

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203568Orig1s000

CHEMISTRY REVIEW(S)

NDA 203568

**KYNAMRO™
(mipomersen sodium) Injection**

Genzyme Corporation

**Joseph Leginus, PhD
Division of Pre-Marketing Assessment III, Branch VII, ONDQA**

**For the Division of
Metabolism and Endocrinology Products**

CHEMISTRY REVIEW #2

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet	3
The Executive Summary	8
I. Recommendations.....	8
A. Recommendation and Conclusion on Approvability	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	8
II. Summary of Chemistry Assessments.....	8
A. Description of the Drug Product(s) and Drug Substance(s)	8
B. Description of How the Drug Product is Intended to be Used.....	11
C. Basis for Approvability or Not-Approval Recommendation	11
III. Administrative.....	12
A. Reviewer's Signature: in DAARTS.....	12
B. Endorsement Block: in DAARTS.....	12
C. CC Block: in DAARTS.....	12
Chemistry Assessment	13

Chemistry Review Data Sheet

1. NDA 203568
2. REVIEW #: 2
3. REVIEW DATE: 4-Dec-2012
4. REVIEWER: Joseph Leginus, PhD
5. PREVIOUS DOCUMENTS:

Previous Documents

Original NDA

Document Date

29-Mar-2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

NDA Amendment

NDA Amendment

Document Date

28-Sep-2012

1-Oct-2012

7. NAME & ADDRESS OF APPLICANT:

Name: Genzyme Corporation
Address: 500 Kendall St. Cambridge, MA 02142
Representative: Jill P. Hillier PhD, Senior Director Regulatory Affairs
Telephone: 781-434-3443

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Kynamro
- b) Non-Proprietary Name (USAN): Mipomersen sodium injection
- c) Code Name/# (ONDC only): CAS No.: 629167-92-6; Laboratory Code: ISIS 301012.
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: This NDA is submitted as a 505(b)(1) application.

Chemistry Review Data Sheet

10. PHARMACOL. CATEGORY:

Mipomersen sodium, an apolipoprotein B synthesis inhibitor, is as an adjunct to maximally tolerated lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol, apolipoprotein B, total cholesterol, non-high density lipoprotein-cholesterol and lipoprotein (a) in patients with homozygous familial hypercholesterolemia.

11. DOSAGE FORM: Solution for Injection

12. STRENGTH/POTENCY: 200 mg/mL

13. ROUTE OF ADMINISTRATION: Subcutaneous Injection

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

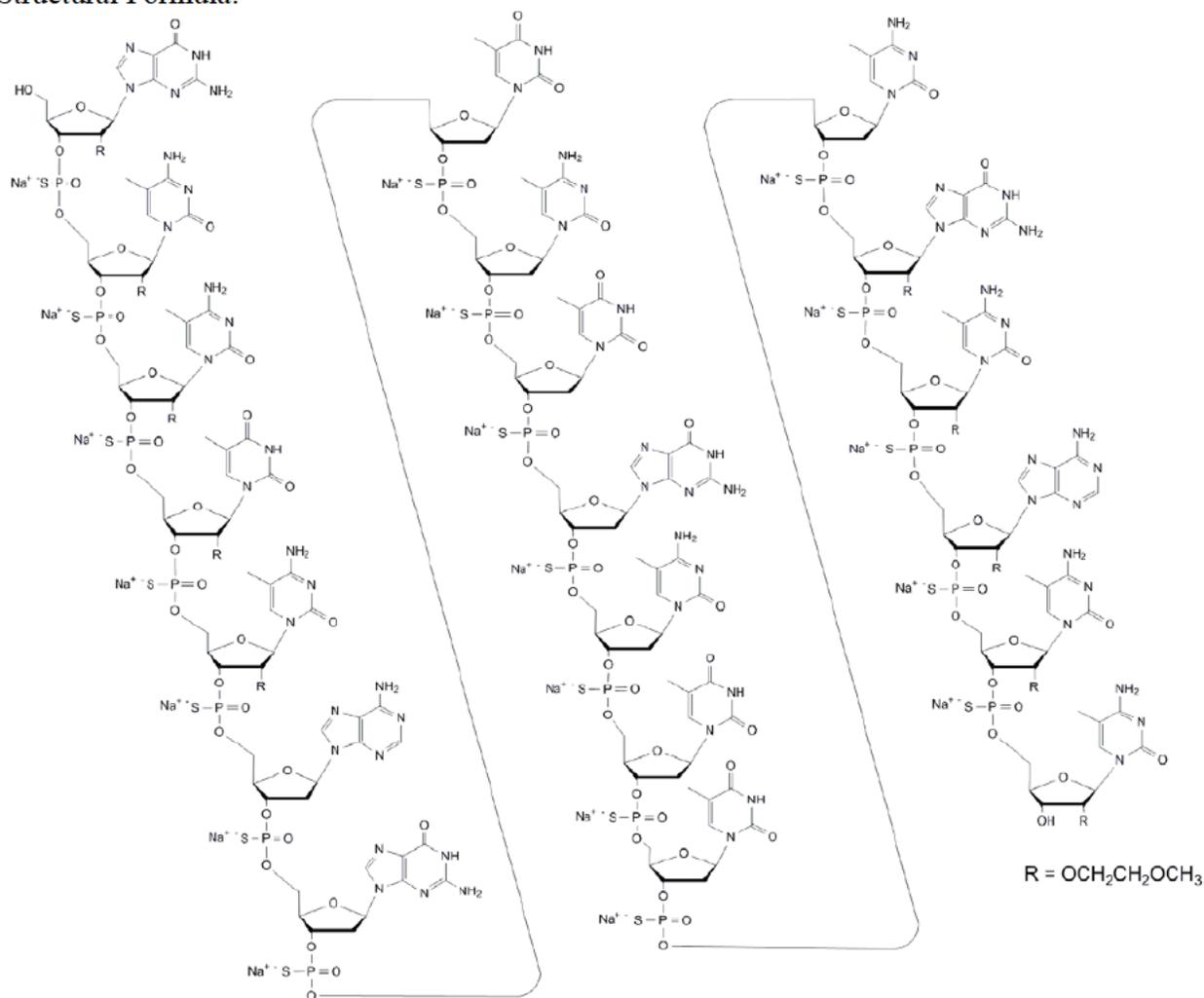
Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 2'-O-(2-methoxyethyl)-P-thioguanlyl-(3'-O→5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'-O→5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'-O→5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'-O→5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'-O→5'-O)-2'-deoxy-P-thioadenylyl-(3'-O→5'-O)-2'-deoxy-P-thioguanlyl-(3'-O→5'-O)-P-thiothymidylyl-(3'-O→5'-O)-2'-deoxy-5-methyl-P-thiocytidylyl-(3'-O→5'-O)-P-thiothymidylyl-(3'-O→5'-O)-2'-deoxy-P-thioguanlyl-(3'-O→5'-O)-2'-deoxy-5-methyl-P-thiocytidylyl-(3'-O→5'-O)-P-thiothymidylyl-(3'-O→5'-O)-2'-deoxy-5-methyl-P-thiocytidylyl-(3'-O→5'-O)-2'-O-(2-methoxyethyl)-P-thioguanlyl-(3'-O→5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'-O→5'-O)-2'-O-(2-methoxyethyl)-P-thioadenylyl-(3'-O→5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'-O→5'-O)-2'-O-(2-methoxyethyl)-5-methylcytidine, nonadecasodium

Chemistry Review Data Sheet

Structural Formula:



Molecular Formula: C₂₃₀H₃₀₅N₆₇O₁₂₂P₁₉S₁₉Na₁₉

Molecular Weight: 7594.9 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code ¹	Status ²	Date Review Completed	Comments
			(b) (4)	1	Adequate	24-Apr-2012	Reviewed by Y. Smith

Chemistry Review Data Sheet

(b) (4)	1	Adequate	24-Aug-2011	Reviewed by O. Stephens
	1	Adequate	25-Jan-2012	Reviewed by S. Fong
	1	Adequate	27-Jan-2006	Reviewed by L. Rodriguez

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	70969	Mipomersen sodium

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	An Overall Compliance recommendation of Acceptable has been provided.	11-Oct-2012	N/A
Pharm/Tox	Proposed limits for impurities in drug substance specifications are acceptable.	14-Nov-2012	Ronald Wange
Biopharm	Not applicable. This is an injectable product, and the commercial formulation was used in Phase 3 studies.		
Methods Validation	Validation may be requested of FDA labs after test methods are finalized.		
EA	Conducted by CMC reviewer. Granting the categorical exclusion as per 21 CFR 25.31(b).	10-Sep-2012	Joseph Leginus

