One serious, fatal case of fulminant liver failure, in the man five months after stopping mipomersen, was assessed in the earlier consultation of 19 June, and we judged it to be probably caused by evolving fatal myocardial infarction. We have not assessed the larger database of patients with other types of serum cholesterol elevation submitted along with the modest numbers with HoFH, for which evaluation for approval was not requested.
- 2) The other question of how to interpret and evaluate the fatty livers seen in so many of the patients receiving these drugs is even more difficult. Despite hundreds of recent papers published about fatty liver disease and its more threatening variant of steatohepatitis that may progress slowly to cirrhosis and carcinoma in some, it is still not known how to tell which persons will progress and which will not. Newer biomarkers of CK18 and others are of research interest, but not yet reliable clinical tools to help us. Clearly we shall have to observe treated patients longer to find out. We have no sure way to distinguish benign non-progressive fatty liver from steatohepatitis with chronic low-grade inflammation that will become worse. At present only liver biopsy can be relied upon to make distinctions. If new drugs are causing both fatty liver and aminotransferase elevations, the problem is even more challenging.

The question of monitoring to detect and act upon possible evidences of liver injury, both during clinical trials but more of concern, after marketing, raises many issues about whether monitoring as usually specified in labeling accomplishes anything useful at all, even if done as advised, and experience has shown unfortunately that it is rarely done at all for very long. In short, the data available are not sufficient to provide assurance that routine monitoring serum aminotransferase activities will protect patients from possible serious liver injury beyond the apparently benign and reversible elevations observed so far. For life-shortening HoFH, long-term treatment with continued observation of liver tests is perhaps reasonable, if it is required to be done, but we are far from ready to advise extending use of these agents to life-time treatment of diverse forms of hypercholesterolemia that is less imminently threatening. If these agents are inducing simple fatty liver that does not ever progress to active steatohepatitis, there would be less concern. We do not know that yet. The combination of frequent induction of fatty liver and elevated serum aminotransferase activities is worrisome.

2) Do the hepatic biomarkers (e.g., CK18 and its fragments, ELF panel) performed by the sponsor provide any clinically useful information?

These are interesting biomarkers whose value has not yet been proved. Detection of hepatic fibrosis without liver biopsy is a research question yet to be answered. We do know that it usually takes years or even decades for progression of steatohepatitis to cirrhosis, and that imaging methods are not sensitive for detecting stages along the way. For relatively short-term studies, as submitted in these NDAs, we are more concerned about induction of acute liver injury in some people, although serious effects might be uncommon. We do not yet know whether these agents are causing heparin-like elevations of serum aminotransferases that do not progress to serious liver dysfunction, or not. Simple levels or grades of elevation of enzyme activities, as proposed and used by the National Cancer Institute, do not really serve as measures of liver dysfunction or clinical severity. The most recent comprehensive review of fatty liver disease not caused by alcohol consumption cites a simple model for likelihood of steatohepatitis (NASH) in those with fatty liver, using serum alanine aminotransferase (ALT) and fasting insulin (FI), (Torres et, 2012) . In that model, the sensitivity and specificity for detecting NASH in people with fatty liver in which prevalence of NASH was 0.30 were both 75% (area-under-receiver-operating characteristic, 0.81), using a cut-off value of -0.806: probability of NASH = $ALT \times 0.042 + FI \times 0.095 - 4.246$.

3) Are the labeled recommendations from the sponsor adequate to assess and monitor liver safety if these drugs were to be approved?

The labeling submitted with the two NDAs shows some variance between the two drugs, and it seems preferable that both be the same, since both are for exactly the same indication. No reason has been established for allowing different labeling and different interpretations. Both drugs appear to cause both fatty liver and elevated serum aminotransferase activities, and so justify the same monitoring methods and frequency, and the same responses to abnormalities detected. Even after one or both of these drugs is approved for treating HoFH (only), we still have much to learn about their long-term effects. Therefore it seems reasonable to require the labeling to state

clearly how the diagnosis of HoFH is to be established. The different draft labeling proposed in the initial NDA submissions at end-February (lomitapide) and end-March (mipomersen) should be made the same, so that all possible additional information can be gathered. The frequency of monitoring, what should be monitored, and what should be done about abnormalities should be standardized, and not left to the vagaries of various treating physicians.

We feel that pretreatment measures of serum alanine and aspartate aminotransferase activities (ALT and AST), alkaline phosphatase activity (ALP), total serum bilirubin concentration (TBL) be done at least twice biweekly, and that on-treatment monthly monitoring of tests be done for a year. If modest elevations of ALT (>3 to 5xULN) are found, the tests should be repeated within a week, preferably at a local laboratory so that results will be immediately available to the treating physician. If ALT >5 to 10xULN, repeat tests within 4 days; and if >10x, within 2 days and treatment interrupted for clinical investigation to determine the probable cause. If none is found, then rechallenge with the drug should be done cautiously, with twice weekly measures of the liver tests. Measuring prothrombin time may also be a useful test of a liver function.

4) Are there subgroups of particular interest (e.g., demographic or baseline characteristics) that we should ensure we study with interest during the review with regard to liver safety?

Because of the extreme rarity of HoFH, it is most unlikely that large numbers of subjects will be available at any location, or even in an entire trial population, sufficient to divide them into subgroups, so this approach is probably not going to be of substantial value. The stratagem of recruiting additional subjects with the more common but less threatening heterozygous form of familial hypercholesterolemia (HeFH) instead does not really address what is being studied and requested here. However, sub-grouping for study of HeFH will make very good sense, (b) (4)

5) Please provide recommendations for several GI/hepatologists who can sit on the AC panel.

Dr. Seeff has recommended Dr. Arun Sanyal or Dr. Anna Mae Diehl as hepatologist, Dr. David Kleiner or Dr. Elizabeth Brunt as hepatopathologist, and Dr. Jeremy Schwimmer or Dr. Joel Lavine as pediatric hepatologist. Dr. Senior adds that perhaps Dr. Will Lee, Dr. Paul Watson, or Dr. Willis Maddrey might be considered as alternate hepatologists. Some of these may already be asked to serve as consultants to the sponsors, and not available to us. If the list is restricted to those who are special government employees, fewer choices are available.

6) Should these products be approved, what monitoring (enhanced pharmacovigilance, registry, etc.) would you propose to further assess liver safety post-approval?

Because efforts at vigilance and monitoring have not been very successful to date, despite vast expenditures of effort and cost, this whole issue needs to be carefully reconsidered. The situation is particularly bad after approval and marketing of new drugs, expansion of the population of patients treated without the rigor imposed during clinical trials of selected subjects. In the “real

world” of post-approval pharmacovigilance, there is dependence on the ability and willingness of physicians to report cases with sufficient detail to enable evaluation of the true severity and likely causes of liver test abnormalities; many physicians never report cases at all, and even those that are reported to sponsoring companies lack necessary information to make a diagnosis of probable cause. Even the monitoring of controlled clinical trials could be improved, but the issue involved will require careful and extensive discussions with the many parties that are concerned and involved.

7) *Are there additional concerns unique to the pediatric population that would necessitate different monitoring of liver safety in pre-approval trials?*

If this study is directed at HoFH, as advertised, then a sizeable proportion of them are pediatric, for many of those afflicted with this dire disorder did not reach full adulthood, in the days before lipid-lowering drug treatment was available. The onset of the disorder begins in infancy and early childhood, when effective treatment might be most valuable in preventing progressive atherosclerosis. There definitely should be pediatric trials conducted, as a condition for approval, and completed within a reasonable time for review and evaluation. This question is an indication that the sponsors really want to study (b) (4) other forms of adult hypercholesterolemia, considerably more common conditions.

In summary, we have many concerns and few answers. We are pushing limits of what is known, and see the treatment of patients with HoFH as an opportunity to learn more about the long term effects of cholesterol lowering despite initiation of fatty liver and causation of possibly non-serious forms of hypertransaminasemia, if no serious cases of hepatotoxicity occur. For most drugs, concern regarding possible adverse effects on the liver focuses on possible development of acute liver injury. This concern holds also for both lomitapide and mipomersen, in view of the frequent occurrence of raised levels of aminotransferases, but there is the second concern of the possible development of chronic liver disease because of the equally common development of fatty liver disease. Little is known about the consequences of drug-induced fatty liver disease, whether it manifests as or progresses to the more serious form of simple fatty liver disease, namely non-alcoholic steatohepatitis (NASH) that may progress over decades to advanced chronic liver disease, cirrhosis and even the development of hepatocellular carcinoma. This is particularly relevant concern since these drugs will presumably be administered to those with HoFH for the rest of their lives. It is therefore imperative that long-term evaluation be performed to address this concern that would include regular screening for evidence of liver dysfunction. Over time, evaluation may need to include performing liver biopsies to fully determine whether there is incipient or even established steatohepatitis that would require consideration of whether or not to continue treatment with one or other drug

There does not seem to be great urgency to approve life-saving drugs for patients in immediate danger. The disease itself, HoFH, although formerly fatal to those affected before the age of child-bearing, in more recent years has shown that death can be delayed considerably by lipid-lowering treatment, so that some patients are surviving into their fifth or sixth decades. We should not repeat the mistakes of the past by allowing approval for an orphan problem to be used to persuade physicians into much more widespread use before we understand the problems we may be causing.

John R. Senior, M.D.

Leonard B. Seeff, M.D.

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/s/

MARGARITA V TOSSA
09/13/2012

ALLEN D BRINKER
09/13/2012

**Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review**

NDA	203568
Brand Name	Kynamro
Generic Name	Mipomersen
Sponsor	Celgene
Indication	Reduce LDL-L, apo B, total cholesterol, non-HDL-C, and Lp(a) in patients with HoFH
Dosage Form	s.c. and i.v. injection
Drug Class	Antisense oligonucleotide (ASO) drug that inhibits expression of apoB-100,
Therapeutic Dosing Regimen	200 mg Mipomersen Subcutaneous (SC) injection
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	200 mg Mipomersen Intravenous (IV) infusion
Submission Number and Date	SDN 001 / 4 June 2012
Review Division	DMEP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

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 $\Delta\Delta\text{QTcF}$ for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 3, indicating that assay sensitivity was established.

In this randomized, double-blinded, crossover, active- and placebo-controlled study, 60 healthy subjects received mipomersen 200 mg s.c., mipomersen 200 mg i.v., placebo, and moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs for 200-mg Mipomersen s.c., 200-mg Mipomersen i.v. and Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	$\Delta\Delta QTcF$ (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.

The suprathreshold dose (200 mg i.v.) produces mean C_{max} and AUC values of 3.8- and 1.2-fold the mean C_{max} and AUC for the therapeutic dose (200 mg s.c.). At these concentrations there are no detectable prolongations of the QT-interval. The concentrations at the clinical high exposure scenario have not been identified. No effect on C_{max} 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.

2 PROPOSED LABEL

2.1 SPONSOR'S PROPOSED LABEL

Nothing proposed

2.2 QT-IRT RECOMMENDED LABEL

We have the following label recommendations which are suggestions only. We defer the final labeling decisions to the review division.

12.2 Pharmacodynamics

Cardiac Electrophysiology -

At a concentration 3.8 times the C_{max} of the maximum recommended dose, mipomersen does not prolong QTc to any clinically relevant extent.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Mipomersen (ISIS 301012) is an antisense oligonucleotide (ASO) drug that inhibits expression of apoB-100, the primary protein constituent of atherogenic lipoproteins.

