London, 21 March 2013
EMA/305826/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kynamro

Solution for injection 189mg

International non-proprietary name: mipomersen

Procedure No. EMEA/H/C/002429/0000

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACE	angiotensin-converting enzyme
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
Amu	atomic mass unit
Apo A	apolipoprotein A
Apo B	apolipoprotein B
ApoB-100	Apolilopropteín B-100
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve to infinity
BID	twice daily
BMI	body-mass index
BRB	bilirubin
C	cholesterol
CDP	clinical development plan
CGE-UV	capillary gel electrophoresis with ultraviolet detection
CHD	coronary heart disease
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	plasma clearance
Cmax	maximum plasma concentration
CNS	central nervous system
CQAs	Critical Quality Attributes
CrCl	creatinine clearance
CRP	C-reactive protein
CSR	clinical study report
CT	computed tomography
CV(S)	cardiovascular
CWL	Cool white fluorescent light
CYP	cytochrome P450
DNA	deoxyribonucleic acid
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
E-R	exposure-response
EU	European Union
FDA	Food and Drug Administration (US)
FH	familial hypercholesterolaemia
FLS	flu like symptom
FTIR	Fourier transform infrared spectroscopy
GC	Gas chromatography
GLP	Good Laboratory Practices
HA	health authority
HDL-C	high density lipoprotein cholesterol
HeFH	heterozygous familial hypercholesterolaemia
HMG-CoA	hydroxyl-methyl-glutaryl-Coenzyme A
HoFH	homozygous familial hypercholesterolaemia
HPLC	High Performance Liquid Chromatography
HsCRP	High sensitivity C-reactive protein
ICAC	independent central adjudication committee
ICH	International Conference on Harmonisation
ICH	International Conference on Harmonization

IDL	intermediate density lipoprotein
	IRMPD-FT-ICR-MS infrared multi-photon decomposition-Fourier transform-ion cyclotron resonance-mass spectrometry
ISR	injection site reaction
IV	intravenous(ly)
i.v.	intravenous(ly)
KF	Karl Fischer
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LDL	low density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LDPE	Low Density Polyethylene
LFT	liver function test
Lp[a]	lipoprotein A
LSC	Liquid scintillation counting
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary of Regulatory Activities
mg	milligram
ml	milliliter
MOE	2′- methoxyethyl
mRNA	messenger RNA
MTD	maximum tolerated dose
MTP	microsomal triglyceride transfer protein
NADPH	nicotinamide adenine dinucleotide phosphate
NMR	Nuclear Magnetic Resonance
NOAEL	no-observed-adverse-effect-level
OLE	open-label extension
PD	pharmacodynamic(s)
PET	primary efficacy timepoint
PFS	Pre-filled syringes
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetic(s)
PO	oral(ly)
Pop-PK	population pharmacokinetics
QD	once daily
QOW	every other week
QW	once weekly
QWBA	quantitative whole-body autoradiography
RBC	red blood parameters
RMP	Risk Management Plan
RNA	ribonucleic acid
ROW	rest of world
SA	Scientific Advice
SAE	serious adverse event
SC	subcutaneous(ly)
s.c.	subcutaneous(ly)
SCE	Summary of Clinical Efficacy
SOP	Standard Operating Procedures
SPC	Summary of Product Characteristics
TC	total cholesterol
ULN	upper limit of normal
US	United States
Vc/F	apparent volume of distribution of the central compartment
VLDL	very low density lipoprotein
WFI	Water for injection

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Genzyme Europe BV submitted on 28 July 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Kynamro, through the centralised procedure under Article 3(2)(a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 September 2010.

The applicant applied for the following indication:

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

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/139/2011 on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP P/139/2011 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance mipomersen contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 22 July 2010. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status

An application for Kynamro was filed in the following countries: USA, Canada, Brazil, South Korea and Mexico.

1.2. Manufacturers

Manufacturer(s) responsible for batch release

Genzyme Limited
37 Hollands Rd, Haverhill, Suffolk, CB9 8PU
United Kingdom

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Arantxa Sancho-Lopez Co-Rapporteur: Pieter de Graeff

CHMP Peer reviewer: Harald Enzmann

- The application was received by the EMA on 28 July 2011.
- The procedure started on 17 August 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 8 November 2011. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 4 November 2011.
- During the meeting on 15 December 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The consolidated List of Questions was sent to the applicant on 16 December 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 March 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 7 May 2012.
- During the CHMP meeting on 24 May 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 21 August 2012.
- During the CHMP meeting on 17 September 2012, outstanding issues were addressed by the

applicant during an oral explanation before the CHMP.

- During the CHMP meeting on 20 September 2012, the CHMP agreed on a 2nd list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP 2nd List of Outstanding Issues on 20 November 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding issues to all CHMP members on 10 December 2012.
- During the meeting on 13 December 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, recommended the refusal of the granting of a Marketing Authorisation for Kynamro.