Chemistry Review Data Sheet

Microbiology	Review of 1) microbiology controls proposed for the drug product, and 2) and (b)(4) processing validation for the drug product.	Pending	Bob Mello
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19. ORDER OF REVIEW: N/A

The Chemistry Review for NDA 203568

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 203568 is recommended for Approval from the standpoint of chemistry, manufacturing and controls. However, the microbiology review consult has not yet been finalized in DARRTS.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

DRUG SUBSTANCE

Mipomersen sodium is a 20-base, synthetic oligonucleotide sodium salt designed to inhibit expression of the apolipoprotein B-100 gene by sequence-specific hybridization to a complementary sequence on the mRNA. (Apolipoproteins are proteins that bind lipids, such as cholesterol, for transport through the circulatory system). It is an oligonucleotide which differs from naturally occurring oligonucleotides by 1) substitution of the phosphate diester internucleotide linkage by a phosphorothioate diester, 2) methylation of the nine cytosine bases and the single uracil base both at the 5-position, and 3) substitution in the 2'-position of the ribose with a 2-methoxyethyl moiety for 10 of the 20 nucleotides (resulting in a "second generation" oligonucleotide). These modifications result in a compound that is more stable *in vivo* and more active than unmodified oligonucleotides.

(b) (4)

Acceptable specifications were proposed for each starting materials.

Executive Summary Section

The structure of mipomersen sodium was elucidated by a variety of analytical and spectrophotometric techniques, including ^1H , ^{13}C , and ^{31}P NMR, mass spectrometry, melting temperature (T_m), elemental analysis, FTIR and X-ray diffraction (b) (4)

Specifications for mipomersen drug substance include appearance, sequence determination (HPLC-MS and T_m), identification (HPLC-MS), assay (HPLC-MS), purity (HPLC-MS), impurity profile (HPLC-MS), (b) (4) (ICP), residual solvents (GC), heavy metals (ICP-MS), water content, (b) (4) (HPLC), pH, bioburden and endotoxin. Descriptions of analytical methods and validation of these methods are appropriately described and justified. Information on batch analyses, reference standards and container closure system is acceptable. Input from Pharmacology/Toxicology reviewer, R. Wange, was requested regarding the adequacy of non-clinical studies for qualifying the process impurities/degradation products at the proposed limits found above (and in the drug substance specifications). Additional comment was requested on the applicant's conclusion that none of the impurities found in the drug substance pose a significant genotoxicity risk.

Thirty-six months of stability data are available on three registration stability batches stored at the proposed long term storage condition (b) (4) and accelerated conditions (b) (4). Based on these data, a retest period of (b) (4) is appropriate for the drug substance when stored in the primary packaging.

DRUG PRODUCT

Kynamro¹, (mipomersen sodium) injection 200 mg/mL is a sterile, preservative-free, clear, colorless to slightly yellow, aqueous solution for subcutaneous injection available in two presentations: single use glass vials and pre-filled glass syringes. Both presentations utilize the identical formulation of mipomersen sodium 200 mg/mL. Other than Water for Injection, there are no excipients in the formulation. (Sodium hydroxide or hydrochloric acid may be added to adjust the pH to 7.5 – 8.5). No preservatives are added given that the product is indicated for single-use injection.

The manufacturing process of the drug product is the standard common process for this type of dosage form: (b) (4)

The drug product in vials will be manufactured by Hospira Inc. and by Genzyme Biosurgery, Ridgefield for pre-filled syringes.

¹ The Division of Medication Error Prevention and Analysis has concluded that the proposed proprietary name, Kynamro, is acceptable (see 11/27/2012 Review). This follows a request by the Applicant to reconsider the name after a 7/6/2012 finding that the proposed proprietary name was unacceptable due to similarities with a pending proposed proprietary name, (b) (4). However, the application (b) (4) was withdrawn, thus there no longer is a concern for name confusion.

Executive Summary Section

The container closure system for the vial consists of a 2 mL, (b) (4) clear glass vial. The vials are stoppered with (b) (4) rubber stoppers (b) (4).

The stoppers are capped (b) (4) with plastic flip-off caps. A total volume (b) (4) is filled into each vial to ensure a 1.0 mL deliverable volume.

The container closure for the prefilled syringe consists of a 1 mL, (b) (4) clear glass syringe with a (b) (4) staked needle and needle shield. Syringes are stoppered with (b) (4) rubber plunger stoppers (b) (4). A total volume (b) (4) is filled into syringes to ensure a 1.0 mL deliverable volume.

The drug product manufacturing process does not increase the levels of any impurities not associated with the drug substance, nor does it contribute any new impurities. Similarly, results from stability studies show no appearance of additional impurities other than those found in the drug substance.

The proposed release specifications include appearance, identity (HPLC), assay (HPLC), individual and total impurities (HPLC), volume of injection in container, pH, osmolality, particulate matter, endotoxin and sterility. The analytical procedures have been properly described and the proposed regulatory methods have been validated. Batch analysis data from 14 lots show that the drug products meet the specifications proposed.

Results from stability studies conducted on three registration batches show:

- The drug product in vials remains stable through a) 24 months at the long-term storage condition of $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$, and b) 6 months at the accelerated condition of $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$. Based on these data, and following the recommendations outlined in ICH QE1 Evaluation of Stability Data, a shelf-life of 30 months is granted for mipomersen sodium injection 200 mg/mL in vials when stored (b) (4). This is in agreement with the Applicant's proposed expiry period for the drug product in vials.
- The drug product in prefilled syringes remains stable through a) 12 months at the long-term storage condition of $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$, and b) 6 months at the accelerated condition of $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$. Based on these data, and following the recommendations outlined in ICH QE1 Evaluation of Stability Data, a shelf-life of 18 months is granted for mipomersen sodium injection 200 mg/mL in prefilled syringes when stored at (b) (4). This is in agreement with the Applicant's proposed expiry period for the drug product in prefilled syringes.

The drug product is photo labile and the primary containers (clear glass vial and syringe) do not provide adequate protection from exposure to light. However, the secondary packaging (b) (4) adequately protects the drug product from degradation due to light.

Executive Summary Section

Genzyme Corporation requested a categorical exclusion from submitting an environmental assessment for the drug product mipomersen sodium 200 mg/mL based on the regulations in 21 CFR, part 25, section 25.31(b). The request is granted.

B. Description of How the Drug Product is Intended to be Used

Mipomersen sodium is an antisense apolipoprotein B (ApoB) synthesis inhibitor. (ApoB is the primary apolipoprotein of low-density lipoproteins [LDL] and is responsible for transporting cholesterol to tissues). Mipomersen inhibits synthesis of apoB-containing lipoproteins by sequence-specific binding to its messenger ribonucleic acid (mRNA) resulting in selective degradation of the mRNA through enzyme-mediated pathways or disruption of mRNA function through binding alone.

Mipomersen sodium 200 mg/mL is indicated as an adjunct to maximally tolerated lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol, apolipoprotein B, total cholesterol, non-high density lipoprotein-cholesterol and lipoprotein A in patients with the genetic disorder, homozygous familial hypercholesterolemia (HoFH). Individuals with HoFH are at a high risk of coronary heart disease at a much younger age than would be expected in the general population due to an accumulated exposure to elevated LDL cholesterol levels.

The proposed dose for this indication is 200 mg once weekly by subcutaneous injection. Each vial or prefilled syringe provides 200 mg of mipomersen sodium in a deliverable volume of 1 milliliter of solution and is intended for single-use only. Mipomersen sodium should be injected into the abdomen, thigh region, or outer area of the upper arm.

C. Basis for Approvability or Not-Approval Recommendation

All items in the List of Deficiencies from Chemistry Review #1 have been satisfactorily addressed in the 28-Sep-2012 and 1-Oct-2012 amendments to the original NDA. See Chemistry Assessment section below for details.

Acceptable cGMP recommendations have been received from the Office of Compliance for all manufacturing and testing facilities. An Overall Compliance recommendation of Acceptable was provided on 11-Oct-2012.