3.2 MARKET APPROVAL STATUS

Mipomersen is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

From IB, Nov 2011

The potential for mipomersen to induce cardiovascular toxicity was assessed as part of toxicology assessments in non-human primates. Heart rate, mean arterial pressure, and

electrocardiogram (ECG) were evaluated in monkeys using surgically implanted telemetry units after single and repeated administration of mipomersen.

No alterations in cardiovascular functions were observed in instrumented monkeys. Additionally, no blocking of hERG current by mipomersen was observed in a stably transfected human embryonic kidney (HEK) 293 cell line expressing hERG at concentrations of up to 150 μ M.

3.4 PREVIOUS CLINICAL EXPERIENCE

From eCTD 2.7.4, ISS

In the pooled Phase 3 studies, more mipomersen-treated patients than placebo-treated patients had events in the SOCs of Cardiac Disorders (9.2% vs. 6.2%, respectively) and Vascular Disorders (11.1% vs. 5.4%). Events were seen in all studies and no clear trend in AEs relative to study population (and thus LDL-C/disease burden) was noted. No particular event type dominated the reported cardiac events. Angina pectoris (3.8% vs. 1.6%) and Palpitations (2.7% vs. 0%) were noted to comprise much of the difference between the mipomersen and placebo groups in the SOC of Cardiac Disorders, while Hypertension (6.5% vs. 3.1%) comprised much of the difference in the SOC of Vascular Disorders.

In OLE study ISIS 301012-CS6, 20.6% of patients were reported to have AEs in the SOC of Cardiac Disorders. The most common event reported in this SOC was Angina pectoris, reported in 7.1% of patients.

Major adverse cardiac events (MACE) were defined retrospectively as events 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 frequency of these events was examined posthoc in the Phase 3 studies and included both the 26-week on-treatment period as well as the 24-week post-treatment follow-up period for those patients not entering the OLE study ISIS 301012-CS6. These events were not prospectively defined or adjudicated across the four Phase 3 studies and the OLE study, and no difference in events was anticipated given the short duration of treatment and follow-up and the total number of patients. The MACE incidence was similar in the mipomersen-treated group (3.4%) and the placebo group (3.1%; ISS Section 8.6.6.1).

The Phase 3 studies required that blood pressure be controlled at study entry. 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%] from the pooled Phase 3 data; Table 10). This disparity was greater in the subpopulation of patients over age 65 (10/59 [16.9%] mipomersen-treated patients \geq 65 years vs 7/199 [3.5%] mipomersen-treated patients age 18 to < 65 years; Table 14).

Table 2: Common On-Treatment Adverse Events (Occurring in $\geq 5\%$ of Patients in Either Treatment Group) by Age, System Organ Class and Preferred Term for Pooled Phase 3 Placebo-Controlled Studies

System Organ Class Preferred Term	Age < 18 years		Age 18-< 65 years		Age ≥ 65 years	
	Placebo (N=4)	Mipomersen (N=3)	Placebo (N=98)	Mipomersen (N=199)	Placebo (N=27)	Mipomersen (N=59)
Any AE, n (%)	3 (75.0)	2 (66.7)	83 (84.7)	191 (96.0)	23 (85.2)	56 (94.9)
Respiratory, thoracic and mediastinal disorders						
Cough	0 (0.0)	0 (0.0)	3 (3.1)	9 (4.5)	2 (7.4)	5 (8.5)
Vascular disorders						
Hypertension	0 (0.0)	0 (0.0)	3 (3.1)	7 (3.5)	1 (3.7)	10 (16.9)

Source: ISS Statistical Tables 3.2.2.1.2.1, 3.2.2.1.2.2, 3.2.2.1.2.3

Note 1: 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.

Note 2: To obtain the number of patients, 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.

Note 3: Patient percentages were based on the total number of treated patients in the particular treatment group.

Source: eCTD 2.7.4, Table 14, page 45.

Reviewer's comments: No syncope, seizures, sudden cardiac deaths or ventricular arrhythmias were reported. No clinically relevant ECG changes were reported. Three deaths were reported in mipomersen-treated patients and occurred during the post-treatment follow-up period. Hypertension was the most common vascular AE, with a higher frequency rate in subjects ≥ 65 years of age.

3.5 (CLINPHARM) CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of mipomersen's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 70,969. The sponsor submitted the study report MIPO2800209 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Randomized Double-Blind Crossover Trial to Define the ECG Effects of Mipomersen (ISIS 301012) using a Therapeutic and a Supratherapeutic Dose compared to Placebo and Moxifloxacin (Positive Control) in Healthy Men and Women: A Thorough ECG Trial

4.2.2 Protocol Number

MIPO2800209

4.2.3 Study Dates

First subject enrolled: 04 February 2010

Last subject completed: 29 June 2010

4.2.4 Objectives

The primary objective of this study was to assess the electrocardiogram (ECG) effects of mipomersen administered as a 200-mg subcutaneous (SC) therapeutic and a 200-mg intravenous (IV; [2-hour infusion]) supra-therapeutic dose relative to placebo in healthy adult male and female subjects.

The secondary objective of his study was to evaluate the safety and pharmacokinetics of mipomersen when administered as a single therapeutic (200 mg) SC and a single supra-therapeutic (200 mg) IV dose.

4.2.5 Study Description

4.2.5.1 Design

This 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 QT/corrected QT (QTc) interval.

Subjects were treated in a 4-way crossover study design (4 periods) with a minimum 5-day washout period between doses to allow each subject's drug blood concentrations to return to less than 5% of his or her maximal value and prevent any carryover effect.

4.2.5.2 Controls

The sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

This study was an open-label for moxifloxacin.

4.2.5.4 Treatment Arms

On Day 1 of Period 1, each subject was randomly assigned to receive 1 of 8 possible treatment sequences to be used for Periods 1 through 4. Each of the 8 treatment sequences used all of the following 4 combinations of mipomersen and control treatment, with each subject receiving both a single 2-hour IV infusion and a single SC injection:

- 200 mg mipomersen IV/placebo SC
- 200 mg mipomersen SC/placebo IV
- 400 mg moxifloxacin IV/placebo SC
- placebo IV/placebo SC

4.2.5.5 Sponsor's Justification for Doses

The ICH E14 guidance on the design and conduct of thorough QT studies recommends examination of 2 dose levels of the investigational product, one at the therapeutic dose and another at a supra-therapeutic dose.

The therapeutic dose used in this study was a single 200-mg SC injection and the supra-therapeutic dose was a single 200-mg IV infusion. The therapeutic dose was selected because it is the dose of mipomersen currently under development for patients with HoFH and severe hypercholesterolemia.

The supra-therapeutic dose regimen of mipomersen was chosen in order to provide a peak (maximum) level of plasma exposure in healthy subjects above the typical range expected to occur in the target population with the therapeutic dose regimen (200 mg SC) and to allow for PK and QTc modeling to assess the effect of drug concentrations on cardiac repolarization. A 2-hour IV infusion was chosen for the supra-therapeutic dose because this route of administration was expected to result in a plasma C_{max} that is typically 5-fold higher (range: 3.4 to 8-fold) than the intended therapeutic SC dose, with an AUC from time 0 to 48 hours that is typically 1.6-fold higher (range: 1.33 to 1.94-fold) than the intended therapeutic SC dose. Doses greater than 200 mg (SC or IV) are associated with a greater incidence of symptoms, such as fever and nausea, and thus, would potentially have impacted the ability to blind the study. The use of an IV supra-therapeutic dose was also supported by the fact that an SC dose exceeding 200 mg would have required multiple injections and potentially increased the AE rate for all subjects.

Reviewer's Comments: The maximum tolerated dose studied is 400 mg i.v. However, since no intrinsic factors (i.e., renal or hepatic impairment, etc.) or extrinsic factors (drug-drug interactions) have been identified to explain PK variability, the sponsor's high exposure scenario has not been identified. The C_{max} for this dose is 3.8-fold that for the intended therapeutic dose (200 mg s.c.).

4.2.5.6 Instructions with Regard to Meals

Subjects received study drug on Day 1 of each period after at least an 8-hour fast. Subjects were allowed to drink water and eat a meal approximately 1 and 2 hours, respectively, after the end of the moxifloxacin, mipomersen, or placebo infusion (3 and 4 hours, respectively, after the s.c. injection).

Reviewer's Comments: Mipomersen is a product for s.c. administration. Therefore effect of food on carfilzomib exposure is not expected.

4.2.5.7 ECG and PK Assessments

PK Assessments:

Serial blood samples were collected for PK analysis on Days 1 and 2 of each treatment period before dosing (0 hour; trough level) and at 1, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10 (Day 1), 14 (Days 1 or 2), 18 (Day 2), and 22.5 hours (Day 2) after initiation of dosing.

ECG Assessments:

On the treatment days, 12-lead ECGs were obtained in triplicate and downloaded from the H-12+ flash card approximately 1 minute apart on Days 1 and 2 of each arm of this crossover study. Baseline time points were obtained on Day 1 before each dose at -45, -30, and -15 minutes. Postdose time points occurred at the following times in each treatment period: 1, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10 (Day 1), 14 (Days 1 or 2), 18 (Day 2), and 22.5 hours (Day 2) after initiation of dosing. Time 0 began at the start of the IV infusion (i.e., the same time as SC injection) as opposed to the end of the infusion (i.e., C_{max}).

Reviewer's Comment: The PK and ECG sampling time points are acceptable as this time course is sufficient to capture ECG effects around the T_{max} (2 hours for i.v. infusion and 3 – 4 hours for s.c. injection) of mipomersen and over a 24-hour, post-dose, time period.

4.2.6 Baseline

The sponsor used time-averaged baseline QTc values on Day 1.

4.2.7 ECG Collection

Intensive 12-Lead Holter monitoring was used to obtain digital ECGs. The centralized core ECG laboratory read all ECGs from Holter monitoring and interpreted the results to assess cardiac repolarization and other cardiac parameters.

Standard 12-Lead ECGs will be obtained while subjects are recumbent. A single safety 12-lead ECG was collected for each subject on Day 1 of each period within 40 minutes before dosing and at 3 hours after initiation of dosing, and at the End-of-Study visit (or upon withdrawal or discontinuation). All ECGs were obtained before the PK samples.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 60 subjects (male and female subjects 18 to 45 years of age) were randomly assigned to study drug, and 55 subjects (91.7%) completed the study. Subjects 1015, 1016, and 1022 discontinued on Day –1 of Period 3 because of lack of compliance (positive urine drug screen results at check-in). Subject 1033 withdrew consent on Day 1 of Period 4. Subject 1038 discontinued by choice on Day 5 of Period 4.

Subject demographics and baseline characteristics are summarized in Table 3.