Steps taken for the re-examination procedure

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Ian Hudson Co-Rapporteur: Andrea Laslop

- The applicant submitted written notice to the EMA on 18 December 2012 to request a re-examination of Kynamro CHMP opinion of 13 December 2012.
- During its meeting on 14-17 January 2013, the CHMP appointed Ian Hudson as Rapporteur and Andrea Laslop as Co-Rapporteur.
- The applicant submitted the detailed grounds for the re-examination on 31 January 2013. The re-examination procedure started on 1 February 2013.
- On 21 February 2013, the CHMP requested the advice of the Pharmacovigilance Risk Assessment Committee (PRAC) on specific questions related to the proposed RMP proposals. The PRAC's recommendation on specific CHMP questions was issued on 7 March 2013.
- The Rapporteur's Assessment Report was circulated to all CHMP members on 8 March 2013. The Co Rapporteur's Assessment Report was circulated to all CHMP members on 8 March 2013.
- During a meeting of the ad hoc expert group on 12 March 2013, experts were convened to consider the grounds for re-examination.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's detailed grounds for re-examination to all CHMP members on 15 March 2013.
- During the CHMP meeting on 18-21 March 2013, the detailed grounds for re-examination were addressed by the applicant during an oral explanation before the CHMP.
- The CHMP noted that the sentence on the new active substance status (section 4 of the Assessment Report) was not accurate and this has therefore been rectified.
- During the meeting on 18-21 March 2013, the CHMP, in the light of the scientific data available and the scientific discussion within the Committee, the CHMP re-examined its initial

opinion and in its final opinion concluded that the application did not satisfy the criteria for authorisation neither under exceptional circumstances nor as conditional MA and did therefore not recommend the granting of the marketing authorisation.

2. Scientific discussion

2.1 Introduction

Familial hypercholesterolaemia (FH), including homozygous FH (HoFH) and severe heterozygous FH (HeFH), is a genetic disorder characterised by mutations in the low-density lipoprotein receptor (LDLr) gene. Typically, high low-density-lipoprotein cholesterol (LDL-C) levels (650-1000 mg/dL) and premature cardiovascular disease occurs. While the HoFH has an overall prevalence of approximately 1:1 000 000, the prevalence of the HeFH population is approximately 1:300 to 1:500, equating to a total of one million patients in the European Union (EU). Diagnosis is normally based on a combination of family history and clinical presentation including a lipid profile.

Patients with HoFH and severe HeFH share similar treatment approaches, i.e. aimed to decrease the LDL-C levels. Statins, ezetimibe, niacin, fibrates, and bile acid sequestrants are used as the usual treatment approach. However, due to the lack of functional LDLr in patients with HoFH and due to the variable LDLr activity in patients with severe HeFH, different lipid-lowering treatment regimens, even at maximal doses, often produce insufficient reductions in LDL-C level. The low-density-lipoprotein (LDL) aphaeresis that selectively removes LDL particles from plasma, is an extracorporeal treatment used as a last therapy resort in these patients. However, such interventional therapy is not widely available and is associated with significant morbidity due to its requirement for chronic vascular access.

It is believed that a reduction in the LDL-C level irrespective of the mechanism of action is associated with a reduction in cardiovascular morbidity and mortality. Although most clinical studies have been conducted with the statins, other mechanisms of action that lower LDL-C might also contribute to the reduction in morbidity and mortality in a similar fashion.

Kynamro contains mipomersen (as mipomersen sodium), an antisense oligonucleotide drug targeted to human messenger ribonucleic acid (mRNA) for apo B-100, the principal apolipoprotein of LDL and its metabolic precursor, very low density lipoprotein (VLDL). It inhibits the synthesis of apolipoprotein B (apo B) by binding to a specific segment of the coding region of the mRNA. In humans, apo B-100 is the principal apolipoprotein associated with very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL) and low density lipoprotein (LDL), comprising approximately 30% to 95% of the proteins in these lipoproteins. The apo B-100 is also a principal component of lipoprotein (a) (Lp[a]), which consists of apolipoprotein (a) covalently bound to the apo B component of an LDL-like particle. Low density lipoprotein cholesterol (LDL-C), apo B and Lp(a) are key risk factors for atherosclerosis.

Mipomersen is complementary to the coding region of the mRNA for apo B-100, and binds by Watson and Crick base pairing. The hybridisation of mipomersen to the cognate mRNA results in RNase H-mediated degradation of the cognate mRNA, thus inhibiting translation of the apo B-100 protein. The binding site for mipomersen is placed within the coding region of the apo B mRNA.

The clinical development program of mipomersen at the time of the submission of the marketing authorisation application included 18 clinical studies. Of these, two long term extension studies were ongoing. A total of 792 healthy volunteers and patients received at least 1 dose of mipomersen sodium. Of those, a total of 390 patients received up to 26 weeks of study medication in the four phase 3 studies (261 patients were treated with mipomersen and 129 patients received placebo).

The proposed indication for Kynamro was:

Kynamro is indicated as an adjunct to maximally tolerated lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol (LDL-C), apo B, total cholesterol (TC), non-high density lipoprotein-cholesterol (non-HDL-C) and lipoprotein (a) [Lp(a)] in patients with homozygous familial hypercholesterolaemia (HoFH) and in patients with severe heterozygous familial hypercholesterolaemia (severe HeFH).

Kynamro was proposed as a product for restricted prescription. Treatment was to be initiated under the supervision of a physician experienced in the treatment of lipid disorders. Kynamro was to be administered subcutaneously as a once weekly injection in the -the outer area of the upper arm, thigh region or abdomen.

It is to be noted, that in the view of the CHMP's negative opinion for Kynamro, the Product Information and Risk Minimisation Plan were not adopted and agreed by the CHMP. Thus, all references to these documents in the report are the proposed draft versions.

2.2. Quality aspects

2.2.1. Introduction

The finished product Kynamro is presented as a sterile, preservative-free, clear, colourless to slightly yellow, aqueous solution for injection containing 189 mg of mipomersen (equivalent to 200 mg mipomersen sodium) as active substance. The other ingredients are water for injection (WFI), sodium hydroxide and hydrochloric acid.