Confirmation was received from Pharmacology/Toxicology that drug substance impurities have been adequately qualified at or above the proposed limits found in the drug substance specifications. As stated in a 14-Nov-2012 email from Pharm/Tox reviewer, Ron Wange, "my calculations provide support for the proposed limits for all but the (b)(4) impurities. As there is no reasonable mechanism by which the (b)(4) impurities could elicit an adverse response qualitatively or quantitatively different than the parental compound, I have no issue with the limit proposed," and "I can say that this lot (CA301012-001) had no genotoxic signal in a full battery of assays." Also see Dr.

Executive Summary Section

Wange's Pharm/Tox Review (3-Dec-2012), "From the P/T perspective, Sponsor has adequately addressed the potential toxicological significance of impurities and degradants (see reviews of study #s 301012-AS18 & GT-348-TX-7)."

The final recommendation from the microbiology product quality standpoint is pending.

This is a 505(b)(1) application where the drug substance, mipomersen sodium, is a New Molecular Entity (NME). The IND for mipomersen sodium (70969) was received on 11/18/2005. On 6/19/2009, the applicant submitted eight CMC questions as part of a Meeting Information Package related to their IND 70,969. A pre-NDA meeting was held on 12/13/2010. The original NDA was submitted on 3/29/2012.

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

Based on acceptable stability data, a shelf-life of a) 30 months is granted for mipomersen sodium injection 200 mg/mL in vials, and b) 18 months is granted for mipomersen sodium injection 200 mg/mL in prefilled syringes when stored ^{(b) (4)} in the secondary packaging ^{(b) (4)} which adequately protects the drug product from degradation due to light.

III. Administrative

A. Reviewer's Signature: in DAARTS

B. Endorsement Block: in DAARTS

C. CC Block: in DAARTS

10 Pages have been Withheld in Full as B4 (CCI/TS)
Immediately Following this Page

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/s/

JOSEPH LEGINUS
12/04/2012

ERIC P DUFFY
12/07/2012

ALI H AL HAKIM
12/07/2012

ONDQA Initial Quality Assessment (IQA) and Filing Review
NDA 203568 (mipomersen sodium)

NDA 203568
Applicant: Genzyme Copr.
Stamp Date: 29-MAR-2012
PDUFA Date: 29-MAR-2012
Established Name: Mipomersen sodium
Proposed Proprietary Name: Kynamro
Dosage form and strength: Solution for injection, 200 mg/mL
Route of Administration: Subcutaneous injection
Indications: Reduction of LDL-C, apo B, total cholesterol, etc.

**OVERALL PRODUCT QUALITY CONCLUSIONS AND
RECOMMENDATIONS**

CMC Lead: Su (Suong) Tran

Is the Product Quality Section of the application fileable from a CMC perspective?		
Yes	No	
<input checked="" type="checkbox"/>	<input type="checkbox"/>	

Are there potential CMC review issues to be forward to the Applicant with the 74 day letter?		
Yes	No	
<input type="checkbox"/>	<input checked="" type="checkbox"/>	

ONDQA Initial Quality Assessment (IQA) and Filing Review
NDA 203568 (mipomersen sodium)

RELATED REVIEW DOCUMENTS:

a. Drug Master Files listed on 356h form:

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)				11-Apr-2007	See details in CMC Summary and Critical Issues.
				22-Nov-2010	
				19-Jan-2011	
				13-Jan-2011	

b. Recommended Consults

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Clin Pharm	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
EES	<input checked="" type="checkbox"/>	<input type="checkbox"/>	EER submitted to OMPQ on 05-APR-2012
Pharm/Tox	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Review of impurity qualification and genotoxicity reports.
Methods Validation	<input type="checkbox"/>	<input type="checkbox"/>	<i>Validation may be requested of FDA labs after test methods are finalized.</i>
EA	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<i>The categorical exclusion claim will be assessed by Primary Reviewer.</i>
New Drug Micro	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
CDRH	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Other	<input type="checkbox"/>	<input type="checkbox"/>	

c. Other Applications or Submissions to note (if any):

IND 70969

d. Previous Communications with the Applicant to note (if any):

Major issues discussed in FDA's 14-JUL-2009 advice letter:

- See FDA's letter in DARRTS (review issues to be evaluated as part of the NDA review).

Major issues discussed in FDA's 23-FEB-2010 advice letter:

- See FDA's letter in DARRTS (review issues to be evaluated as part of the NDA review).

Major issues discussed at the 13-DEC-2010 PreNDA meeting:

- FDA agreed that 18-month long term stability data for the vial-packaged product and 6-month long term stability data for the syringe-packaged product will be acceptable for the NDA filing.

Does the submission contain any of the following elements?

	Yes	No	Comments
Botanical Products	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Combination Products	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Nanotechnology	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
PET	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
QbD Elements	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
SPOTS	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

ONDQA Initial Quality Assessment (IQA) and Filing Review
NDA 203568 (mipomersen sodium)

Is a team review recommended?		
Yes	No	Suggested expertise for team
<input type="checkbox"/>	<input checked="" type="checkbox"/>	

CMC Summary and Critical Issues

This is an electronic NDA, filed as a 505(b)(1) application.

The drug substance mipomersen sodium is a small synthetic New Molecular Entity. It is a 20-base, synthetic oligonucleotide and an antisense inhibitor of apolipoprotein B-100.

The drug product is a sterile solution for injection packaged in 1-mL single-dose vials and single-dose pre-filled syringes. The drug concentration is 200 mg/mL mipomersen sodium in sterile water for injection. There is no excipient in the formulation. HCl and/or NaOH may be added for pH adjustment to 7.5-8.5.

The drug product is stored under refrigerated conditions, protected from light.

Clinical dose: 200 mg once weekly (daily exposure = 28.6 mg).

Drug substance

ONDQA Initial Quality Assessment (IQA) and Filing Review

NDA 203568 (mipomersen sodium)

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 pathways or, alternatively, destabilisation or disruption of the mRNA's metabolism and function through binding alone.

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 more active than unmodified oligonucleotides.

Mipomersen is manufactured by a multi-step, solid-phase synthesis, in which the growing oligonucleotide is assembled on a solid support resin comprising cross-linked polystyrene beads to which a linker molecule is attached. Nucleotide units are added to the molecule by sequential coupling of the appropriate phosphoramidite starting materials. Each phosphoramidite is added by means of a 4-step cycle that is repeated 20 times to build up the complete molecule. Reaction by-products are removed from the synthesis column by solvent washes. The sequence of the product is defined by the order of addition of the phosphoramidites. The sequence is confirmed by in-process failure sequence analysis of the crude product and melting temperature and mass spectrometry analysis of the drug substance.

The International Union of Pure and Applied Chemistry (IUPAC) chemical name is 2'-*O*-(2-methoxyethyl)-*P*-thioguananylyl-(3'-*O*→5'-*O*)-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiocytidylyl-(3'-*O*→5'-*O*)-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiouridylyl-(3'-*O*→5'-*O*)-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiocytidylyl-(3'-*O*→5'-*O*)-2'-deoxy-*P*-thioadenylyl-(3'-*O*→5'-*O*)-2'-deoxy-*P*-thioguananylyl-(3'-*O*→5'-*O*)-*P*-thiothymidylyl-(3'-*O*→5'-*O*)-2'-deoxy-5-methyl-*P*-thiocytidylyl-(3'-*O*→5'-*O*)-*P*-thiothymidylyl-(3'-*O*→5'-*O*)-2'-deoxy-*P*-thioguananylyl-(3'-*O*→5'-*O*)-*P*-thiothymidylyl-(3'-*O*→5'-*O*)-2'-deoxy-5-methyl-*P*-thiocytidylyl-(3'-*O*→5'-*O*)-*P*-thiothymidylyl-(3'-*O*→5'-*O*)-2'-deoxy-5-methyl-*P*-thiocytidylyl-(3'-*O*→5'-*O*)-2'-*O*-(2-methoxyethyl)-*P*-thioguananylyl-(3'-*O*→5'-*O*)-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiocytidylyl-(3'-*O*→5'-*O*)-2'-*O*-(2-methoxyethyl)-*P*-thioadenylyl-(3'-*O*→5'-*O*)-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiocytidylyl-(3'-*O*→5'-*O*)-2'-*O*-(2-methoxyethyl)-5-methylcytidine, nonadecasodium