Table 3: Summary of Demographics and Baseline Characteristics (All Randomized Subjects)

No. of subjects (%)	Treatment Sequence ^a								Overall (N = 60)
	1 (N = 8)	2 (N = 8)	3 (N = 7)	4 (N = 7)	5 (N = 8)	6 (N = 7)	7 (N = 7)	8 (N = 8)	
Age (years)									
Mean (SD)	31.9 (7.88)	33.8 (6.30)	31.4 (9.22)	24.4 (6.32)	31.9 (8.39)	29.0 (7.81)	30.0 (8.33)	31.4 (9.97)	30.6 (8.06)
Median	31.5	32.0	30.0	23.0	32.5	27.0	31.0	29.5	30.0
Minimum, Maximum	21, 45	25, 45	21, 45	19, 38	22, 45	21, 42	19, 40	19, 45	19, 45
Gender, No. (%)									
Male	3 (37.5)	4 (50.0)	4 (57.1)	3 (42.9)	3 (37.5)	1 (14.3)	3 (42.9)	4 (50.0)	25 (41.7)
Female	5 (62.5)	4 (50.0)	3 (42.9)	4 (57.1)	5 (62.5)	6 (85.7)	4 (57.1)	4 (50.0)	35 (58.3)
Race, No. (%)									
White	7 (87.5)	6 (75.0)	5 (71.4)	5 (71.4)	8 (100.0)	6 (85.7)	6 (85.7)	6 (75.0)	49 (81.7)
Black or African American	1 (12.5)	2 (25.0)	0	2 (28.6)	0	1 (14.3)	1 (14.3)	2 (25.0)	9 (15.0)
Asian	0	0	1 (14.3)	0	0	0	0	0	1 (1.7)
American Indian or Alaska Native	0	0	1 (14.3)	0	0	0	0	0	1 (1.7)
Ethnicity, No. (%)									
Hispanic or Latino	4 (50.0)	3 (37.5)	4 (57.1)	1 (14.3)	5 (62.5)	1 (14.3)	1 (14.3)	3 (37.5)	22 (36.7)
Not Hispanic or Latino	4 (50.0)	5 (62.5)	3 (42.9)	6 (85.7)	3 (37.5)	6 (85.7)	6 (85.7)	5 (62.5)	38 (63.3)
Height (cm)									
Mean (SD)	160.55 (7.706)	166.83 (7.097)	167.43 (6.110)	168.84 (11.622)	163.29 (11.427)	164.74 (9.870)	171.06 (8.467)	168.89 (5.116)	166.35 (8.769)
Median	162.00	165.40	166.70	164.90	160.15	163.60	172.40	169.80	166.25
Minimum, Maximum	145.1, 170.6	157.6, 180.9	158.9, 175.0	155.6, 187.0	150.0, 180.0	153.2, 181.4	158.7, 182.0	160.3, 176.3	145.1, 187.0

Table 11-1 is continued on the next page.

Source: CSR, Table 11-1

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary endpoints were time-matched baseline-adjusted mean differences between mipomersen (200 mg s.c. and 200 mg i.v.) and placebo in QTcF. The sponsor used a mixed effects model and the results are presented in Table 4. This model included gender, time, treatment, time-by-treatment interaction as fixed effect terms. Baseline QTcF was included as a covariate and subject and subject as random effect. The upper limits of the 2-sided 90% CI for mipomersen 200 mg s.c. and mipomersen 200 mg i.v. were below 10 ms.

Table 4: Sponsor Results of $\Delta \Delta$ QTcF

Mipomersen 200 mg SC	Mipometson 200 mg IV	Moxifloxacin 400 mg
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	Estimate	Lower Bound	Upper Bound	Estimate	Lower Bound	Upper Bound	Estimate	Lower Bound	Upper Bound
1	-0.4	-2.6	1.7	-1.4	-3.6	0.8	9.7	6.5	12.9
2	-0.8	-2.9	1.3	-2.0	-4.2	0.2	16.9	13.7	20.1
2.5	0.0	-2.1	2.2	-0.2	-2.4	2.0	13.8	10.6	17.0
3	-1.4	-3.5	0.7	-0.8	-3.0	1.4	12.6	9.4	15.8
3.5	-1.7	-3.9	0.4	0.2	-2.0	2.4	12.6	9.4	15.8
4	0.6	-1.5	2.7	1.0	-1.2	3.2	13.8	10.6	17.0
5	-1.2	-3.3	0.9	0.4	-1.9	2.6	11.3	8.1	14.5
6	-0.6	-2.7	1.5	0.8	-1.5	3.0	11.1	7.9	14.3
8	0.4	-1.7	2.5	-0.7	-2.9	1.5	10.3	7.1	13.5
10	-1.4	-3.5	0.8	-2.2	-4.5	0.0	9.0	5.8	12.2
14	-0.6	-2.7	1.5	-1.4	-3.6	0.8	6.8	3.6	10.0
18	-3.0	-5.1	-0.8	-4.5	-6.7	-2.3	5.5	2.3	8.7
22.5	-2.0	-4.2	0.1	-1.8	-4.0	0.5	7.6	4.4	10.7
Time average	-0.9	-2.4	0.5	-1.0	-2.4	0.5	10.9	9.4	12.3

Source: Clinical Study Report No., Section 114.1.2, Table 11-3, Pg75/655

Reviewer's Comments: We will provide our independent analysis results in Section 5.2. Our analyses results are similar to those provided by the sponsor.

4.2.8.2.2 Assay Sensitivity

The sponsor used the same mixed model to analyze the Δ QTcF effect for moxifloxacin. The analysis results were presented in Table 4. The largest lower bound of the 2-sided 90% CI was greater than 5 ms. Thus, assay sensitivity in this thorough QTcF study was established.

4.2.8.2.3 Categorical Analysis

Categorical analysis was used to summarize in the categories of QTc \leq 450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and $>$ 500 ms, and changes from baseline QTc \leq 30 ms, between 30 and 60 ms, and $>$ 60 ms. No subject's absolute QTc $>$ 480 ms and Δ QTc $>$ 60 ms.

4.2.8.2.4 Additional Analyses

Mipomersen had no effects on HR, PR, and QRS interval duration or cardiac morphology.

4.2.8.3 Safety Analysis

Twenty-eight subjects (46.7%) reported at least 1 TEAE considered related to study-drug. Treatment-related TEAEs included the following: injection site induration, erythema, pain, pruritus, hemorrhage, and reaction; influenza-like illness; infusion site erythema, pruritus, and induration; asthenia; headache; dizziness; nausea; diarrhea; and blurred vision. These TEAEs were reported by the highest percentage of subjects (24.1%) after 200-mg mipomersen SC plus placebo i.v., and by smaller percentages of subjects (15.5%-5.1%) after all other treatments.

There were no deaths, SAEs, or AEs that led to study drug discontinuation.

Subject #1041 had post-baseline heart rate increases $>$ 30 bpm and \leq 44 bpm after the 200 mg i.v. and s.c. dose respectively. Subject MIPO2800209-01-1009 had a post baseline HR change of 31 bpm after the i.v. dose. Both subjects had post dose HR $>$ 100 bpm. Both events were clinically meaningful. It seems unlikely that these events are related to study drug.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results of mipomersen are presented in Table 5. The suprathreshold dose (200 mg i.v.) produces mean C_{max} and AUC values of 3.8- and 1.2-fold the mean C_{max} and AUC for the therapeutic dose (200 mg s.c.).

Table 5: Mean (%CV) Plasma Pharmacokinetic Parameters of Mipomersen

Parameter (unit)	200-mg Mipomersen SC (N = 58)	200-mg Mipomersen IV (2-hour infusion) (N = 56)
AUC _{0-22.5h} (ng·h/mL)	51200 (23.6)	63900 (18.5)
C_{max} (ng/mL)	5860 (32.6)	22100 (19.8)
T_{max} (h) ^a	3.60 (1.10, 8.10)	2.10 (2.08, 2.33)

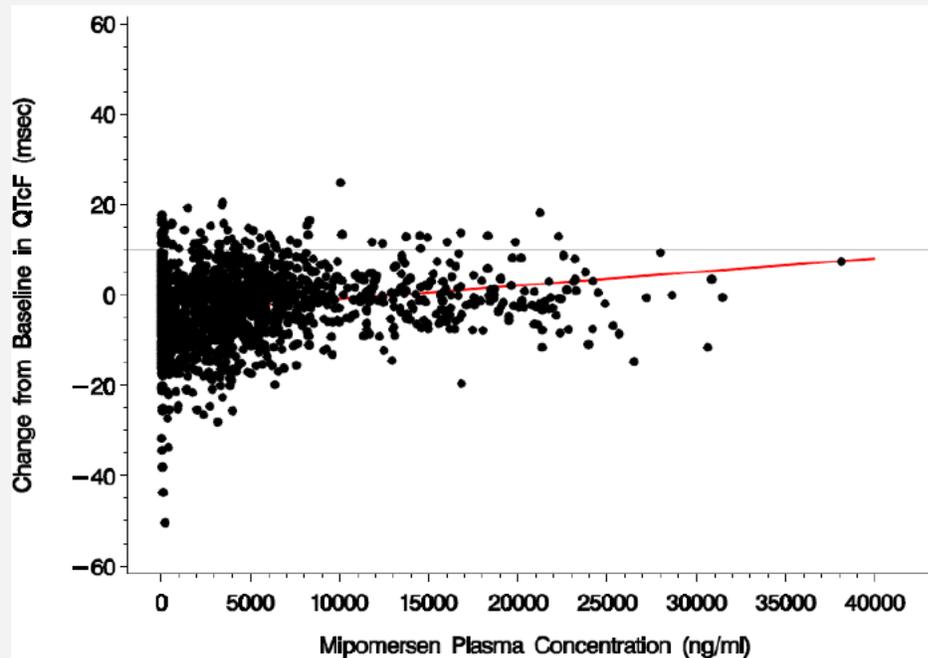
(Source: Sponsor's Clinical Study Report, Table 11-4)

4.2.8.4.2 Exposure-Response Analysis

The sponsor conducted an exposure-response analyses for QTcF change from baseline (not placebo corrected) and concluded this analysis does not support any effect of mipomersen on cardiac repolarization.

Figure 1 illustrates the relationship between the exposure (plasma concentration of mipomersen) and the effect (change in QTcF from Baseline) for mipomersen.

Figure 1. QTcF Change from Baseline versus Mipomersen Plasma Concentration



(Source: Sponsor's Clinical Study Report, Figure 11-6)

The results of the PK-PD model showed that the slope for the mipomersen plasma concentration effect on QTcF was 0.00025, and the predicted QTcF mean change from baseline values at C_{max} for the mipomersen therapeutic (200 mg SC) and supra-therapeutic (200 mg IV) doses was -2.4187 ms and 1.6868 ms, respectively

Reviewer's Comments: The sponsor found a significant relationship with Δ QTcF (Figure 1) whereas the reviewer's analysis indicates no significant exposure-response relationship exists for Δ QTcF. While heart rate appeared to increase by about 10 beats per minute 4 hours after initiating treatment, this was an effect that was observed consistently in the placebo and the moxifloxacin treatment groups in addition to the mipomersen treatment groups. Thus, it is reasonable to correct for placebo response and use Δ QTcF. Regardless, because the sponsor's slope of the relationship was so small, both analyses reach the same conclusion that mipomersen does not have a clinically relevant effect on cardiac repolarization at the studied exposures.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

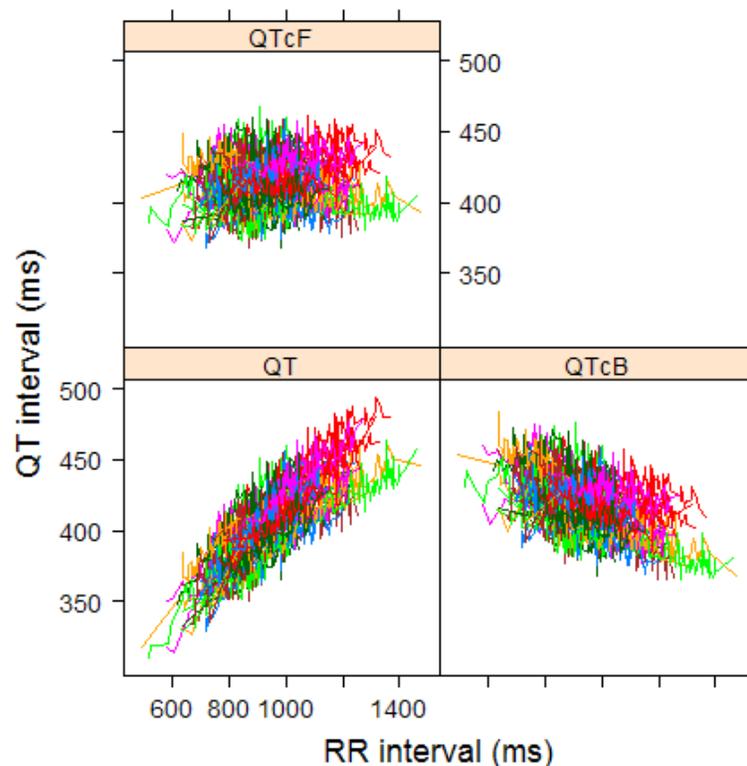
We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 6, it appears that QTcF is better than QTcB. Therefore, this statistical reviewer used QTcF for the primary statistical analysis. This is consistent with the sponsor's choice of QTcF for their primary analysis.