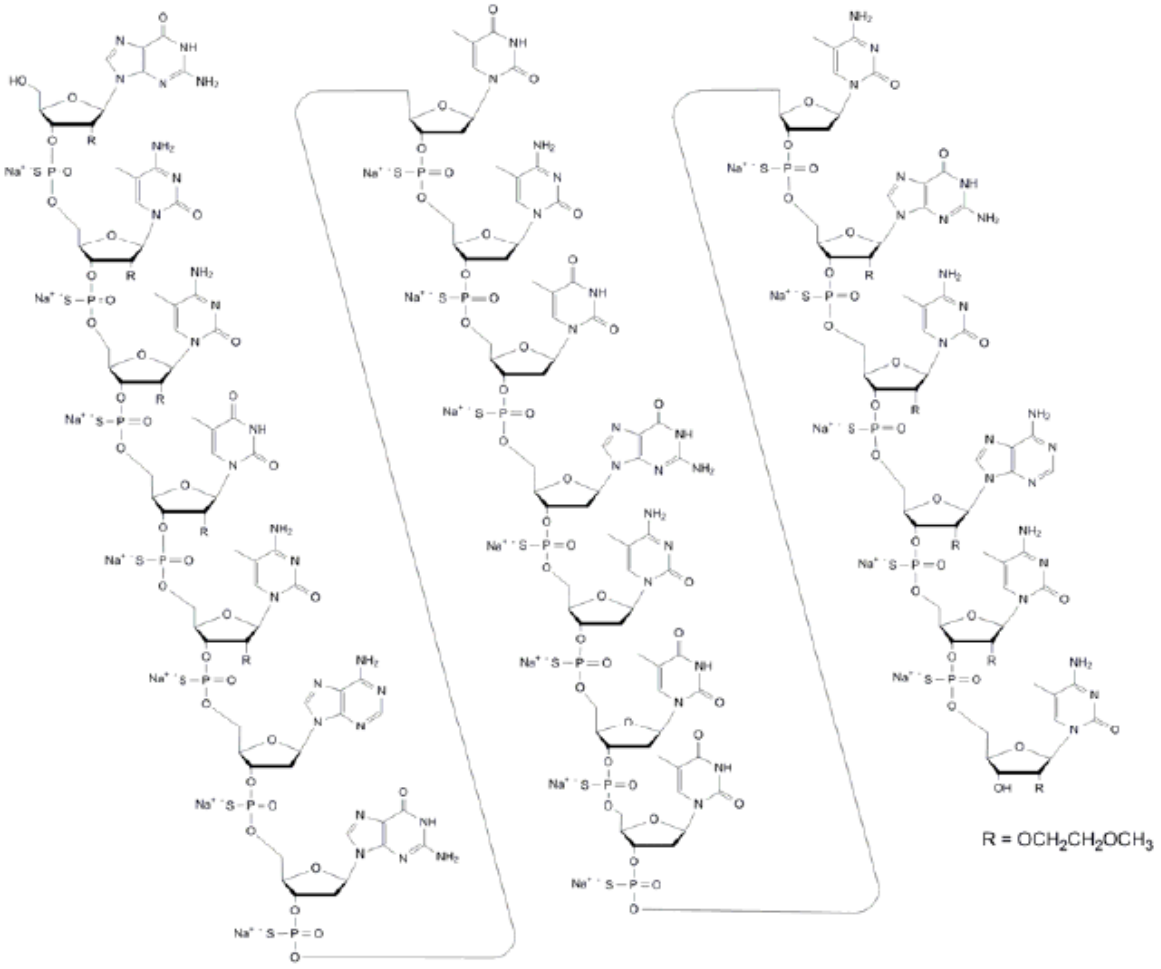
The product is available in type I glass vials with a butyl rubber stopper and aluminium overseal, and type I glass syringes with staked needle, bromo-butyl rubber stopper, plunger rod and safety device.

2.2.2. Active Substance

Mipomersen sodium is a 20-mer synthetic second-generation 2'-methoxyethyl antisense oligonucleotide inhibitor of apolipoprotein B-100 (apoB-100) synthesis.

It is a white to yellow amorphous hygroscopic solid which 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. Its molecular formula is $C_{230}H_{305}N_{67}\ O_{122}\ P_{19}\ S_{19}\ Na_{19}$ and its molecular weight is 7594.9 g/mol.

The chemical name of mipomersen sodium is DNA, d(P-thio)([2′-O-(2-methoxyethyl)]rG-[2′-O-(2-methoxyethyl)]m5rC-[2′-O-(2-methoxyethyl)]m5rC-[2′-O-(2-methoxyethyl)]m5rU-[2′-O-(2-methoxyethyl)]m5rC-A-G-T-m5CT-G-m5C-T-T-m5C-[2′-O-(2-methoxyethyl)]rG-[2′-O-(2-methoxyethyl)]m5rC-[2′-O-(2-methoxyethyl)]rA-[2′-O-(2-methoxyethyl)]m5rC-[2′-O-(2-methoxyethyl)]m5rC), sodium salt (1:19) (9CI). Its structural formula is shown in the figure below:



The chemical structure of mipomersen has been confirmed using several techniques which include nuclear magnetic resonance (NMR), mass spectrometry,complement hybridization, elemental analysis and Fourier transform infrared spectroscopy (FTIR). . Both the method of manufacture and the results of the proof of structure studies support the structural assignment for mipomersen.