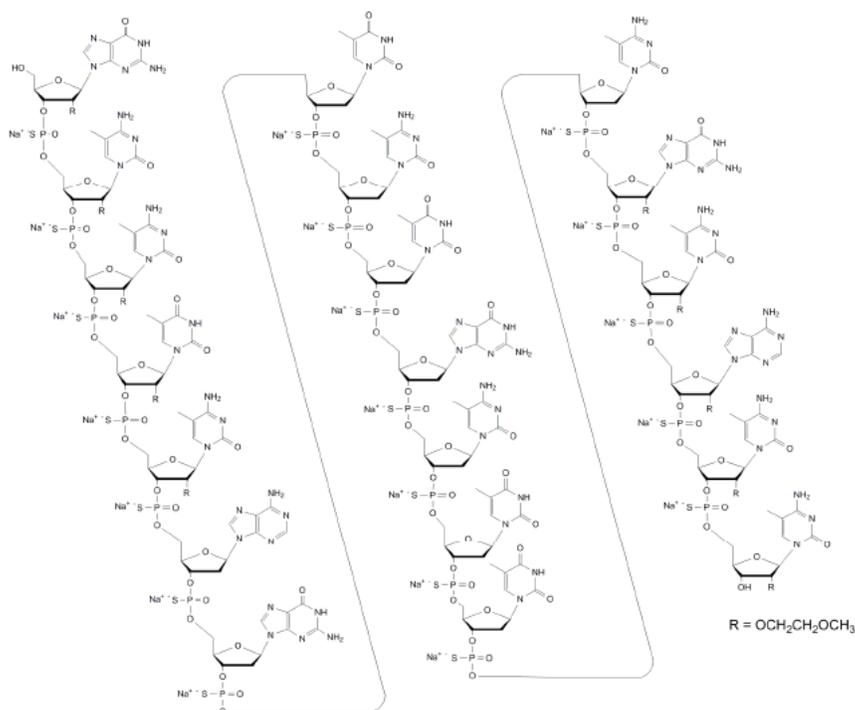
The mipomersen sequence can be written in shorthand as follows:



The underlined residues are 2'-*O*-(2-methoxyethyl) nucleosides, all other residues are 2'-deoxynucleosides.

ONDQA Initial Quality Assessment (IQA) and Filing Review
NDA 203568 (mipomersen sodium)

Figure 1: Structure of Mipomersen Sodium



Molecular formula: C₂₃₀H₃₀₅N₆₇O₁₂₂P₁₉S₁₉Na₁₉

Molecular weight: 7594.9 g/mol

Stereochemistry: The absolute configuration of each 2-deoxy-D-ribose unit is (1*R*, 3*S*, 4*R*). The absolute configuration of each 2-*O*-(2-methoxyethyl)-D-ribose unit is (1*R*, 2*R*, 3*R*, 4*R*). The absolute configuration at each phosphorous atom is undefined and hence mipomersen sodium is a mixture of 2¹⁹ diastereomers. Further information regarding stereochemistry is provided in 3.2.S.3.1 Section 1.2.

Characterization. A summary of the structural and physicochemical characterization of the drug substance is copied below. Information is included in the NDA on the stereochemistry of the nucleosides and internucleoside linkages. The sequence confirmation is by infrared multi-photon decomposition-Fourier transform-ion cyclotron resonance-mass spectrometry.

ONDQA Initial Quality Assessment (IQA) and Filing Review
NDA 203568 (mipomersen sodium)

Mipomersen sodium is a white to yellow, amorphous, hygroscopic solid. The typical pH range of a 1% aqueous (w/v) solution of mipomersen is 8.5 to 8.8. Mipomersen does not have a defined melting point and decomposes above 225°C. Due to their high aqueous solubility and charge density, the partition coefficient is considered to be negligible for oligonucleotides such as mipomersen sodium.

Mipomersen sodium is freely soluble in water and in aqueous sodium acetate buffer (pH 3.5), soluble in methanol, and insoluble in acetone, ethanol, acetonitrile, isopropyl alcohol, and chloroform.

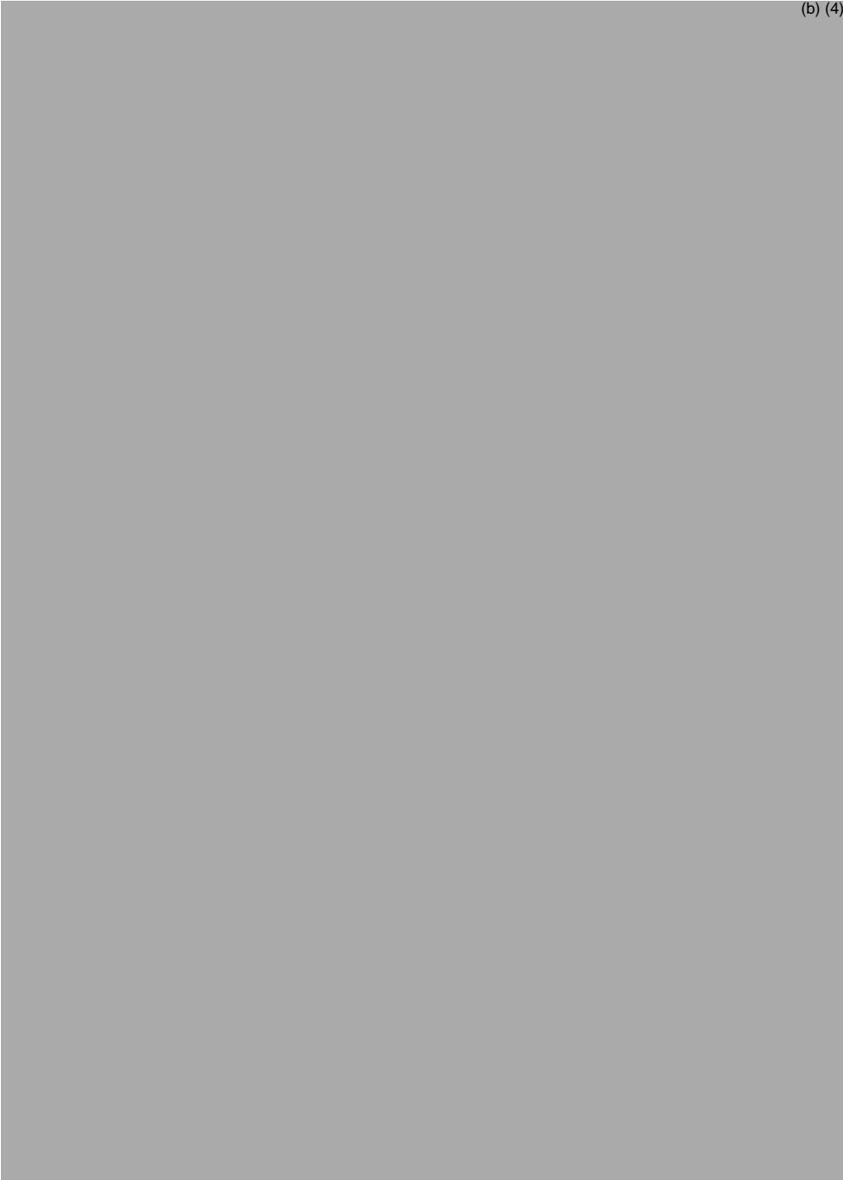
The chemical structure of mipomersen was confirmed using several techniques, which included proton, carbon and phosphorus nuclear magnetic resonance (NMR) spectroscopy, electrospray ionisation mass spectrometry, infrared multi-photon decomposition-Fourier transform-ion cyclotron resonance-mass spectrometry (IRMPD-FT-ICR-MS), complement hybridisation, elemental analysis, and Fourier transform infrared spectroscopy (FTIR). The tests were performed early in development on working reference standard lot WRS-1801 and later in development on primary reference standard lot PRS-301012-01. All results are consistent with the structure of mipomersen. Full detail is provided in [3.2.S.3.1](#).

Manufacturing process. Mipomersen is manufactured by the standard solid phase phosphoramidite oligonucleotide synthesis (reference: Beaucage, 1981, Tetrahedron Lett).

(b) (4)

ONDQA Initial Quality Assessment (IQA) and Filing Review
NDA 203568 (mipomersen sodium)

(b) (4)



Comparability of the product used in the clinical studies, stability studies, and commercial

product. The applicant states that all drug substance batches were manufactured at the commercial site (Isis Pharmaceuticals, Carlsbad CA) and that a similar process (with a few differences) was used to produce the primary stability batches, phase 3 clinical batches, and validation/commercial batches. The reviewer will evaluate the manufacturing differences and determine whether any would affect the efficacy and safety profiles of the commercial product. The batches of interest are CA301012-014 through CA301012-023.