Table 6: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	Correction Method			
	QTcB		QTcF	
	N	MSSS	N	MSSS
200-mg mipomersen IV / Placebo Subcutaneous	56	0.0041	56	0.0013
200-mg mipomersen Subcutaneous / Placebo IV	58	0.0046	58	0.0018
400-mg moxifloxacin IV / Placebo Subcutaneous	58	0.0074	58	0.0012
Placebo IV / Placebo Subcutaneous	59	0.0037	59	0.0014
All	60	0.0046	60	0.0010

The QT-RR interval relationship is presented in Figure 2 together with the Bazett's (QTcB) and Fridericia (QTcF).

Figure 2: QT, QTcB, and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for the Study Drug

The statistical reviewer used mixed model to analyze the Δ QTcF effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 7. The largest upper bounds of the 2-sided 90% CI for the mean differences between mipomersen 200 mg s.c. and placebo, and between mipomersen 200 mg i.v. and placebo are 2.7 ms and 3.1 ms, respectively.

Table 7: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Mipomersen 200-mg s.c., Mipomersen 200-mg i.v., and Moxifloxacin 400 mg

		200-mg mipomersen IV / Placebo Subcutaneous				200-mg mipomersen Subcutaneous / Placebo IV				400-mg moxifloxacin IV / Placebo Subcutaneous					
		Δ QTcF		Δ QTcF		Δ QTcF		$\Delta\Delta$ QTcF		Δ QTcF		$\Delta\Delta$ QTcF			
Time (h)	Placebo	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	Adj.* 90% CI
1	0.8	56	-0.5	-1.3	(-3.0, 0.5)	58	0.2	-0.5	(-2.3, 1.2)	58	10.5	9.7	(8.0, 11.5)	(7.4, 12.1)	
2	1.1	56	-0.9	-1.9	(-3.9, 0.1)	58	0.2	-0.9	(-2.9, 1.1)	58	18.0	16.9	(14.9, 18.9)	(14.2, 19.7)	
2.5	0.8	56	0.7	-0.1	(-2.1, 1.8)	58	0.8	-0.0	(-2.0, 1.9)	58	14.7	13.8	(11.9, 15.8)	(11.2, 16.5)	
3	0.0	55	-0.8	-0.8	(-2.7, 1.2)	58	-1.5	-1.5	(-3.4, 0.5)	58	12.6	12.6	(10.7, 14.5)	(10.0, 15.2)	
3.5	1.1	56	1.4	0.3	(-1.8, 2.5)	58	-0.7	-1.8	(-3.9, 0.4)	58	13.7	12.6	(10.5, 14.7)	(9.7, 15.5)	
4	-0.9	56	0.2	1.1	(-0.9, 3.1)	58	-0.4	0.5	(-1.4, 2.5)	58	12.9	13.8	(11.9, 15.8)	(11.2, 16.5)	
5	-1.5	56	-1.1	0.4	(-2.0, 2.8)	58	-2.6	-1.0	(-3.4, 1.3)	58	9.8	11.4	(9.0, 13.7)	(8.2, 14.6)	
6	-6.5	56	-5.7	0.8	(-1.4, 3.0)	58	-6.9	-0.4	(-2.6, 1.9)	58	4.7	11.2	(9.0, 13.4)	(8.2, 14.3)	
8	-9.6	56	-10.2	-0.6	(-2.8, 1.6)	58	-9.1	0.5	(-1.7, 2.7)	58	0.7	10.4	(8.2, 12.6)	(7.4, 13.4)	
10	-4.0	56	-6.2	-2.2	(-4.5, 0.2)	57	-5.3	-1.3	(-3.6, 1.1)	58	5.0	9.0	(6.7, 11.4)	(5.8, 12.2)	
14	-5.2	56	-6.6	-1.3	(-4.0, 1.3)	57	-5.7	-0.4	(-3.0, 2.2)	58	1.6	6.9	(4.2, 9.5)	(3.3, 10.4)	
18	4.3	56	-0.2	-4.4	(-7.2, -1.7)	57	1.4	-2.8	(-5.6, -0.1)	58	9.9	5.6	(2.9, 8.3)	(1.9, 9.3)	
22.5	-2.2	56	-3.9	-1.7	(-4.0, 0.6)	57	-4.1	-2.0	(-4.3, 0.3)	58	5.4	7.6	(5.3, 9.9)	(4.5, 10.7)	

* Bonferroni adjustment for 4 time points.

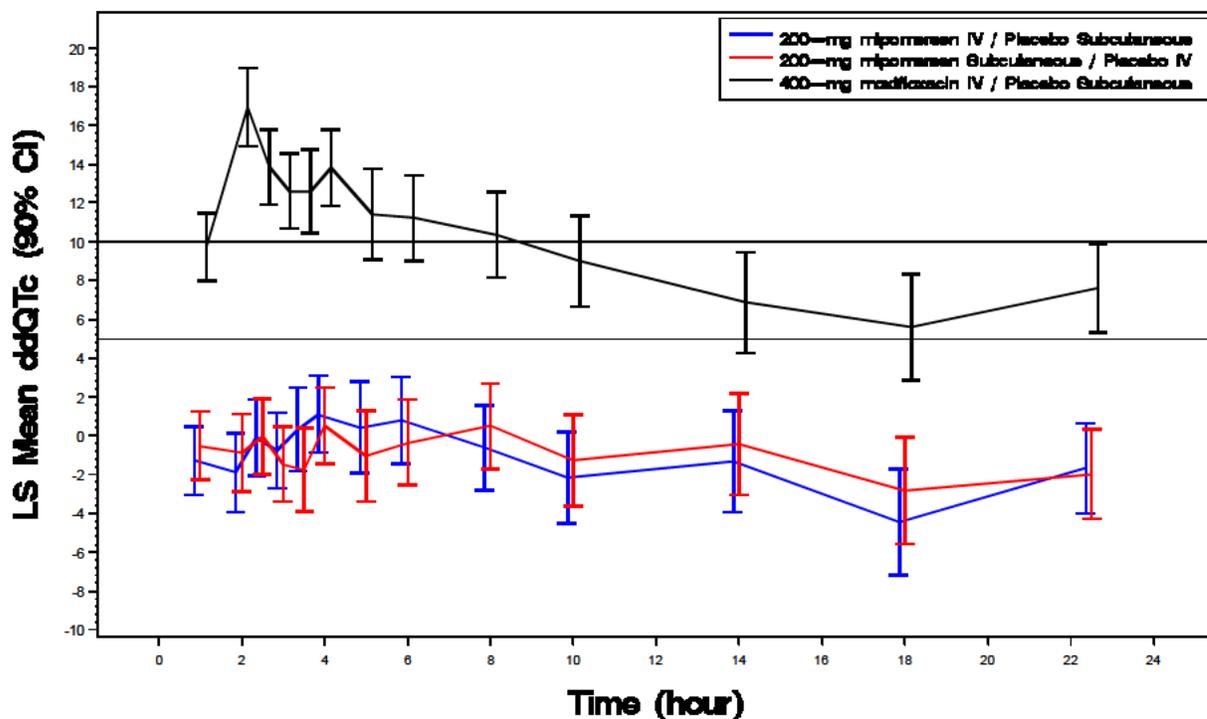
5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 7. The largest unadjusted 90% lower confidence interval is 11.9 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 11.2 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

5.2.1.3 Graph of $\Delta\Delta$ QTcF Over Time

Figure 3 displays the time profile of $\Delta\Delta$ QTcF for mipomersen groups and moxifloxacin 400 mg.

Figure 3: Mean and 90% CI $\Delta\Delta$ QTcF Time Course for Mipomersen (200-mg s.c. and 200-mg i.v.) and Moxifloxacin 400 mg



5.2.1.4 Categorical Analysis

Table 8 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, and between 450 ms and 480 ms. No subject's QTcF is above 480 ms.

Table 8: Categorical Analysis for QTcF

Treatment Group	Total N	Value ≤ 450 ms	450 ms < Value ≤ 480 ms
200-mg mipomersen IV / Placebo Subcutaneous	56	55 (98.2%)	1 (1.8%)
200-mg mipomersen Subcutaneous / Placebo IV	58	57 (98.3%)	1 (1.7%)
400-mg moxifloxacin IV / Placebo Subcutaneous	58	48 (82.8%)	10 (17.2%)
Placebo IV / Placebo Subcutaneous	59	58 (98.3%)	1 (1.7%)

Table 9 lists the categorical analysis for Δ QTcF. No subject's change from baseline is above 60 ms.

Table 9: Categorical Analysis for ΔQTcF

Treatment Group	Total N	Value≤30 ms	30 ms<Value≤60 ms
200-mg mipomersen IV / Placebo Subcutaneous	56	56 (100%)	0 (0.0%)
200-mg mipomersen Subcutaneous / Placebo IV	58	58 (100%)	0 (0.0%)
400-mg moxifloxacin IV / Placebo Subcutaneous	58	53 (91.4%)	5 (8.6%)
Placebo IV / Placebo Subcutaneous	59	59 (100%)	0 (0.0%)

5.2.2 HR Analysis

The statistical reviewer used mixed model to analyze the ΔHR effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 10. The largest upper bounds of the 2-sided 90% CI for the mean differences between mipomersen 200 mg s.c. and placebo, and between mipomersen 200 mg i.v. and placebo are 7.5 bpm and 6.6 bpm, respectively. Table 11 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 10: Analysis Results of ΔHR and ΔΔHR for Mipomersen 200-mg s.c., Mipomersen 200-mg i.v., and Moxifloxacin 400 mg