Mipomersen is a phosphorothioated oligonucleotide which differs from naturally occurring oligonucleotides by substitution of the phosphate diester internucleotide linkage by a phosphorothioate moiety, resulting in a compound which is more stable *in vivo* and *in vitro*.

The absolute configuration at each phosphorous atom of the phosphorothioate diester internucleotide linkages is undefined. Since mipomersen contains 19 phosphorothioate diester linkages, the drug substance is a mixture of 2^{19} diasteroisomers. It has been demonstrated that the stereochemistry of the phosphorothioate linkage as manufactured by the proposed route of synthesis is reproducible. In addition, an in-depth discussion on the potential impact of the differences in the mixture of diastereoisomers on product safety and efficacy has been presented.

Manufacture

Mipomersen sodium is obtained from one manufacturer in accordance with the current Good Manufacturing Practices. A QP declaration issued by the Qualified Person has been provided.

Mipomersen sodium is manufactured in a multi-step process which is divided into four distinct operations: computer-controlled solid-phase synthesis (the nucleotide assembly of mipomersen), liquid chromatography purification, final deprotection and precipitation, and isolation of the drug substance by freeze drying.

The stereochemical integrity of the sugar residues of mipomersen is assured by the use of phosphoramidite starting materials derived from chirally pure nucleosides. No new chiral carbon centers are created during oligonucleotide synthesis, purification or isolation.

The process has been adequately described and satisfactory specifications have been set for starting materials, reagents and intermediate products. The use of starting materials and reagents of defined structure and purity, combined with a well-characterised, validated and automated chemical synthesis that is subject to a series of in-process controls and verification steps ensures the construction of the correct oligonucleotide base sequence.

The critical or non-critical character of each of the process parameters has been adequately justified. The critical parameters of the four steps of the manufacturing process have been identified and proven acceptable operating ranges have been set.

The critical quality attributes (CQAs) of mipomersen that are directly impacted by manufacturing process parameters have been adequately described and, the relationships between the steps of the manufacturing process and each CQA have been also indicated. Other CQAs of mipomersen drug substance, not impacted directly by the manufacturing process have also been described.

The applicant validated each step of the synthetic process separately. The results demonstrate that each unit operation is in a state of control and therefore the process can consistently produce mipomersen sodium of acceptable quality.

The active substance is packaged in two LDPE bags, closed with cable ties, which are placed inside a multilayer aluminium/nylon foil bag, heat sealed and kept inside a HDPE drum. Specifications and analytical reports for the packaging components have been presented and the suitability of the polyethylene bags for use with food and pharmaceuticals (Commission Regulation (EU) No 10/2011) has been confirmed.

Specification

The active substance specification includes tests for appearance, sequence determination, identification, assay, purity and impurity profile, sodium counter ion, heavy metals (ICP-MS), pH of 1% (w/v) aqueous solution (Ph. Eur.), residual solvents (GC), native water (KF), sodium acetate (HPLC), bacterial endotoxins (Ph. Eur.) and microbial enumeration tests (Ph. Eur.).

A reasoned discussion on impurities arising from the starting materials, the route of synthesis or degradation has been provided. The levels of the impurities are supported by the results of toxicological studies and appropriate specifications have been set.

All active substance specifications are considered adequately justified.

The non-compendial analytical procedures have been satisfactorily described and validated in accordance with the ICH guidelines.

Batch analysis data is provided on twenty development batches and three commercial scale validation batches produced with the proposed synthetic route. The results indicate satisfactory compliance with the agreed specification and uniformity from batch to batch.

Stability

Stability studies have been carried out in accordance with ICH conditions on three pilot scale batches and two sportive batches of the active substance packed in a scaled down version of the commercial container closure system from the proposed manufacturer.

Samples were stored for up to 36 months under long term conditions (-20°C±5°C) and for 36 months under accelerated conditions (5°C ± 3°C). Additional stability data at elevated temperatures have been presented: 36 months at 25°C ± 2°C/60% RH ± 5% RH, 3 months at 30°C ± 2°C /65% RH ± 5% RH, and 6 months at 40°C ± 2°C /75% RH ± 5% RH.

All batches have been tested for conformance with the specification using stability indicating analytical methods.

The following parameters were tested: appearance, assay, purity, impurity profile, water content, microbial enumeration and bacterial endotoxins. During the stability testing no significant trends in assay, purity, or impurity profile have been observed at any storage condition, regardless of water content.

Forced degradation studies were conducted under conditions of thermal, acidic, basic, and oxidative stress. These studies indicate that mipomersen is prone to deamination at elevated temperature and pH.

Confirmatory photostability testing of drug substance was conducted. The results indicate that while mipomersen drug substance is not completely impervious to the effects of UVA and cool white fluorescent light (CWL), the rate of photodegradation is slow. The use of aluminised secondary packaging ensures mipomersen drug substance is completely protected from light degradation during storage.

Stability data under long-term and accelerated conditions, as well as forced degradation studies indicate that the drug substance manufactured by the proposed supplier is sufficiently stable. The stability results support the retest period.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The aim of the pharmaceutical development program for Kynamro was to obtain an injectable sterile dosage form for subcutaneous administration of mipomersen sodium. Since the active substance is a synthetic oligonucleotide of polyanionic nature, freely water soluble (>300 mg/mL) at physiologic pH, it was straightforward to formulate an aqueous solution.