ONDQA Initial Quality Assessment (IQA) and Filing Review
NDA 203568 (mipomersen sodium)

Table 3: Description of Mipomersen Batches

Batch	Batch Size (kg)	Date of Manufacture	Intended Use/ Purpose
CA301012-001	(b) (4)	22 May 2003	Reference standard, Clinical, Nonclinical, Stability, Development
CA301012-002		19 Apr 2004	Clinical, Nonclinical, Development
CA301012-003		20 Dec 2004	Clinical, Nonclinical, Development
CA301012-004		27 Dec 2004	Clinical, Development
CA301012-005		17 Nov 2006	Clinical, Development
CA301012-006		15 Jun 2007	Clinical, Nonclinical, Development
CA301012-007		2 Nov 2007	Clinical, Nonclinical, Development
CA301012-008		7 Jan 2008	Clinical, Nonclinical, Development
CA301012-009		28 Jan 2008	Clinical, Development
CA301012-010		11 Jul 2008	Clinical, Nonclinical, Development
CA301012-011		25 Jul 2008	Clinical, Nonclinical, Development
CA301012-012		28 Jul 2008	Nonclinical, Development
CA301012-013		8 Aug 2008	Clinical, Development
CA301012-014		30 Sept 2008	Clinical, Stability (registration)
CA301012-015		6 Oct 2008	Clinical, Stability (registration)
CA301012-016		13 Oct 2008	Clinical, Stability (registration)
CA301012-017		18 Oct 2009	Clinical, Nonclinical, Stability
CA301012-018		19 Mar 2010	Clinical
CA301012-019		15 Jun 2010	Clinical
CA301012-020		28 Jun 2010	Clinical
CA301012-021		15 Oct 2010	Process Validation
CA301012-022		29 Oct 2010	Process Validation
CA301012-023		5 Nov 2010	Process Validation

Specification. The drug substance specification is copied here. The attributes are appropriate for this type of drug substance. Based on the characterization data, the reviewer will determine whether additional testing should be required.

ONDQA Initial Quality Assessment (IQA) and Filing Review
NDA 203568 (mipomersen sodium)

Table 1: Specification for Mipomersen Sodium Drug Substance

Test	Method	Acceptance Criterion
Appearance	Visual (AM-00080/ TM014-06)	(b) (4)
(b) (4)	ICP-OES (AM-00226)	(b) (4)
Heavy Metals	ICP-MS (AM-00224)	(b) (4)
pH of 1% (w/v) aqueous solution	USP<791> & PhEur 2.2.3	(b) (4)
Residual Solvents	GC (AM-00222)	(b) (4)
(b) (4)	KF (AM-00219/ TM002-15)	(b) (4)
(b) (4)	HPLC (AM-00220/ TM003-137)	(b) (4)
Bacterial Endotoxins	USP<85> / PhEur 2.6.14	(b) (4)
Microbial Enumeration Tests	USP<61> / PhEur 2.6.12	(b) (4)

ONDQA Initial Quality Assessment (IQA) and Filing Review
NDA 203568 (mipomersen sodium)

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 as the sum of full length, fully thioated oligonucleotide (n) and full length (P=O)₁

Lack of bioassay. Whether this testing should be required will be evaluated by the reviewer. A bioassay may not be necessary given the size and function of the drug substance. It is a relatively small oligonucleotide (20 residues). Its function is to inhibit the expression of the apo B-100 gene by binding

ONDQA Initial Quality Assessment (IQA) and Filing Review
NDA 203568 (mipomersen sodium)

to a complementary sequence on mRNA to cause degradation of the mRNA and/or disruption of the mRNA's function. The function of mipomersen depends on its specific sequence, which is confirmed by different tests in the characterization study and in the drug substance specification (i.e., failure sequence analysis by ion pair-HPLC-TOF-MS, melting point of mipomersen-complement duplexes, assay by ion pair HPLC-UV-MS).

Impurities. The NDA includes a lengthy discussion on impurities. The applicant separates them into impurities resulting from starting materials/reagents and impurities resulting from the synthesis. In addition, there are two specified impurities [REDACTED] (b) (4) that result from both the starting materials and the synthesis. Certain impurities [REDACTED] (b) (4) [REDACTED] are grouped in the drug substance specification, and the reviewer will determine whether the grouping is adequately justified. All limits proposed in the specification have accompanied by qualification levels (copied below), which will be confirmed by the [PharmTox](#) team.

[REDACTED] (b) (4)

ONDQA Initial Quality Assessment (IQA) and Filing Review
NDA 203568 (mipomersen sodium)

(b) (4)

In addition, impurities were assessed for genotoxicity potential by basic screening, in cerebro analysis, threshold of toxicological concern (TTC) calculations, and quantitative structure activity relationship (using DEREK). The applicant concludes that no (b) (4) impurity is detectable below the TTC (b) (4) and no (b) (4) impurity is potentially mutagenic, which will be confirmed by the [PharmTox](#) team.

Stability. The primary stability data are sufficient in quantity for the NDA filing. The reviewer will determine a retest dating period for the drug substance based on all available data.

Stability studies for three consecutive registration batches of mipomersen sodium drug substance were initiated at Isis Pharmaceuticals Inc. (Carlsbad, CA, USA), according to approved stability protocols (b) (4)

(b) (4)

ONDQA Initial Quality Assessment (IQA) and Filing Review
NDA 203568 (mipomersen sodium)

(b) (4)

Drug product

The drug product is a sterile solution for injection packaged in single-dose vials and in single-dose pre-filled syringes. The drug concentration is 200 mg/mL in sterile water for injection. **There is no excipient in the formulation.** HCl and/or NaOH may be added for pH adjustment to 7.5-8.5.

Overfill. The vial product includes [REDACTED] (b) (4). The primary reviewer will confirm that this additional amount is adequately justified by data, that it is used to compensate for lost drug during delivery and not for stability problems.

Established name and dosage strength. The dosage strength (200 mg/mL) is based on the salt. Labeling has the accurate “mipomersen sodium” as the established name of the product.

Comparability of the product used in the clinical studies, stability studies, and commercial product.

Primary stability batches of the vial product were manufactured at the commercial site at Hospira, McPherson KS [REDACTED] (b) (4). All three batches (E9005, E9006, E9009) were used in clinical studies.

Primary stability batches of the pre-filled-syringe product were manufactured at the commercial site at Genzyme, Ridgefield NJ at the commercial [REDACTED] (b) (4) scale. All three batches (CL10002, CL10004, CL10006) were used in clinical studies.

ONDQA Initial Quality Assessment (IQA) and Filing Review
NDA 203568 (mipomersen sodium)

Manufacturing process of the drug product. The manufacturing process of the drug product is the standard common process for this type of dosage form: [REDACTED] (b) (4)

(b) (4)

Drug product specification.

The drug product specification is copied here. The same specification is used for both vial and syringe products.

- **Limits on degradation products.** The applicant states that these drug substance impurities are also potential drug product degradants: [REDACTED] (b) (4)

(b) (4)

ONDQA Initial Quality Assessment (IQA) and Filing Review
NDA 203568 (mipomersen sodium)

Test (Method)	Method Number	Acceptance Criteria	
		Release	End of Shelf Life
Appearance (Visual)	TM014-19/ USAC1111	Clear, colourless to slightly yellow solution, essentially (practically) free from visible particles	
Identification (IP-HPLC-UV-MS ^a)	AM-00184/ TM003-136	(b) (4)	
Assay (% label claim) (IP-HPLC-UV-MS)	AM-00184/ TM003-136		
Purity (%) (IP-HPLC-UV-MS) ISIS 301012^c (b) (4)	AM-00184/ TM003-136		
Degradation Products (%) (IP-HPLC-UV-MS) (b) (4)	AM-00184/ TM003-136		
(b) (4)			
Volume of Injection in Container (mL) (USP ^f <1>/ PhEur ^g 2.9.17)	TM015-66/ USAC1113		
pH (USP <791>/ PhEur 2.2.3)	TM007-18/ USAC1111		
Osmolality (mOsm/kg) (USP <785>)	TM013-08		
Particulate Matter (particles/ container) (USP <788>/ PhEur 2.9.19)	MTM063/ USMB1085		
Bacterial Endotoxins (EU/mL) (USP <85>/ PhEur 2.6.14)	MTM064/ BXMB1004		
Sterility (USP <71>/ PhEur 2.6.1/ BXMB1009)	USP <71>/ PhEur 2.6.1	Complies	

^a Ion pair-high performance liquid chromatography with ultraviolet and mass spectrometry detection
^b Not Required
(b) (4)
^d Not Less Than
^e Not More Than
^f United States Pharmacopoeia
^g European Pharmacopoeia

ONDQA Initial Quality Assessment (IQA) and Filing Review
NDA 203568 (mipomersen sodium)

Container closure systems for product distribution.