	Placebo	200-mg mipomersen IV / Placebo Subcutaneous				200-mg mipomersen Subcutaneous / Placebo IV				400-mg moxifloxacin IV / Placebo Subcutaneous			
	ΔHR	ΔHR		ΔΔHR		ΔHR		ΔΔHR		ΔHR		ΔΔHR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
1	0.3	56	-0.5	-0.8	(-2.1, 0.6)	58	0.6	0.4	(-1.0, 1.7)	58	3.0	2.7	(1.4, 4.0)
2	1.2	56	1.3	0.1	(-1.8, 1.9)	58	2.2	1.0	(-0.8, 2.9)	58	8.1	6.9	(5.1, 8.8)
2.5	0.8	56	1.1	0.3	(-1.1, 1.7)	58	0.4	-0.5	(-1.8, 0.9)	58	3.2	2.4	(1.1, 3.8)
3	0.8	55	0.5	-0.4	(-1.7, 0.9)	58	1.3	0.5	(-0.8, 1.7)	58	3.5	2.7	(1.4, 3.9)
3.5	0.7	56	1.6	0.9	(-0.6, 2.5)	58	1.1	0.4	(-1.1, 2.0)	58	2.6	1.9	(0.3, 3.4)
4	1.0	56	1.8	0.8	(-0.5, 2.2)	58	1.0	0.1	(-1.2, 1.4)	58	2.8	1.9	(0.6, 3.2)
5	8.6	56	10.5	1.8	(-0.1, 3.8)	58	9.3	0.6	(-1.3, 2.6)	58	10.8	2.2	(0.2, 4.1)
6	10.0	56	10.9	0.9	(-1.3, 3.1)	58	9.0	-1.0	(-3.2, 1.2)	58	11.4	1.3	(-0.8, 3.5)
8	6.2	56	7.6	1.4	(-0.6, 3.3)	58	7.6	1.4	(-0.5, 3.3)	58	8.3	2.1	(0.2, 4.0)
10	3.0	56	7.1	4.1	(2.1, 6.1)	57	4.4	1.4	(-0.6, 3.4)	58	5.0	2.0	(0.0, 4.0)
14	5.2	56	9.5	4.4	(2.1, 6.6)	57	8.2	3.0	(0.8, 5.2)	58	6.3	1.2	(-1.0, 3.4)
18	-0.4	56	2.5	2.9	(0.9, 4.9)	57	2.3	2.7	(0.6, 4.7)	58	0.6	1.0	(-1.0, 3.0)
22.5	1.1	56	5.0	3.9	(1.7, 6.2)	57	6.3	5.2	(3.0, 7.5)	58	2.0	1.0	(-1.2, 3.2)

Table 11: 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%)

5.2.3 PR Analysis

The statistical reviewer used mixed model to analyze the ΔPR effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 12. The largest upper bounds of the 2-sided 90% CI for the mean differences between mipomersen 200 mg s.c. and placebo, and between mipomersen 200-mg i.v. and placebo are 3.9 ms 2.6 ms, respectively. Table 13 presents the categorical analysis of PR. One subject who experienced PR interval greater than 200 ms was in both mipomersen 200-mg s.c. and 200-mg i.v. groups.

Table 12: Analysis Results of ΔPR and ΔΔPR for 200 mg Mipomersen s.c., 200 mg Mipomersen i.v., and Moxifloxacin 400 mg

Time (h)	Placebo	200-mg mipomersen IV / Placebo Subcutaneous				200-mg mipomersen Subcutaneous / Placebo IV				400-mg moxifloxacin IV / Placebo Subcutaneous			
	ΔPR	ΔPR		ΔΔPR		ΔPR		ΔΔPR		ΔPR		ΔΔPR	
	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
1	-0.5	56	-0.2	0.4	(-1.6, 2.4)	58	0.3	0.8	(-1.2, 2.8)	58	0.4	0.9	(-1.1, 2.9)
2	-0.6	56	-0.6	-0.0	(-2.0, 1.9)	58	-1.1	-0.5	(-2.5, 1.4)	58	-1.6	-1.0	(-3.0, 0.9)
2.5	-2.0	56	-3.6	-1.7	(-3.5, 0.2)	58	-1.7	0.3	(-1.6, 2.1)	58	-1.7	0.3	(-1.6, 2.1)
3	-1.4	55	-3.2	-1.8	(-4.0, 0.3)	58	-1.5	-0.1	(-2.3, 2.0)	58	-3.5	-2.1	(-4.3, 0.0)
3.5	-1.4	56	-4.0	-2.6	(-4.6, -0.6)	58	-1.8	-0.4	(-2.4, 1.5)	58	-3.5	-2.1	(-4.0, -0.1)
4	-2.7	56	-3.0	-0.3	(-2.1, 1.5)	58	-2.5	0.3	(-1.5, 2.0)	58	-3.6	-0.9	(-2.7, 0.8)
5	-4.0	56	-4.0	0.0	(-2.5, 2.5)	58	-2.6	1.4	(-1.1, 3.9)	58	-6.1	-2.1	(-4.6, 0.4)
6	-6.0	56	-7.0	-1.0	(-3.4, 1.5)	58	-5.2	0.8	(-1.6, 3.2)	58	-7.8	-1.8	(-4.2, 0.6)
8	-6.2	56	-6.9	-0.7	(-3.2, 1.7)	58	-7.1	-0.9	(-3.4, 1.5)	58	-9.0	-2.8	(-5.3, -0.4)
10	-4.5	56	-3.9	0.6	(-1.6, 2.7)	57	-5.1	-0.6	(-2.7, 1.6)	58	-7.3	-2.8	(-5.0, -0.7)
14	-2.8	56	-3.1	-0.3	(-2.5, 2.0)	57	-2.2	0.6	(-1.7, 2.9)	58	-5.9	-3.1	(-5.4, -0.9)
18	1.5	56	1.7	0.1	(-2.3, 2.6)	57	0.9	-0.6	(-3.0, 1.8)	58	-0.2	-1.7	(-4.1, 0.7)
22.5	0.6	56	0.6	-0.0	(-2.1, 2.1)	57	-0.1	-0.7	(-2.8, 1.3)	58	-0.6	-1.2	(-3.3, 0.8)

Table 13: Categorical Analysis for PR

Treatment Group	Total N	PR < 200 ms	PR ≥ 200 ms
200-mg mipomersen IV / Placebo Subcutaneous	56	55 (98.2%)	1 (1.8%)
200-mg mipomersen Subcutaneous / Placebo IV	58	57 (98.3%)	1 (1.7%)
400-mg moxifloxacin IV / Placebo Subcutaneous	58	58 (100%)	0 (0.0%)
Placebo IV / Placebo Subcutaneous	59	56 (94.9%)	3 (5.1%)

5.2.4 QRS Analysis

The statistical reviewer used mixed model to analyze the Δ QRS effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 14. The largest upper bounds of the 2-sided 90% CI for the mean differences between mipomersen 200 mg s.c. and placebo, and between mipomersen 200 mg i.v. and placebo are 1.3 ms and 1.1 ms, respectively. Table 15 presents the categorical analysis of QRS. Two subjects who experienced QRS interval greater than 110 ms were in both mipomersen 200-mg s.c. and 200-mg i.v. groups.

Table 14: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for 200 mg Mipomersen IV, 200 mg Mipomersen SC, and Moxifloxacin 400 mg

Time (h)	Placebo	200 mg mipomersen IV / Placebo Subcutaneous				200 mg mipomersen Subcutaneous / Placebo IV				400 mg moxifloxacin IV / Placebo Subcutaneous			
	Δ QRS	Δ QRS		$\Delta\Delta$ QRS		Δ QRS		$\Delta\Delta$ QRS		Δ QRS		$\Delta\Delta$ QRS	
	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
1	0.2	56	-0.5	-0.6	(-1.2, -0.1)	58	0.1	-0.1	(-0.6, 0.5)	58	0.1	-0.0	(-0.6, 0.5)
2	0.0	56	-0.2	-0.3	(-0.9, 0.4)	58	-0.2	-0.2	(-0.8, 0.4)	58	-0.4	-0.4	(-1.0, 0.2)
2.5	-0.5	56	-0.3	0.2	(-0.4, 0.9)	58	-0.1	0.4	(-0.2, 1.0)	58	-0.2	0.4	(-0.3, 1.0)
3	-0.3	55	0.2	0.4	(-0.2, 1.1)	58	0.1	0.3	(-0.3, 1.0)	58	-0.5	-0.3	(-0.9, 0.4)
3.5	0.0	56	0.4	0.4	(-0.2, 1.0)	58	0.3	0.2	(-0.4, 0.9)	58	-0.4	-0.4	(-1.0, 0.2)
4	-0.6	56	-0.1	0.5	(-0.1, 1.1)	58	0.1	0.7	(0.0, 1.3)	58	-0.9	-0.3	(-0.9, 0.3)
5	1.5	56	1.6	0.1	(-0.9, 1.0)	58	1.6	0.1	(-0.8, 1.0)	58	1.0	-0.5	(-1.4, 0.4)
6	0.3	56	-0.2	-0.4	(-1.3, 0.4)	58	0.8	0.5	(-0.3, 1.3)	58	-0.8	-1.1	(-1.9, -0.3)
8	-0.8	56	-1.0	-0.2	(-1.0, 0.6)	58	-0.6	0.2	(-0.5, 1.0)	58	-1.1	-0.3	(-1.1, 0.4)
10	-0.7	56	-1.0	-0.3	(-1.0, 0.5)	57	-0.2	0.5	(-0.2, 1.3)	58	-1.0	-0.3	(-1.0, 0.5)
14	0.5	56	-0.5	-1.0	(-1.9, -0.2)	57	-0.1	-0.6	(-1.5, 0.2)	58	-0.1	-0.6	(-1.5, 0.2)
18	0.8	56	-0.1	-1.0	(-1.7, -0.2)	57	0.8	-0.0	(-0.8, 0.7)	58	0.6	-0.3	(-1.0, 0.5)
22.5	0.0	56	-0.3	-0.3	(-0.9, 0.3)	57	-0.1	-0.1	(-0.7, 0.5)	58	0.1	0.0	(-0.6, 0.6)

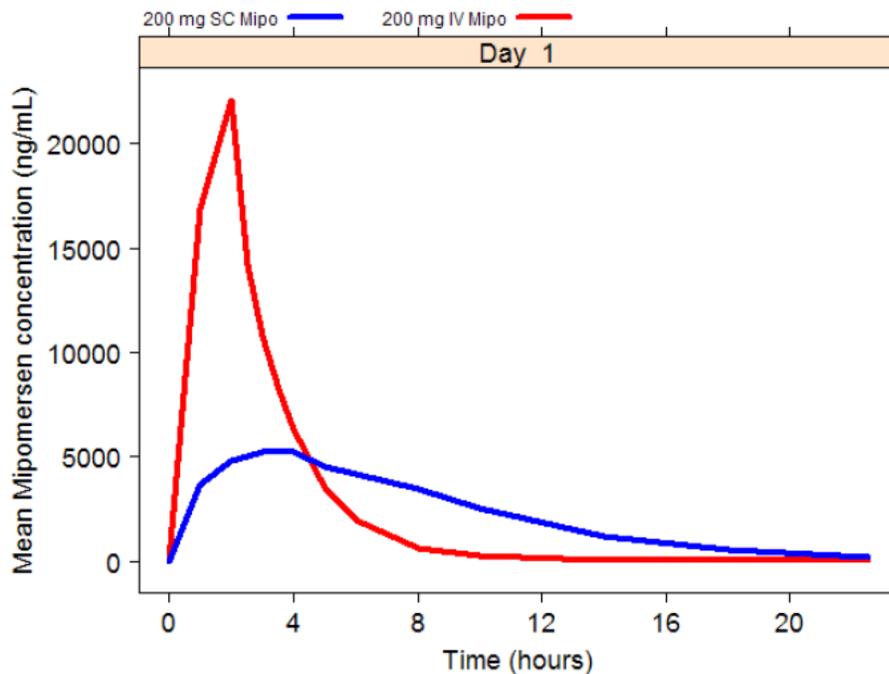
Table 15: Categorical Analysis for QRS

Treatment Group	Total N	QRS < 110 ms	QRS ≥ 110 ms
200-mg mipomersen IV / Placebo Subcutaneous	56	55 (98.2%)	1 (1.8%)
200-mg mipomersen Subcutaneous / Placebo IV	58	57 (98.3%)	1 (1.7%)
400-mg moxifloxacin IV / Placebo Subcutaneous	58	58 (100%)	0 (0.0%)
Placebo IV / Placebo Subcutaneous	59	58 (98.3%)	1 (1.7%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