The product was initially developed as a liquid formulation containing mipomersen dissolved in WFI. Subsequently, a lyophilised formulation was developed for the purpose of providing greater dosing flexibility (different strengths and diluents) during clinical studies. Early clinical experience led to the selection of a clinical dose of 200 mg of mipomersen sodium per week as the formulation for pivotal clinical trials, the registration batches and commercial application. The selection of the 200 mg/mL liquid formulation was based on the fact that: (i) it provides a convenient dose volume (1.0 mL); (ii) it exhibits a relatively low solution viscosity, facilitating drug product manufacturing and dosing; and (iii) it has an acceptable tonicity for subcutaneous administration, avoiding the need to add excipients to adjust tonicity. In addition, mipomersen sodium in solution at 200 mg/mL demonstrates moderate buffering capacity, which precludes the need to include a buffer in the formulation. Nevertheless, if necessary, sodium hydroxide and hydrochloric acid are used to adjust the final pH of the formulation to 7.5 to 8.5.

During development, minor changes to the manufacturing process were introduced. These changes showed to have no impact on the quality or performance of the drug product.

All the excipients and diluents used in the formulation are described the Ph. Eur. They are controlled in accordance with the specifications and methods established in the corresponding monograph.

The primary packaging proposed are clear Type I glass 2 mL vial with a butyl rubber stopper and aluminium overseal, or clear Type I glass 1 ml syringe with staked needle, bromo-butyl rubber stopper, plunger rod and safety device. The material complies with Ph. Eur. requirements and it is adequate to support the stability and use of the product.

The pre-filled syringe presentation was developed after establishment of the formulation in vials. No changes to the formulation were required. Both presentations are aseptically filled, single-use, injectable solutions at a 200 mg/mL concentration prepared through the same formulation process. Compatibility studies of the formulation with different types of glass vials, rubber stoppers and different pre-filled syringe configurations were conducted to select the most suitable container closure system. An overfill of the vials and the syringes is used to ensure the minimal extractable volume of 1.0 mL

For the development of the manufacturing process consideration was given to the possibility of terminally sterilising the finished vials or syringes by heat. However data obtained showed that the standard overkill autoclave cycle, 121°C for 15 minutes, caused unacceptable levels of degradation of the active ingredient, and increase of impurities. Therefore, sterile filtration was selected as sterilisation method.

Adventitious agents

No excipients derived from animal or human origin have been used.

Manufacture of the product

The manufacturing process with its in-process controls and acceptance criteria has been described in detail and a flow chart has been provided. Kynamro is manufactured by dissolving mipomersen sodium into WFI. This is followed by pH adjustment, potency, and dilution to the desired strength. Then the solution is pre-filtered and a sample taken for bioburden testing. The solution is then sterilized by filtration through 0.22µm filters and filled into the syringes or vials under aseptic

conditions. Following filling and sealing each individual syringe and vial is visually inspected. Finally, the vials and syringes are labelled, packaged, stored and shipped.

Several critical process parameters such as i) adequate mixing to achieve complete dissolution and solution homogeneity; ii) drug product pH and potency, iii) pre-filtration bioburden; iv) end of run drug product sterile filter membrane integrity; and iv) fill weight have been identified.

Since the drug product is manufactured using a non-standard process, aseptic processing, in accordance with NfG on process validation the applicant provided process validation results for three consecutive production scale batches of vials and pre-filled syringes (PFS). These data show that the product can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this parenteral preparation.

Product specification

The finished product release specification include appropriate tests for appearance (visual), identification, assay, purity and degradation products, uniformity of dosage units-mass variation (Ph. Eur.), volume of injection in the container (Ph. Eur.), pH (Ph. Eur.), osmolality (USP), particulate matter (Ph. Eur.), bacterial endotoxins (Ph. Eur.) and sterility (Ph. Eur.).

In this product osmolality is tested according to the USP and not the Ph.Eur. as the freezing point technique described in the Ph.Eur. is not recommended for use with oligonucleotide solutions.

The product specifications cover appropriate parameters for this dosage form. Appropriate data have been presented to justify the release specifications for each quality characteristic that is controlled. Impurities and degradation products have been evaluated and found to be acceptable from the point of view of safety.

The analytical methods have been properly described or reference to the Ph.Eur. methods has been made. The non-compendial analytical methods have been validated in accordance with ICH guidelines, and have shown to be stability-indicating.

Batch analysis data on fourteen pilot scale batches (vials) and three commercial scale batches (PFS) confirm consistency and uniformity of manufacture and indicate that the process is capable and under control.

Stability of the product

Data from stability studies on three pilot scale batches of vials and three commercial scale batches of pre-filled syringes have been provided. Samples were stored under long-term conditions (5ºC±3 ºC) for up to 24 months (vials) or 12 months (PFS), and under accelerated conditions (25ºC±2 ºC/60%RH ±5% RH) for up to 6 months. In addition, results from up to 24 months (vials) or 12 months (PFS) of storage at 30ºC±2 ºC/60%RH ±5% RH, and 6 months at 40ºC±2ºC/75%RH ±5% RH have been presented. The conditions used in the stability studies are in accordance with ICH requirements.

In addition to the registration batches, five clinical batches of vials and one experimental batch of PFS were placed on stability providing up to 36 months of supporting stability data.

All batches have been tested for appearance, particulate matter, pH, assay, purity, degradation products, sterility and bacterial endotoxins. Some batches were also tested for deamination. In addition, the PFS have been tested for syringe functionality (breakout and gliding forces).