For the vial product:

(b) (4) 2 mL, clear glass vials are filled with mipomersen sodium injection solution. The vials are stoppered with (b) (4) rubber stoppers (b) (4) (b) (4). The vials are capped with an (b) (4) flip-off cap. A total volume (b) (4) is filled into the vials to ensure a 1.0 mL deliverable volume. Complete details and specifications are provided in 3.2.P.7-vial.

For the pre-filled syringe product:

(b) (4) mL, (b) (4) clear glass syringes with (b) (4) staked needles and needle shields are filled with mipomersen sodium injection solution. The syringes are stoppered with (b) (4) rubber plunger stoppers (b) (4). (b) (4) The syringes are then assembled with a plunger rod and safety device. A total volume (b) (4) is filled into the syringes to ensure a 1.0 mL deliverable volume. Complete details and specifications are provided in 3.2.P.7-pfs.

- **Safety of the packaging components.** The applicant states that the glass component in both vial and syringe is (b) (4) glass. There is no chemical treatment of the glass. The rubber stoppers in both systems were tested per USP <381> (and USP <661> in addition for the syringe stopper).
- **Suitability of the packaging components.** The primary stability batches were packaged in the proposed commercial container closure systems.
- **DMFs.** The primary reviewer will review information in the NDA and DMFs per internal policy on the review of container closure systems.

Stability of the drug product.

A sufficient amount of stability data is submitted for filing purposes as previously discussed with FDA. At the 13-DEC-2010 PreNDA meeting, FDA agreed that 18-month long term (5 °C) stability data for the

ONDQA Initial Quality Assessment (IQA) and Filing Review
NDA 203568 (mipomersen sodium)

vial-packaged product and 6-month long term (5 °C) stability data for the syringe-packaged product will be acceptable for the NDA filing. Other stability data include 6-month accelerated (25 °C), photostability, freeze-thaw cycling, thermal stress, and photolytic stress. The reviewer will determine the final expiry based on all available data and per ICH Q1E Evaluation of Stability Data.

Facility

List of facilities included in EER:

Table 1: Drug Substance Manufacturer Information

Facility Location	Registration No.	Contact	Operations
Isis Pharmaceuticals Inc. 2280-2282 Faraday Avenue Carlsbad, CA United States 92008	DUNS: 011829916	Joseph Johnston 760-603-2383 jjohnston@isisph.com	cGMP manufacture, packaging, labelling, analytical testing & storage
(b) (4)			
Genzyme Ltd Haverhill Operations 37 Hollands Road Haverhill, Suffolk United Kingdom CB9 8PU	DUNS: 229522842	Christopher Homan +44-1440-716471 christopher.homan@genzyme.com	Analytical testing

ONDQA Initial Quality Assessment (IQA) and Filing Review
NDA 203568 (mipomersen sodium)

Table 2: Drug Product Manufacturer Information

Facility Location	Registration No.	Contact	Operations
Hospira Inc. 1776 North Centennial Drive McPherson, KS United States 67460	DUNS: 030606222	Robert Williford 1-620-241-6200 x6189 robert.williford@hospira.com	cGMP compounding (b) (4) (b) (4) vial filling & inspection, sterility testing (release) and storage
Hospira SpA Via Fosse Ardeatine, 2 20060 Liscate, Milano Italy	DUNS: 564165541	Marco Scanziani +39-02-9545-4330 marco.scanziani@hospira.com	Sterility testing for release to the European market
Genzyme Haverhill 37 Hollands Road Haverhill, Suffolk United Kingdom CB9 8PU	DUNS: 229522842	Christopher Homan +44-1440-716471 christopher.homan@genzyme.com	Analytical testing. Packaging, labelling and storage. Qualified person release for EU markets
(b) (4)			
Genzyme Ridgefield 1125 Pleasant View Terrace Ridgefield, NJ United States 07657	DUNS: 098066215	Sam Spagnuolo 201-402-5586 sam.spagnuolo@genzyme.com	cGMP compounding, (b) (4) (b) (4) syringe filling & inspection, analytical testing, packaging, labelling and storage.
Isis Pharmaceuticals Inc. 2280-2282 Faraday Avenue Carlsbad, CA United States 92008	DUNS: 011829916	Joseph Johnston 760-603-2383 jjohnston@isisph.com	Analytical testing

ONDQA Initial Quality Assessment (IQA) and Filing Review
NDA 203568 (mipomersen sodium)

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL					
	Parameter	Yes	No	N/A	Comment
1.	Is the CMC section organized adequately?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
3.	Are all the pages in the CMC section legible?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
B. FACILITIES*					
	Parameter	Yes	No	N/A	Comment
5	Is a single, comprehensive list of all involved facilities available in one location in the application?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
6	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
7	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
8	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

ONDQA Initial Quality Assessment (IQA) and Filing Review
NDA 203568 (mipomersen sodium)

9	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
1	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT					
	Parameter	Yes	No	N/A	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
D. MASTER FILES (DMF/MAF)					
	Parameter	Yes	No	N/A	Comment
12.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

ONDQA Initial Quality Assessment (IQA) and Filing Review
NDA 203568 (mipomersen sodium)

E. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)					
	Parameter	Yes	No	N/A	Comment
13.	Does the section contain a description of the DS manufacturing process?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
14.	Does the section contain identification and controls of critical steps and intermediates of the DS(in process parameters)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
15.	Does the section contain information on impurities?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
16.	Does the section contain information regarding the characterization of the DS?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
17.	Does the section contain controls for the DS?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
18.	Has stability data and analysis been provided for the drug substance?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
19.	Does the application contain Quality by Design (QbD) information regarding the DS?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
20.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
21.	Does the section contain container and closure information?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
F. DRUG PRODUCT (DP)					
	Parameter	Yes	No	N/A	Comment
22.	Does the section contain quality controls of excipients?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
23.	Does the section contain information on composition?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
24.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
25.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
26.	Is there a batch production record and a proposed master batch record?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
27.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
28.	Have any biowaiver been requested?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
29.	Does the section contain description of to-be-marketed container/closure system and presentations?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
30.	Does the section contain controls of the final drug product?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
31.	Has stability data and analysis been provided to support the requested expiration date?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
32.	Does the application contain Quality by Design (QbD) information regarding the DP?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
33.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

ONDQA Initial Quality Assessment (IQA) and Filing Review
NDA 203568 (mipomersen sodium)

G. METHODS VALIDATION (MV)					
	Parameter	Yes	No	N/A	Comment
34.	Is there a methods validation package?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
H. MICROBIOLOGY					
	Parameter	Yes	No	N/A	Comment
35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See Microbiology filing review
I. LABELING					
	Parameter	Yes	No	N/A	Comment
36.	Has the draft package insert been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
37.	Have the immediate container and carton labels been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
38.	Does section contain tradename and established name?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
J. FILING CONCLUSION					
	Parameter	Yes	No	N/A	Comment
39.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
40.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
41.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

This document will be signed in DARRTS by the following:

CMC Lead
 Branch Chief

{See appended electronic signature page}

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

/s/

SUONG T TRAN
05/14/2012

ALI H AL HAKIM
05/14/2012

NDA 203568

**TRADENAME™
(mipomersen sodium) Injection¹**

Genzyme Corporation

**Joseph Leginus, PhD
Division of Pre-Marketing Assessment III, Branch VII, ONDQA**

**For the Division of
Metabolism and Endocrinology Products**

CHEMISTRY REVIEW #1

¹ The Division of Medication Error Prevention and Analysis has concluded that the originally proposed proprietary name of the drug product, KYNAMRO™ is not acceptable from a safety perspective. A new proprietary name has not yet been accepted.