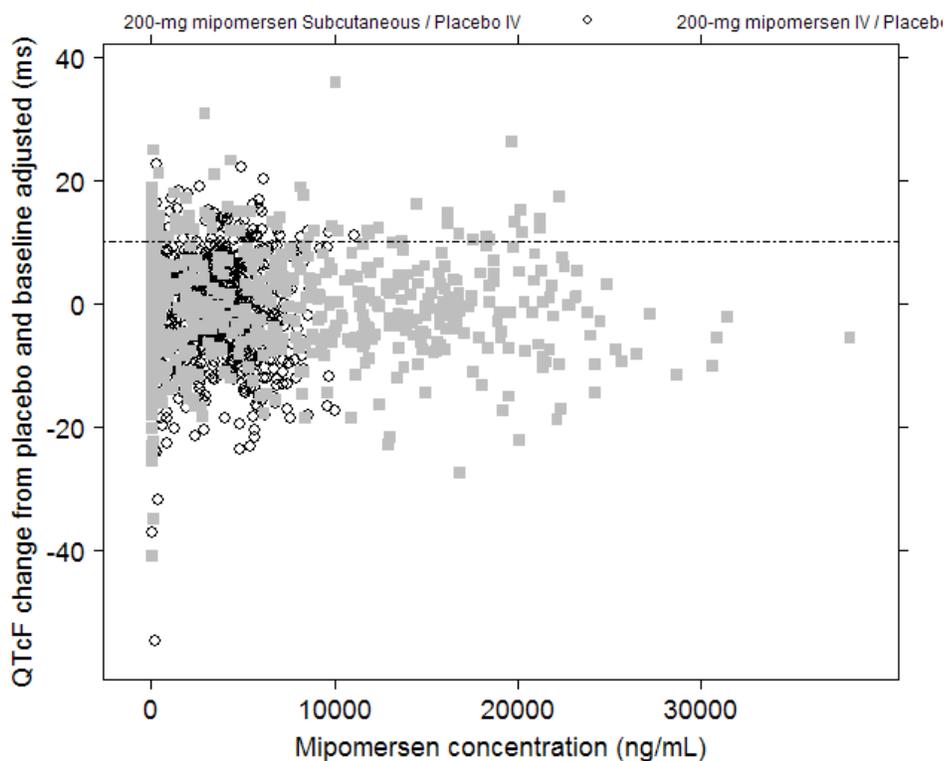
The mean drug concentration-time profile is illustrated in Figure 4.

Figure 4: Mean Mipomersen concentration-time profiles for 200 mg s.c. (blue line) and 200 mg i.v. (red line)



The relationship between $\Delta\Delta\text{QTcF}$ and mipomersen concentrations is visualized in Figure 5 with no significant exposure-response relationship. Mipomersen is not expected to increase $\Delta\Delta\text{QTcF}$ within the studied exposure range.

Figure 5: $\Delta\Delta$ QTcF vs. Mipomersen concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics 99% of the ECGs were annotated in the primary lead II, with less than 0.02 % of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

One subject had a post-baseline PR > 200 ms (207 ms) which was not clinically meaningful. Two subjects had a QRS > 110 ms (111 ms).

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	200 mg SC weekly	
Maximum tolerated dose	400 mg SC or IV	
Principal adverse events	<p>The principal common adverse events potentially related to mipomersen include:</p> <ol style="list-style-type: none"> 1. Injection site reactions (commonly local erythema, pain, tenderness and discoloration) <ol style="list-style-type: none"> a. Seen at least once in 84.3% of mipomersen patients and 33.3% of placebo patients during the six-month pooled Phase 3 clinical studies 2. Flu-like symptoms (influenza-like illness, pyrexia, chills, myalgia, arthralgia, malaise, or fatigue) <ol style="list-style-type: none"> a. Observed in 29.9% of mipomersen patients and 16.3% of placebo patients in the six-month pooled Phase 3 clinical studies 3. Hepatic effects including: <ol style="list-style-type: none"> a. Elevations in serum transaminases (specifically ALT) <ol style="list-style-type: none"> i. ALT elevations ≥ 3 x ULN were observed in 16.5% of mipomersen-treated patients at least 1 during the 26 week treatment period in the six-month pooled Phase 3 clinical studies. ii. 8.4% of mipomersen-treated patients had ALT levels ≥ 3 x ULN on at least 2 consecutive occasions (at least 7 days apart) following dosing. No patients exhibited consecutive ALT elevations ≥ 3 x ULN in the placebo group. b. Increase in hepatic fat <ol style="list-style-type: none"> i. Measured at baseline and after 6 months of treatment by MRI in two phase three studies with results demonstrating a median increase in hepatic fat fraction of 9.6 percentage points in mipomersen-treated patients versus zero in placebo patient 4. Inflammatory/immunological effects which include: <ol style="list-style-type: none"> a. Transient increases in hsCRP post dosing with no chronic increases noted b. Positive antibody formation in 30 of the 50 exposed patients in Phase 3 study ISIS 301012-CS5 and OLE study ISIS 301012-CS6. 	
Maximum dose tested	Single Dose	400 mg SC and IV.
	Multiple Dose	IV: 400 mg qod x 3 doses, which was followed by SC doses once weekly thereafter for additional three weeks. SC: 400 mg once weekly for 10 weeks.
Exposures Achieved at Maximum Tested Dose	Single Dose (400 mg)	SC C_{max} : 7.6 ± 0.81 $\mu\text{g/mL}$ SC AUC_{0-48h} : 106 ± 17 $\mu\text{g}\cdot\text{h/mL}$

	Multiple Dose (400 mg once weekly)	SC C _{max} : 7.15 µg/mL IV C _{max} : 37.9 ± 5.0 µg/mL SC AUC _{0-48h} : 109 µg•h/mL IV AUC _{0-48h} : 148 ± 14µg•h /mL
Range of linear PK	Dose-dependent and close to dose-proportional plasma PK has been observed over a dose range of 50–400 mg.	
Accumulation at steady state	Little or no accumulation based on plasma C _{max} and AUC estimates after single and multiple dosing in shorter term studies (dosing ≤3 months). However, accumulation is expected based on a terminal half-life of 1 to 2 months and once weekly dosing. Trough profiles in most patients from longer term studies (Phase 3 and OLE studies) appeared to have approached or achieved steady-state within 6 months after treatment initiation.	
Metabolites	Chain-shortened oligonucleotides.	
Absorption	Absolute/Relative Bioavailability (based on plasma exposure)	54–78% (SC relative to IV) and is independent of dose. Plasma bioavailability estimates after SC administration may underestimate the ultimate complete absorption of ISIS 301012. Non-human primate studies have shown that the entire dose is ultimately distributed to tissues such that there is little or no difference in end organ drug concentrations between IV and SC administration.
	T _{max}	Mean values range from 2.67–7.5 h (SC dosing). Mean values range from 1.95–2.02 h (2 hr IV infusion; i.e., end of infusion).
Distribution	V _{ss}	V _{ss} is estimated to be ~530 L based on a population PK analysis using a 2-compartment structure model, in which the estimated central volume of distribution (V _c) and peripheral volume of distribution (V _p) were 8.7 L and 522 L, respectively.
	% bound	84.8–95.8% bound to plasma proteins at mipomersen plasma concentrations ranging from 0.1 to 600 µM (7.59 to 152 µg/mL). Mipomersen binds with high capacity to albumin, α ₂ -macroglobulin, and α ₁ -acid glycoprotein, and the drug is highly bound (>90%) to these proteins at clinically relevant concentrations (1–8 µg/mL).

Elimination	Route	<ul style="list-style-type: none"> • Primary route: Nuclease metabolism in tissues • Other routes: Renal excretion • These processes are rather slow. In animals, once in the tissues, mipomersen is eliminated slowly with the half-life being in the range of 13 to 34 days in the primary organs involved (kidney and liver). Similar to animals, urinary recovery was limited in the humans, only less than 4% recovered within the 24 hours post dose. Both mipomersen and putative shorter oligonucleotide metabolites were identified in human urine.
	Terminal t_{1/2}	<ul style="list-style-type: none"> • Approximately 1 to 2 months in healthy volunteers and patients. <p>Note: mean distribution phase t_{1/2} values range from 3.5–8.3 h (SC dosing) and 0.67–1.67 h (IV dosing).</p>
	CL	The population PK analysis, which encompasses data from Phase 1 to Phase 3 and open-label extension studies, has found that mipomersen clearance decreases over time. There appear to be two subpopulations, one with fast decaying clearance (11.4% patients) and the other with slower decaying clearance (88.6% patients). The clearance has been predicted to decrease from 2.76 L/hr on the first day of dosing to 2.07 L/h after 1 year of dosing for the slow decay population; and from 5.65 L/h on the first day of dosing to 0.79 L/h after 1 year of dosing for the fast decay population.
Intrinsic Factors	Age	Age was evaluated in a population PK analysis as a covariate, and it was not found to be predictive of variability of mipomersen PK.
	Sex	Gender differences in plasma exposure measures for mipomersen have been observed in earlier clinical trials where females tended to have higher values of dose-normalized C _{max} and AUC than males. The effect of gender on mipomersen trough concentrations has appeared to be absent or less pronounced in larger clinical trials. Gender was evaluated in a population PK analysis as a covariate, and it was not found to be predictive of variability of mipomersen PK.
	Weight	Body weight was evaluated in a population PK analysis as a covariate, and it was not found to be predictive of variability of mipomersen PK.
	Race	Race was evaluated in a population PK analysis as a covariate, and it was not found to be predictive of variability of mipomersen PK.