In the case of the vials, no statistically significant change in any stability-indicating attribute was observed when the drug product was stored at the 5ºC or 25ºC condition. However, the 25ºC storage condition cannot be accepted as long-term storage condition since only 6 month data have been provided at this temperature, and no extrapolation is possible from the data at 30ºC or 40ºC as some statistically significant trends were observed at these two temperatures. For this reason the proposed storage conditions are : “Store in a refrigerator (2°C – 8°C)”. However in no case there was result which exceeded the proposed specification limits.

In the case of the PFS, no statistically significant change in any stability-indicating attribute was observed when the drug product was stored at the 5ºC. Although some statistically significant trends were observed at 25ºC or 40ºC, in no case there was result which exceeded the proposed specification limit.

Forced degradation studies were also conducted, using acidic, basic, oxidative and thermal stress conditions. The results were comparable to those obtained with the drug substance.

In addition, three pilot scale batches of vials and one pilot scale batch of PFS were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products (ICH Q1B). The results indicate that the product is sensitive to light and for both the vial and PFS configurations protection from light during long-term storage is required. This protection is provided by the paperboard carton secondary packaging.

Furthermore, a study was conducted to determine the effects of repeated freezing and thawing of the product. The results indicate that the product is not adversely affected by storage at -20°C and the processes of freezing and thawing. The extent of the 30°C and 40°C registration stability data, coupled with results from the freeze-thaw cycling study, support temperature excursions, e.g., during shipping or after pharmacy dispensing, up to 30°C for up to 60 days and up to 40°C for up to 7 days, protected from light, with no special precautions to protect from freezing required.

The proposed shelf-life of 18 months (for the PFS) and 30 months (for the vials) with the labelled storage condition “Store in a refrigerator (2°C – 8°C)” has been justified by the stability data provided

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Kynamro contains a complex active substance, a synthetic oligonucleotide. Despite the complexity of the molecule, the data provided demonstrate that it is manufactured by a process which has been shown to be reproducible and adequately controlled. The finished product is a sterile medicinal product manufactured by a fully validated aseptic filtration process.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic. At the time of the

CHMP opinion, there were no unresolved quality issues which could have an impact on the benefit/risk ratio of the medicinal product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Based on the data provided the quality of this medicinal product is considered to be acceptable. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Mipomersen is an antisense apolipoprotein B (apoB) synthesis inhibitor that inhibits synthesis of apoB-containing lipoproteins by blocking the target protein translation by antisense oligonucleotides (ASO). It was intended to treat a limited group of patients with the most extreme forms of familial hypercholesterolaemia (FH), those with homozygous FH and severe heterozygous FH, whose risk of coronary heart disease (CHD) is very high due to an accumulated exposure to elevated atherogenic lipoproteins, and who remain at high risk due to high low-density lipoprotein cholesterol (LDL-C) levels. As discussed in section on Clinical aspects, the indication was later on restricted to the use of mipomersen in HoFH patients only. Nevertheless, the non-clinical development was conducted addressing both patient sub-groups.

The non-clinical pharmacology, pharmacokinetic, and toxicology studies reported in this dossier were conducted respecting the established guidelines. The drug substance used was physically and chemically comparable to that produced for clinical trials and ultimately for marketing. The non-clinical programme of mipomersen was designed to identify and differentiate effects specifically related to inhibition of apoB RNA as well as nonspecific effects related to chemical structure. In the toxicity studies, the monkey was used as the non-rodent species because of the close relationship with pharmacokinetic behaviour in man that has been established for this class of compounds and because the primate is considered to be more representative of the relevant toxicology endpoints. The submitted ERA includes the evaluation of potential risks of mipomersen sodium solution for injection to the environment and precautionary and safety measures to be taken for administration, disposal, and labelling.

The majority of non-clinical studies were performed in compliance with GLP standards. Some toxicology studies were conducted non-GLP. Since these studies were exploratory, the absence of GLP compliance is not considered to compromise the overall scientific integrity of the experimental results. There were no deviations which affected the quality or integrity of the data during the non-GLP studies. The GLP compliance declaration is considered acceptable to the CHMP.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro studies

The *in vitro* pharmacologic activity of mipomersen (ISIS 301012) was characterised in human hepatoma cell lines (HepG2, Hep3B) and in human and cynomolgus monkey primary hepatocytes. Mipomersen significantly reduced both apoB mRNA and protein levels after 24-hour treatment in human primary hepatocytes. The half maximal inhibitory concentration (IC50) for mRNA reduction in these cells was <10 nM. When a series of mismatches were introduced into the mipomersen sequence and tested in HepG2 cells, a single mismatch abolished pharmacologic activity. The binding site for mipomersen lies within the coding region (exon 22) of the apoB mRNA. The effects of mipomersen were highly sequence-specific. Control ASOs (ISIS 113529, a mismatch control) differed in sequence and did no suppress apoB mRNA.

Given that optimal hybridization between an antisense oligonucleotide and its target mRNA strand could be negatively influenced by the presence of a single nucleotide polymorphism (SNP) a study (GT-348-EF-33) was performed to identify potential unknown SNPs from the ISIS 301012 target region (exon 20, boundary of intron 20) from the apoB-100 gene region. A total of 213 sample DNAs from 4 ethnic groups (Caucasian, African-American, Asian, and Hispanic) were analysed and no SNPs were found within the exon or within the antisense target region in all tested individuals.