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet	3
The Executive Summary	7
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used.....	10
C. Basis for Approvability or Not-Approval Recommendation	10
III. Administrative.....	11
A. Reviewer's Signature: in DAARTS.....	11
B. Endorsement Block: in DAARTS	11
C. CC Block: in DAARTS.....	11
Chemistry Assessment	12
I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body of Data	12
S DRUG SUBSTANCE.....	12
P DRUG PRODUCT.....	71
A APPENDICES	N/A
R REGIONAL INFORMATION	123
II. Review of Common Technical Document-Quality (Ctd-Q) Module 1	123
A. Labeling & Package Insert.....	123
B. Environmental Assessment or Claim of Categorical Exclusion.....	133
List of Deficiencies To Be Communicated.....	Error! Bookmark not defined.

Chemistry Review Data Sheet

1. NDA 203568
2. REVIEW #: 1
3. REVIEW DATE: 10-Sep-2012
4. REVIEWER: Joseph Leginus, PhD
5. PREVIOUS DOCUMENTS:

Previous Documents

N/A

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original NDA

Document Date

29-Mar-2012

7. NAME & ADDRESS OF APPLICANT:

Name: Genzyme Corporation
Address: 500 Kendall St. Cambridge, MA 02142
Representative: Jill P. Hillier PhD, Senior Director Regulatory Affairs
Telephone: 781-434-3443

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
- b) Non-Proprietary Name (USAN): Mipomersen sodium
- c) Code Name/# (ONDC only): CAS No.: 629167-92-6; Laboratory Code: ISIS 301012.
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: This NDA is submitted as a 505(b)(1) application.

Chemistry Review Data Sheet

10. PHARMACOL. CATEGORY:

Mipomersen sodium, an apolipoprotein B synthesis inhibitor, is as an adjunct to maximally tolerated lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol, apolipoprotein B, total cholesterol, non-high density lipoprotein-cholesterol and lipoprotein (a) in patients with homozygous familial hypercholesterolemia.

11. DOSAGE FORM: Solution for Injection

12. STRENGTH/POTENCY: 200 mg/mL

13. ROUTE OF ADMINISTRATION: Subcutaneous Injection

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

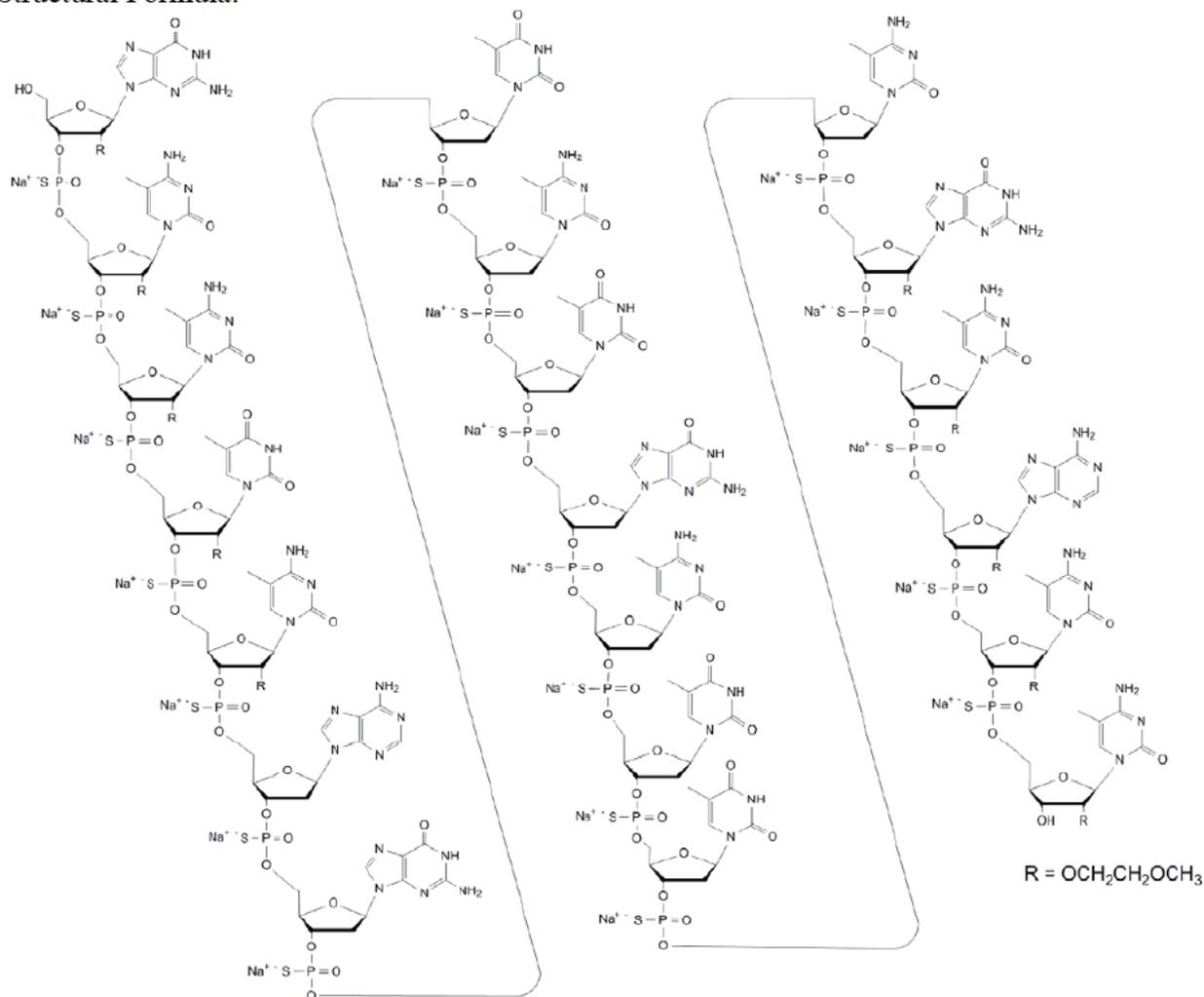
Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 2'-O-(2-methoxyethyl)-P-thioguanlyl-(3'-O→5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'-O→5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'-O→5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'-O→5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'-O→5'-O)-2'-deoxy-P-thioadenylyl-(3'-O→5'-O)-2'-deoxy-P-thioguanlyl-(3'-O→5'-O)-P-thiothymidylyl-(3'-O→5'-O)-2'-deoxy-5-methyl-P-thiocytidylyl-(3'-O→5'-O)-P-thiothymidylyl-(3'-O→5'-O)-2'-deoxy-P-thioguanlyl-(3'-O→5'-O)-2'-deoxy-5-methyl-P-thiocytidylyl-(3'-O→5'-O)-P-thiothymidylyl-(3'-O→5'-O)-2'-deoxy-5-methyl-P-thiocytidylyl-(3'-O→5'-O)-2'-O-(2-methoxyethyl)-P-thioguanlyl-(3'-O→5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'-O→5'-O)-2'-O-(2-methoxyethyl)-P-thioadenylyl-(3'-O→5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'-O→5'-O)-2'-O-(2-methoxyethyl)-5-methylcytidine, nonadecasodium

Chemistry Review Data Sheet

Structural Formula:



Molecular Formula: C₂₃₀H₃₀₅N₆₇O₁₂₂P₁₉S₁₉Na₁₉

Molecular Weight: 7594.9 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code ¹	Status ²	Date Review Completed	Comments
(b) (4)				1	Adequate	24-Apr-2012	Reviewed by Y. Smith
				1	Adequate	24-Aug-2011	Reviewed by O. Stephens

Chemistry Review Data Sheet

(b) (4)	1	Adequate	25-Jan-2012	Reviewed by S. Fong
	1	Adequate	27-Jan-2006	Reviewed by L. Rodriguez

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	70969	Mipomersen sodium

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending.		
Pharm/Tox	A request for the safety evaluation of impurities was made.	Pending	Ronald Wange
Biopharm	Not applicable. This is an injectable product, and the commercial formulation was used in Phase 3 studies.		
Methods Validation	Validation may be requested of FDA labs after test methods are finalized.		
EA	Conducted by CMC reviewer. Granting the categorical exclusion as per 21 CFR 25.31(b).	10-Sep-2012	Joseph Leginus
Microbiology	Review of 1) microbiology controls proposed for the drug product, and 2) and (b) (4) processing validation for the drug product.	Pending	Bob Mello

19. ORDER OF REVIEW: N/A

The Chemistry Review for NDA 203568

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The recommendation from a CMC perspective is pending a) satisfactory responses to the deficiencies identified in Review #1, and b) confirmation from Pharmacology/Toxicology that drug substance impurities have been adequately qualified at or above the proposed limits found in the drug substance specifications.