	Hepatic & Renal Impairment	<p>The effects of hepatic impairment on mipomersen PK have not been studied.</p> <p>A study examining the effects of renal impairment on mipomersen PK has not been conducted. 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.</p>
Extrinsic Factors	Drug interactions	<p>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 addition, in vitro studies demonstrated that mipomersen is not a substrate or an inhibitor of the P-gp transporter. Consequently, it is not expected that mipomersen would be directly involved in drug-drug interactions involving CYP450 enzymes or the P-gp transporter (see section 5.2).</p> <p>Co-administration of mipomersen with warfarin, simvastatin or ezetimibe did not result in a PK or pharmacodynamic interaction. Further, a population PK analysis showed no effect on mipomersen PK of medications commonly used in the indicated population, including statins, other lipid lowering medications, beta blockers, ACE inhibitors and platelet aggregation inhibitors.</p>
	Food Effects	Not applicable as mipomersen is used via SC administration clinically.
Expected High Clinical Exposure Scenario	<p>To date, mipomersen plasma exposure has been monitored and measured primarily by trough levels, and in some studies, by post-dose levels (1.5 to 6 hours post-dose), after weekly SC administration. Inter-subject variability in plasma trough and post-dose levels is high. For example, in the open-label extension study ISIS 301012-CS6, the ranges of observed plasma 4 hours post-dose levels and trough levels after 6-month dosing are 350-12975 ng/mL (N=26) and 9.4-1435 ng/mL (N=77). No intrinsic characteristics have been identified to be related to this high inter-subject variability in plasma exposure.</p> <p>Based on the limited known or expected effects of extrinsic factors (such as DDI) on mipomersen plasma exposure measures, it is unlikely that mipomersen plasma exposure would change dramatically as a result of any changes in these extrinsic factors.</p> <p>Mipomersen is a chronically administered drug, and is intended for self-administration. Therefore, an error in dosing is one potential mechanism for which a high clinical exposure scenario may occur. However, if mipomersen were to be administered more frequently than the recommended weekly schedule, accumulation in plasma would be minimal as the majority of the AUC is accounted for in the first 24 hours following administration.</p>	

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/s/

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Memorandum

Date: 6/20/2012
To: Eileen Craig, MD, Medical Officer
From: Eugenio Andraca-Carrera, Ph.D.
Statistical reviewer
Division of Biometrics 7
Office of Biostatistics

Through: Mat Soukup, Ph.D.
Statistical team leader
Division of Biometrics 7
Office of Biostatistics

Drug: Mipomersen
Sponsor: ISIS Pharmaceuticals
NDA: 203568
Subject: Analysis of broad and narrow SMQs for cardiovascular safety

1. Introduction

Mipomersen is a cholesterol-reducing drug administered by subcutaneous injection. Upon request from the Division of Metabolism and Endocrinology Products (DMEP), we conducted a search of cardiovascular (CV) adverse events included in pre-specified Broad and Narrow MedDRA SMQs in 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 memorandum briefly describes the trials used in analyses, the SMQs included in the Broad and Narrow CV searches, and the estimated Relative Risk for CV events comparing mipomersen to placebo.

2. Clinical Trials

Four Phase 3 clinical trials, identified by DMEP, were used in this analysis: trials **CS5**, **CS7**, **CS12** and **MIPO3500108**. These four trials were randomized, double-blind, placebo controlled and were conducted between September 2007 and October 2010. All subjects randomized to mipomersen received a weekly injection of mipomersen 200 mg. The four trials had a 26 weeks treatment period and a 24-week post treatment follow-up period. The analysis of interest in this document includes only the 26 week treatment

period per the request of the medical officer. Table 1 shows the sample size in the four trials.

Table 1. Sample size by trial

Trial	Sample Size	
	Mipomersen 200mg	Placebo
CS5	34	17
CS7	83	41
CS12	105	53
MIPO108	39	19
Total:	261	130

All information used in this analysis, including randomized treatment, length of treatment period, type of adverse events and date of adverse events were extracted from analysis datasets named ADAE.xpt submitted for each of the four trials of interest.

3. Broad and Narrow SMQ search.

Adverse events were extracted from the variable AEDECOD, labelled “Dictionary-Derived Term”, in files ADAE.xpt. Values of the variable AEDECOD correspond to MedDRA Preferred Terms. Adverse events were classified according to a Broad and a Narrow search of MedDRA SMQs corresponding to cardiovascular adverse events.

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”.

4. Statistical Methodology

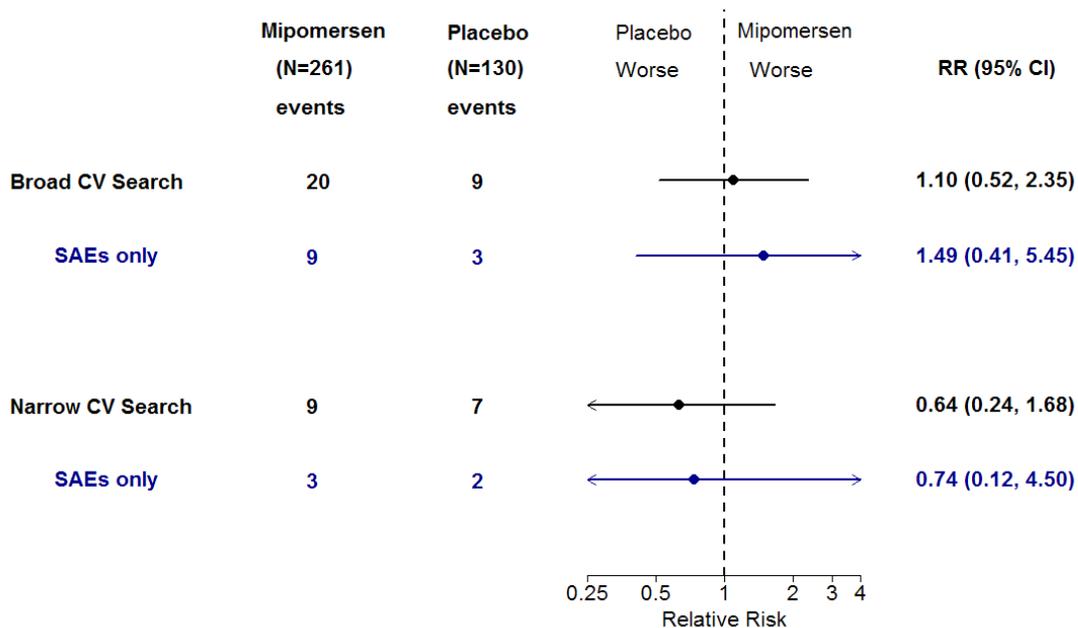
The Mantel-Haenszel Relative Risk of adverse events in the Broad and Narrow CV searches, and its corresponding 95% confidence interval, were estimated comparing mipomersen 200 mg to placebo. A forest plot was produced to summarize the results.

5. Results

There were a total of 20 subjects on mipomersen (N=261) and 9 subjects on placebo (N=130) with a reported adverse event in the “Broad” SMQ search category. There were 9 subjects on mipomersen and 7 subjects on placebo with a reported adverse event in the “Narrow” SMQ search category. Figure 1 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 upper bound of the 95% confidence interval suggests that it may be reasonable to rule out a RR of “Broad” CV events larger than 2.35, and a RR of “Narrow” CV events larger than 1.68. However, note that the estimates of the RR and corresponding 95% confidence intervals reported here are sensitive to small changes in the number of events in either randomized arm, and that the adverse events used in this analysis were not pre-specified and adjudicated. Therefore, these results should be interpreted with caution. If a more precise estimate of the cardiovascular risk of mipomersen is required, a larger study with a pre-specified and adjudicated cardiovascular outcome should be considered. Also, note that the four clinical trials used in this analysis included data up to 26 weeks. These data provide no information on the long-term cardiovascular safety of mipomersen.

Figure 1. Relative Risk of Broad and Narrow Cardiovascular SMQs



Appendix. List of adverse events in the Broad and Narrow CV searches.

Trial	Subject ID	Treatment*	Study Day		Preferred term	MedDRA Code	Serious AE	Broad	Narrow
			End of treatment	Start of AE					
301012-CS05	1500-8881	ISIS 301012 200 mg	190	156	Angina pectoris	10002383	N	1	0
301012-CS05	1523-8309	ISIS 301012 200 mg	192	44	Acute coronary syndrome	10051592	Y	1	1
301012-CS05	1530-8081	ISIS 301012 200 mg	190	141	Blood creatine phosphokinase increased	10005470	N	1	1
301012-CS07	1503-7426	ISIS 301012 200 mg	191	181	Angina pectoris	10002383	Y	1	0
301012-CS07	1505-7023	ISIS 301012 200 mg	128	16	Angina pectoris	10002383	N	1	0
301012-CS07	1506-7324	ISIS 301012 200 mg	190	56	Angina pectoris	10002383	N	1	0
301012-CS07	1578-7165	Placebo	189	189	Coronary artery disease	10011078	Y	1	0
301012-CS07	1578-7437	Placebo	191	170	Carotid artery stenosis	10007687	N	1	1
301012-CS07	1579-7079	ISIS 301012 200 mg	190	98	Myocardial ischaemia	10028600	N	1	0
301012-CS07	1587-7289	ISIS 301012 200 mg	190	190	Electrocardiogram T wave inversion	10014395	N	1	0
301012-CS07	1589-7479	ISIS 301012 200 mg	197	178	Acute myocardial infarction	10000891	Y	1	1
301012-CS07	1589-7479	ISIS 301012 200 mg	197	178	Coronary artery disease	10011078	N	1	0
301012-CS07	1589-7479	ISIS 301012 200 mg	197	197	Infarction	10061216	N	1	1
301012-CS07	1597-7270	Placebo	191	58	Blood creatine phosphokinase increased	10005470	N	1	1
301012-CS07	1623-7247	Placebo	191	15	Blood creatine phosphokinase increased	10005470	N	1	1
301012-CS07	1623-7247	Placebo	191	2	Myocardial ischaemia	10028600	N	1	0
301012-CS12	1535-2369	Placebo	187	110	Acute coronary syndrome	10051592	Y	1	1
301012-CS12	1535-2369	Placebo	187	Unknown ¹	Angina pectoris	10002383	N	1	0
301012-CS12	1547-1420	Placebo	120	112	Acute myocardial infarction	10000891	Y	1	1
301012-CS12	1597-1033	ISIS 301012 200 mg	193	265**	Dysarthria	10013887	N	0	0
301012-CS12	1597-1277	ISIS 301012 200 mg	190	190	Angina pectoris	10002383	N	1	0
301012-CS12	1633-2169	ISIS 301012 200 mg	190	113	Blood creatine phosphokinase increased	10005470	N	1	1
301012-CS12	1636-1254	ISIS 301012 200 mg	190	334**	Blood creatine phosphokinase increased	10005470	N	1	1
301012-CS12	1646-1374	ISIS 301012 200 mg	102	326**	Blood creatine phosphokinase increased	10005470	N	1	1
301012-CS12	1660-1242	ISIS 301012 200 mg	190	134	Carotid artery stenosis	10007687	N	1	1
301012-CS12	1664-2055	Placebo	190	273**	Acute myocardial infarction	10000891	Y	1	1
301012-CS12	1681-1008	ISIS 301012 200 mg	188	14	Blood creatine phosphokinase increased	10005470	N	1	1
301012-CS12	1681-1008	ISIS 301012 200 mg	188	216**	Blood creatine phosphokinase increased	10005470	N	1	1
301012-CS12	1681-1095	ISIS 301012 200 mg	114	114	Angina pectoris	10002383	Y	1	0
301012-CS12	1681-1358	ISIS 301012 200 mg	142	67	Angina unstable	10002388	Y	1	0
301012-CS12	1681-2132	ISIS 301012 200 mg	191	325**	Acute myocardial infarction	10000891	Y	1	1
301012-CS12	1681-2132	ISIS 301012 200 mg	191	127	Angina pectoris	10002383	N	1	0
301012-CS12	1681-2132	ISIS 301012 200 mg	191	174	Coronary artery disease	10011078	Y	1	0
301012-CS12	1681-2358	ISIS 301012 200 mg	190	338**	Blood creatine phosphokinase increased	10005470	N	1	1