In vivo studies

The pharmacology of an optimised murine-specific apoB antisense inhibitor, ISIS 147764, was evaluated in a variety of hyperlipidaemia models: C57BL/6 mice fed a high fat diet, apoE-deficient mice, LDLr-deficient mice and C57BL/6 mice fed a normal chow diet.

In mice that were administered the murine-specific apoB ASO *via* intraperitoneal injection apoB, the mRNA levels in liver were reduced to 36-90% as a function of dose and time. Moreover, this reduction resulted in the concomitant reductions of total cholesterol, LDL-C, and non-HDL subclasses. The pharmacological effects of the 6-week drug administration were prolonged and remained at nearly maximal levels for 2 weeks after dosing cessation, and then gradually returned to control levels over the following 6-8 weeks.

A 14-week study in human apoB transgenic mice with advanced atherosclerotic lesions was performed to evaluate the pharmacological effects. Dose-dependent effects on liver apoB mRNA were observed, with up to 89% reduction compared to saline controls, accompanied by reductions in LDL-C and aortic sinus plaque burden. These reductions were also observed in hamster and rabbit. In addition, it was noted that administration of a monkey-specific apoB inhibitor (ISIS 326358) to HF fed monkeys suppressed total serum cholesterol, LDL-C and apoB in a dose- and time-dependent fashion.

Effects of Apo B ASO Inhibition on Atherosclerosis

Antisense inhibition of apoB reduced atherosclerosis was examined in three independent murine models. Administration of the mouse-specific apoB ASO, mipomersen sodium, for 12 weeks produced a significant and dose-dependent reduction in apoB mRNA level. In ApoE-deficient mice, it resulted in reduced aortic plaque volume and atherosclerotic plaque burden in whole aortae.

Furthermore, in LDLr-deficient mice that contained the human apoB genomic transgene, it also reduced human apoB mRNA and serum apoB-100 protein. Reductions in LDL-C levels and the blunting of atherosclerosis were also observed. Mice are among the most sensitive species regarding to nonspecific proinflammatory effects to ASO. The level of inflammatory effects was mild enough to not contribute to the atherosclerotic process.

Effects of ApoB Inhibition on Hepatic Steatosis

Several experiments were performed to determine whether hepatosteatosis was exacerbated in high fat fed mice with fatty liver model. Inhibition of apoB in chronic studies up to 22 weeks did not result in an increased hepatic steatosis. There was an initial increase in hepatic TG levels after 2 weeks of treatment but, by 6 weeks, these levels returned to the values comparable with controls.

The functional effects of apoB inhibition on hepatic TG levels were studied in several experiments using transcriptional or DNA and metabolomic microarrays. It was concluded that these effects were likely the result of secondary, compensatory mechanisms coincident with apo B-100 inhibition. In a high fat-fed monkey study where monkeys were treated with monkey-specific ASO for 4 or 5 weeks, there were no signs of hepatic steatosis. After an array analysis of lipogenic genes, a reduction in gene expression was observed in mice and monkey models, which is likely to be associated with reduction in fatty acid synthesis.

Effects of ApoB inhibition on intestinal Apo B-48 Protein and dietary fat absorption

The small intestine is another important site of apoB expression in processing dietary lipids. Experiments were performed in HF fed mice in order to determine if apoB mRNA is reduced in the intestine and whether there were any effects on intestinal apoB-48 protein abundance or dietary fat absorption as a result of apoB ASO treatment. The apoB-48 protein levels and absolute chylomicron particle number were unchanged and dietary fat and cholesterol absorption was unaffected.

Effects of ApoB inhibition compared to microsomal triglyceride transfer protein (MTP) inhibition

Overall, six assays were performed to compare the pharmacological effects of antisense inhibition of apoB with the effects of both, the small molecule and the antisense inhibition of MTP. In these studies an antisense inhibitor to MTP (ISIS 144477) was used, which is the same chemical class as the murine apoB ASO. One study incorporated the small molecule inhibitor of MTP, BMS-212122, which inhibits MTP systematically and displays very different pharmacological/pharmacokinetic properties than the apoB (ISIS 147764) or MTP ASOs (ISIS 144477). Reductions in hepatic secretion of TG and apoB plasma cholesterol levels, VLDL and LDL particle numbers were observed. In addition, the ASO-mediated apoB inhibition did not increase hepatic triglyceride or alanine aminotransferase (ALT) levels and did not result in hepatic steatosis. While these findings were observed in apoB ASO treated mice, none were observed in MTP ASO treated animals.

Apart from the *in vitro* studies in human and cynomolgus monkey hepatocytes, *in vivo* studies in hyperlipidaemia models of mice and monkeys were carried out. Mipomersen was identified as the optimal 2'-MOE antisense inhibitor to reduce human apoB mRNA levels among 400 oligonucleotides tested showing a high sequence-specificity. Reductions in serum cholesterol, LDL-C, non-HDL subclasses and apoB levels were observed in mice, monkeys, rabbits and hamster. Effects of apoB inhibition on atherosclerosis hepatic steatosis and intestinal apoB-48 protein were also assessed and it was observed that antisense inhibition of apoB reduced the overall aspects of atherosclerosis.

The studies aimed to characterise the pharmacodynamic profile of mipomersen are considered adequate and sufficient information about the pharmacological activity of mipomersen has been provided. Therefore, no further pharmacodynamic studies are considered necessary.