At this time, the Office of Compliance has not issued an acceptable cGMP recommendation for one drug product manufacturing site (Genzyme Biosurgery). An Overall Compliance recommendation is pending as of 10-Sep-2012.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

DRUG SUBSTANCE

Mipomersen sodium is a 20-base, synthetic oligonucleotide sodium salt designed to inhibit expression of the apolipoprotein B-100 gene by sequence-specific hybridization to a complementary sequence on the mRNA. (Apolipoproteins are proteins that bind lipids, such as cholesterol, for transport through the circulatory system). It is an oligonucleotide which differs from naturally occurring oligonucleotides by 1) substitution of the phosphate diester internucleotide linkage by a phosphorothioate diester, 2) methylation of the nine cytosine bases and the single uracil base both at the 5-position, and 3) substitution in the 2'-position of the ribose with a 2-methoxyethyl moiety for 10 of the 20 nucleotides (resulting in a "second generation" oligonucleotide). These modifications result in a compound that is more stable *in vivo* and more active than unmodified oligonucleotides.

The manufacturing process for mipomersen sodium is a multi-step process (b) (4)

(b) (4)

(b) (4). The molecular

Executive Summary Section

formula of mipomersen sodium is $C_{230}H_{305}N_{67}O_{122}P_{19}S_{19}Na_{19}$ and its molecular weight is 7595 g/mol.

(b) (4)

Acceptable specifications were proposed for each starting materials.

The structure of mipomersen sodium was elucidated by a variety of analytical and spectrophotometric techniques, including 1H , ^{13}C , and ^{31}P NMR, mass spectrometry, melting temperature (T_m), elemental analysis, FTIR and X-ray diffraction.

(b) (4)

(b) (4)

Specifications for mipomersen drug substance include appearance, sequence determination (HPLC-MS and T_m), identification (HPLC-MS), assay (HPLC-MS), purity (HPLC-MS), impurity profile (HPLC-MS), (b) (4) (ICP), residual solvents (GC), heavy metals (ICP-MS), water content, (b) (4) (HPLC), pH, bioburden and endotoxin. Descriptions of analytical methods and validation of these methods are appropriately described and justified. Information on batch analyses, reference standards and container closure system is acceptable. Input from Pharmacology/Toxicology reviewer, R. Wange, was requested regarding the adequacy of non-clinical studies for qualifying the process impurities/degradation products at the proposed limits found above (and in the drug substance specifications). Additional comment was requested on the applicant's conclusion that none of the impurities found in the drug substance pose a significant genotoxicity risk.

Thirty-six months of stability data are available on three registration stability batches stored at the proposed long term storage condition (b) (4) and accelerated conditions (b) (4). Based on these data, a retest period (b) (4) is appropriate for the drug substance when stored in the primary packaging.

DRUG PRODUCT

Mipomersen sodium injection 200 mg/mL is a sterile, preservative-free, clear, colorless to slightly yellow, aqueous solution for subcutaneous injection available in two presentations: single use glass vials and pre-filled glass syringes. Both presentations utilize the identical formulation of mipomersen sodium 200 mg/mL. Other than Water for Injection, there are no excipients in the formulation. (Sodium hydroxide or hydrochloric acid may be added to adjust the pH to 7.5 – 8.5). No preservatives are added given that the product is indicated for single-use injection.

The manufacturing process of the drug product is the standard common process for this type of dosage form: (b) (4)

The drug product in vials will be manufactured by Hospira Inc. and by Genzyme Biosurgery, Ridgefield for pre-filled syringes.

Executive Summary Section

The container closure system for the vial consists of a 2 mL, (b) (4) (b) (4) clear glass vial. The vials are stoppered with (b) (4) rubber stoppers (b) (4).

The stoppers are capped (b) (4) with plastic flip-off caps. A total volume (b) (4) is filled into each vial to ensure a 1.0 mL deliverable volume.

The container closure for the prefilled syringe consists of a 1 mL, (b) (4) clear glass syringe with (b) (4) staked needle and needle shield. Syringes are stoppered with (b) (4) rubber plunger stoppers (b) (4). A total volume (b) (4) is filled into syringes to ensure a 1.0 mL deliverable volume.

The drug product manufacturing process does not increase the levels of any impurities not associated with the drug substance, nor does it contribute any new impurities. Similarly, results from stability studies show no appearance of additional impurities other than those found in the drug substance.

The proposed release specifications include appearance, identity (HPLC), assay (HPLC), individual and total impurities (HPLC), volume of injection in container, pH, osmolality, particulate matter, endotoxin and sterility. The analytical procedures have been properly described and the proposed regulatory methods have been validated. Batch analysis data from 14 lots show that the drug products meet the specifications proposed.

Results from stability studies conducted on three registration batches show:

- The drug product in vials remains stable through a) 24 months at the long-term storage condition of $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$, and b) 6 months at the accelerated condition of $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$. Based on these data, and following the recommendations outlined in ICH QE1 Evaluation of Stability Data, a shelf-life of 30 months is granted for mipomersen sodium injection 200 mg/mL in vials when stored at (b) (4). This is in agreement with the Applicant's proposed expiry period for the drug product in vials.
- The drug product in prefilled syringes remains stable through a) 12 months at the long-term storage condition of $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$, and b) 6 months at the accelerated condition of $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$. Based on these data, and following the recommendations outlined in ICH QE1 Evaluation of Stability Data, a shelf-life of 18 months is granted for mipomersen sodium injection 200 mg/mL in prefilled syringes when stored at (b) (4). This is in agreement with the Applicant's proposed expiry period for the drug product in prefilled syringes.

The drug product is photo labile and the primary containers (clear glass vial and syringe) do not provide adequate protection from exposure to light. However, the secondary

Executive Summary Section

packaging (b) (4) adequately protects the drug product from degradation due to light.

Genzyme Corporation requested a categorical exclusion from submitting an environmental assessment for the drug product mipomersen sodium 200 mg/mL based on the regulations in 21 CFR, part 25, section 25.31(b). The request is granted.

B. Description of How the Drug Product is Intended to be Used

Mipomersen sodium is an antisense apolipoprotein B (ApoB) synthesis inhibitor. (ApoB is the primary apolipoprotein of low-density lipoproteins [LDL] and is responsible for transporting cholesterol to tissues). Mipomersen inhibits synthesis of apoB-containing lipoproteins by sequence-specific binding to its messenger ribonucleic acid (mRNA) resulting in selective degradation of the mRNA through enzyme-mediated pathways or disruption of mRNA function through binding alone.

Mipomersen sodium 200 mg/mL is indicated as an adjunct to maximally tolerated lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol, apolipoprotein B, total cholesterol, non-high density lipoprotein-cholesterol (b) (4) in patients with the genetic disorder, homozygous familial hypercholesterolemia (HoFH). Individuals with HoFH are at a high risk of coronary heart disease at a much younger age than would be expected in the general population due to an accumulated exposure to elevated LDL cholesterol levels.

The proposed dose for this indication is 200 mg once weekly by subcutaneous injection. Each vial or prefilled syringe provides 200 mg of mipomersen sodium in a deliverable volume of 1 milliliter of solution and is intended for single-use only. Mipomersen sodium should be injected into the abdomen, thigh region, or outer area of the upper arm.

C. Basis for Approvability or Not-Approval Recommendation

The recommendation from a CMC perspective is pending a) satisfactory responses to the deficiencies identified in Review #1, b) acceptability of microbiology information regarding sterility assurance of the drug product, c) an Acceptable recommendation from the Office of Compliance for manufacturing facilities associated with this application, and d) confirmation from Pharmacology/Toxicology that drug substance impurities have been adequately qualified at or above the proposed limits found in the drug substance specifications.

This is a 505(b)(1) application where the drug substance, mipomersen sodium, is a New Molecular Entity (NME). The IND for mipomersen sodium (70969) was received on 11/18/2005. On 6/19/2009, the applicant submitted eight CMC questions as part of a Meeting Information Package related to their IND 70,969. A pre-NDA meeting was held on 12/13/2010. The original NDA was submitted on 3/29/2012.

Executive Summary Section

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

III. Administrative

- A. Reviewer's Signature:** in DAARTS
- B. Endorsement Block:** in DAARTS
- C. CC Block:** in DAARTS

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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/

JOSEPH LEGINUS
09/11/2012

ALI H AL HAKIM
09/11/2012