301012-CS12	1682-1256	Placebo	190	1	Blood creatine phosphokinase increased	10005470	N	1	1
301012-CS12	1682-1362	Placebo	190	-7**	Blood creatine phosphokinase increased	10005470	N	1	1
MIPO3500108	1010-1005	Placebo	180	57	Blood creatine phosphokinase increased	10005470	N	1	1
MIPO3500108	3000-1046	ISIS 301012 200 mg	191	159	Angina unstable	10002388	Y	1	0
MIPO3500108	3000-1046	ISIS 301012 200 mg	191	Unknown ²	Cerebrovascular accident	10008190	N	1	1
MIPO3500108	3002-1027	ISIS 301012 200 mg	190	158	Acute myocardial infarction	10000891	Y	1	1
MIPO3500108	3002-1027	ISIS 301012 200 mg	190	205**	Acute myocardial infarction	10000891	Y	1	1
MIPO3500108	3002-1031	Placebo	190	77	Angina pectoris	10002383	N	1	0
MIPO3500108	5002-1056	ISIS 301012 200 mg	199	100	Angina pectoris	10002383	Y	1	0
MIPO3500108	5002-1056	ISIS 301012 200 mg	199	213**	Cerebrovascular accident	10008190	Y	1	1
MIPO3500108	5002-1056	ISIS 301012 200 mg	199	183	Prinzmetal angina	10036759	Y	1	0
MIPO3500108	5002-1056	ISIS 301012 200 mg	199	190	Prinzmetal angina	10036759	Y	1	0
MIPO3500108	6000-1032	ISIS 301012 200 mg	190	3	Angina pectoris	10002383	N	1	0
MIPO3500108	6000-1032	ISIS 301012 200 mg	190	10	Angina pectoris	10002383	N	1	0
MIPO3500108	6000-1032	ISIS 301012 200 mg	190	161	Angina pectoris	10002383	N	1	0
MIPO3500108	6000-1032	ISIS 301012 200 mg	190	17	Blood creatine phosphokinase increased	10005470	N	1	1
MIPO3500108	6000-1032	ISIS 301012 200 mg	190	85	Coronary artery disease	10011078	N	1	0
MIPO3500108	6000-1032	ISIS 301012 200 mg	190	162	Coronary artery disease	10011078	N	1	0

*Mipomersen is referred to as "ISIS 301012 200 mg" in the clinical trials datasets.

**These events occurred outside of the treatment period and are not included in the analysis.

¹This event may be excluded from analyses since subject 1535-2369 had one other reported adverse event that meets the requirements for Serious, Broad and Narrow adverse events.

²The reported date for this event is "2010-04". Since the last treatment date reported for this subject was "2010-04-28"; this event occurred either during the treatment period or within 2 days of the last treatment date. Therefore we considered this event as occurring within the treatment period.

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/s/

EUGENIO ANDRACA-CARRERA
07/02/2012

MATTHEW J SOUKUP
07/02/2012
Concur

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 203568 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: KYNAMRO Established/Proper Name: Mipomersen sodium Dosage Form: Injection Strengths: 200 mg/mL		
Applicant: Genzyme Corp. Agent for Applicant (if applicable):		
Date of Application: 3/29/2012 Date of Receipt: 3/29/2012 Date clock started after UN:		
PDUFA Goal Date: 1/29/2013		Action Goal Date (if different):
Filing Date: 5/28/2012		Date of Filing Meeting: 5/14/2012
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication: Indicated as an adjunct to maximally tolerated lipid lowering medications and diet to reduce low density lipoprotein-cholesterol (LDL-C), apolipoprotein B (apo B), total cholesterol (TC), non high-density lipoprotein cholesterol (non-HDL-C), and lipoprotein (a) [Lp (a) in patients with homozygous familial hypercholesterolemia (HoFH).		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input checked="" type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

Other (drug/device/biological product)

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (*if OTC product*):

List referenced IND Number(s): 70969

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>																				
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>		<p>X</p>																		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		X		
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	X			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby 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.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		X		
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>				

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>				
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>				
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	X			
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			Labeling will be sent once the PI is substantially complete
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send <i>WORD</i> version if available)	X			Labeling will be sent once the PI is substantially complete
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	X Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) -Liver Consult sent to OSE -REMS Consult to OSE -Immunogenicity Consult <i>If yes, specify consult(s) and date(s) sent:</i>	X X X			4/19/2012 4/4/2012 4/25/2012
Meeting Minutes/SPAs	YES	NO	NA	Comment

End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>		X		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 12/13/2010 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 5/14/2012

NDA #: 203568

PROPRIETARY NAME: KYNAMRO

ESTABLISHED/PROPER NAME: mipomersen sodium

DOSAGE FORM/STRENGTH: 200 mg/mL Injection

APPLICANT: Genzyme Corporation

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Indicated as an adjunct to maximally tolerated lipid lowering medications and diet to reduce low density lipoprotein-cholesterol (LDL-C), apolipoprotein B (apo B), total cholesterol (TC), non high-density lipoprotein cholesterol (non-HDL-C), and lipoprotein (a) [Lp (a) in patients with homozygous familial hypercholesterolemia (HoFH).

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	K. Johnson	Y
	CPMS/TL:	E. Galliers	N
Cross-Discipline Team Leader (CDTL)	E. Colman		Y
Clinical	Reviewer:	E. Craig	Y
	TL:	E. Colman	Y
Social Scientist Review (for OTC products) N/A	Reviewer:		
	TL:		
OTC Labeling Review (for OTC products) N/A	Reviewer:		
	TL:		
Clinical Microbiology (for antimicrobial products) N/A	Reviewer:		

	TL:		
Clinical Pharmacology	Reviewer:	I. Zadezensky	Y
	TL:	J. Vaidyanathan	Y
Biostatistics	Reviewer:	J. Choudhury	Y
	TL:	T. Sahlroot	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	R. Wange	Y
	TL:	K. Davis Bruno	Y
Statistics (carcinogenicity)	Reviewer:	Steven Thomson	N
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	JinHai Wang	N
	TL:	Susan Kirschner	N
Product Quality (CMC)	Reviewer:	J. Leginus	Y
	TL:	S. Tran	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	R. Mello	Y
	TL:		
CMC Labeling Review	Reviewer:	J. Leginus	Y
	TL:	S. Tran	Y
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Reasol Agustin	Y
	TL:	Y. Maslov	Y
OSE/DRISK (REMS)	Reviewer:	J. Weaver	N
	TL:	C. LaCivita	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	M. Marsh	Y
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	S. Leibenhaut	Y
	TL:	J. Pohlman	N
Controlled Substance Staff (CSS) N/A	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> 	<input checked="" type="checkbox"/> YES Date if known: 10/18/2012 <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter</p>

<u>CMC Labeling Review</u>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Curt Rosebraugh, MD	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
X	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. X Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> X Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)

	<ul style="list-style-type: none"> • notify OMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at:</p> <p>http://erom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]</p>
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

KATI JOHNSON
05/24/2012

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 203568

Application Type: New NDA

Name of Drug: KYNAMRO (mipomersen sodium) Injection, 200 mg/mL

Applicant: Genzyme Corporation

Submission Date: March 29, 2012

Receipt Date: March 29, 2012

1.0 Regulatory History and Applicant's Main Proposals

ISIS 301012 (now called Mipomersen) is an antisense oligonucleotide targeted to apoB-100, the principal apolipoprotein of atherogenic LDL-C and its metabolic precursor, VLDL. ISIS Pharmaceuticals was the initial sponsor of the IND. They requested a pre-IND meeting in June 2005 to discuss their proposed Phase 3 protocol for Homozygous Familial Hypercholesterolemia (HoFH)

(b) (4)

The firm was notified that, during the internal meeting, it became clear that the agency had insufficient information to be able to discuss their Phase 3 plans. There were concerns with the dose selection (200 mg), renal toxicity and inflammatory responses in animals. The firm was advised to instead conduct a small Phase 2 dose ranging study to determine the dose. The firm was also advised to submit the IND and request an End-of-Phase 2 (EOP2) meeting.

The IND was submitted November 17, 2005. The initial IND contained Phase 2 dose-ranging studies in both HoFH (CS8) and HeFH (CS9).

Fast Track Designation for HoFH was requested April 11, 2006, which was denied May 30, 2006 because the development program, as described, was not designed to determine a cardiovascular benefit.

The firm requested an EOP2 meeting on May 4, 2007, which was granted. An internal meeting was held on September 5, 2007. Again, it was determined that the clinical questions could not be addressed until some preclinical findings were resolved. On January 4, 2007, the firm submitted a draft 6-month interim report of a one-year cynomolgus monkey toxicity study. The final interim report of the one year toxicity study was submitted on June 8, 2007. The new finding after one year of dosing was that animals treated with drug developed arterial (peri)vasculitis and intimal hyperplasia. The vasculitis was observed in the GI tract in 3 monkeys and in multiple organs in another 2 monkeys. 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.

Selected Requirements of Prescribing Information (SRPI)

It has been the firm's position that the vasculitis is due to complement activation and this activation does not occur in humans at the proposed dose levels. In addition, complement and inflammatory markers will be monitored in the proposed Phase 3 studies. 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.

On January 22, 2008, the sponsor was notified that the IND was on partial clinical hold and that only high-risk patients could be studied. This population was defined as:

- 10 year risk for CVD \geq 20%
- taking a maximum statin dose
- still not at LDL goal

As additional clinical information became available, the partial clinical hold was modified on July 29, 2011 to permit studies of less than six months' duration in patients who are not at high risk for CVD.

On July 23, 2008, the sponsorship of the application was transferred to Genzyme Corporation.

A pre-NDA meeting was held on December 10, 2010. The firm was proposing to submit an NDA containing data to support (b) (4) HoFH (b) (4)

The application was submitted March 29, 2012 for the HoFH indication (b) (4)

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

Minor SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix. These will be corrected during labeling negotiations with the firm.

Selected Requirements of Prescribing Information (SRPI)

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is

Selected Requirements of Prescribing Information (SRPI)

the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

YES

6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

YES

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment:

Product Title

YES

10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

YES

Selected Requirements of Prescribing Information (SRPI)

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning

N/A

12. All text must be **bolded**.

Comment:

N/A

13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

N/A

14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

N/A

15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

N/A

16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A

17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A

18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A

19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

N/A

20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES

Selected Requirements of Prescribing Information (SRPI)

21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment:

Dosage Forms and Strengths

- YES** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- NO** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment: *There is only a single contraindication, but it is bulleted. If this remains the only contraindication following the review, then the bullet will be deleted.*

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- NO** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment: *The sponsor has chosen the first bullet above even though they are proposing a Medication Guide. This will be corrected during labeling negotiations.*

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

Selected Requirements of Prescribing Information (SRPI)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.
Comment:
- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: **“FULL PRESCRIBING INFORMATION: CONTENTS”**.
Comment:
- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
Comment:
- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.
Comment:
- YES** 32. All section headings must be **bolded** and in UPPER CASE.
Comment:
- YES** 33. All subsection headings must be indented, not bolded, and in title case.
Comment:
- YES** 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading **“FULL PRESCRIBING INFORMATION: CONTENTS”** must be followed by an asterisk and the following statement must appear at the end of TOC: **“*Sections or subsections omitted from the Full Prescribing Information are not listed.”**
Comment:
-

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: **“FULL PRESCRIBING INFORMATION”**.
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.
Comment:
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS

Selected Requirements of Prescribing Information (SRPI)

6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

- N/A** 43. Must have a heading in UPPER-CASE, containing the word **“WARNING”** (even if more than one Warning, the term, **“WARNING”** and not **“WARNINGS”** should be used) and other words to identify the subject of the Warning (e.g., **“WARNING: SERIOUS INFECTIONS”**).

Selected Requirements of Prescribing Information (SRPI)

Comment:

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- YES** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- NO** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment: *The sponsor should have use bullet #1. This will be corrected during labeling negotiations.*

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/s/

KATI JOHNSON
05/24/2012