Secondary pharmacodynamic studies

Potential secondary pharmacodynamic effects of mipomersen were evaluated using an in vitro screen. The high throughput profile consists of a broad collection of approximately 80 transmembrane and soluble receptors, ion channels and monamine transporters. There were only a few receptors that demonstrated binding at a concentration of 10ìM (CCK1, CCK2, GAL2, PDGF, CXCR2, MC4). These results likely reflect a nonspecific interaction of mipomersen with these specific receptors at a single concentration. The CHMP noted that the concentration at which these interactions have been tested is much higher than the C_{max} achieved in humans, and these findigs are therefore not likely to be relevant to humans.

Safety pharmacology programme

Four safety pharmacology studies were conducted with mipomersen to evaluate potential effects on cardiac function, respiratory system, and the central nervous system, as required by the relevant CHMP guidelines. Mipomersen was concluded to be negative in blocking hERG at concentrations up to 150 ìM. There were no effects on respiration rate, tidal volume, minute volume and on behavioural function at any dose level tested. Lower body temperature in mice treated with mipomersen was transient and not toxicologically significant. The safety pharmacology data of mipomersen were completed with data from a toxicology study in monkeys, which confirmed the lack of cardiac findings. The CHMP noted that monkeys instead of dogs were used in the cardiovascular safety study. However, taking into account the suitability of the monkey model showed for the preclinical development it is considered acceptable. The submitted studies and their results are satisfactory.

Pharmacodynamic drug interactions

No formal pharmacodynamic drug interaction studies were conducted with mipomersen. Considering the nature of the product (antisense apolipoprotein B synthesis inhibitor) and the clinical development, this is agreed by the CHMP.

2.3.3. Pharmacokinetics

Within antisense oligonucleotides, many of the drug properties are relatively independent of their specific sequence due to similarities in physicochemical properties such as oligomer length, solubility, hydrophilicity, and protein binding properties. As a result, the pharmacokinetic properties of different sequences are closely comparable within a class of oligonucleotides. Therefore, the pharmacokinetics of mipomersen and not of species specific sequences was investigated. The absorption, distribution, metabolism, elimination (ADME) properties of mipomersen were evaluated in vitro and in vivo and across multiple species (mouse, rat, dog, and monkey). In general, the

ADME properties are typically not altered by repeated administration, with accumulation of mipomersen in plasma in the post-distribution phase (trough plasma concentration) reaching steady-state within three (mouse) to six (monkey) months of repeated dosing. Following i.v. administration, mipomersen exhibits low plasma clearance (1.0 to 2.3 mL/min/kg) and a long apparent terminal half-life (16 to 30 days) is observed in rats and monkeys, resulting from slow nuclease metabolism of mipomersen in tissues. Mipomersen is rapidly absorbed, and absorption into systemic circulation is approximately 100% complete in the monkey following s.c. administration. Mipomersen is rapidly and broadly distributed to most tissues evaluated in mouse, rat, dog, and monkey, with highest tissue concentrations in the kidneys and liver. Tissue exposure to mipomersen is generally dose-dependent, and appears to involve a saturable process at higher doses. The apparent terminal half-life of mipomersen in various tissues including the liver and kidneys ranges from 8 to 35 days in the species studied (rat and monkey), with a half-life of 34 days in monkey liver. After repeated s.c. administration, the degree of accumulation is consistent with the range of the half-life of mipomersen and the frequency of administration. The accumulation in tissues reaches a steady-state in 3 (mouse) to 6 (monkey) months and appears to be dose-dependent.

Mipomersen was neither taken up by the placenta nor transported to the embryo or foetus. Radioactivity was broadly distributed to tissues following s.c. administration of [3H] mipomersen with highest tissue concentrations in the kidney, liver, spleen, bone marrow, mesenteric lymph nodes, thyroid/parathyroid gland and hair free skin. However, based on the chemical structure, it is unlikely that this would lead to toxicity.

Mipomersen is metabolised via slow metabolism by ubiquitous endo- and exonucleases present in most tissues. A total of 29 oligonucleotide metabolites, with base length ranging from 5-nucleotide to 19-nucleotide were detected in the monkey tissue. In rats receiving a single i.v. dose (5 mg/kg [3H]-mipomersen), approximately 15% of the administered total radioactivity was excreted in urine collected between 0 and 24 hours. In mice and monkeys, a small per cent of the dose was excreted in urine in 0 to 24 hours post dose, which is consistent with that observed in humans. No unique human metabolites were detected and mipomersen was the most abundant oligonucleotide detected.

Overall, the excretion of mipomersen and metabolites is slow in the pre-clinical species which is in agreement with the observed long terminal half-life of mipomersen. The main excretion route is via urine in form of mipomersen. The excretion results in the pre-clinical species were comparable with humans. Mipomersen in circulation is highly bound to plasma proteins (85 to 96%), and the binding is concentration-independent in the concentrations ranging from 1 to 20 ìM across the studied species of mouse, rat, dog, and monkey. There was no significant effect on the binding of mipomersen or statins (atorvastatin or simvastatin) in each other's presence to human plasma proteins. Data indicate that the potential for mipomersen to be involved in CYP450-dependent or P-gp transporter-mediated drug-drug interactions is remote since mipomersen does not induce CYP1A2, CYP2B6, and CYP3A4 isozymes at concentrations of 1 to 500 ìg/mL, or inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 isozymes from 8 to 800 ìg/mL. Additionally, mipomersen was found not to be an inhibitor or a substrate of P-gp transporter.

Overall, the observed non-clinical pharmacokinetic properties of mipomersen support the proposed dosing regimen for therapeutic use. The submitted results of pharmacology studies were considered appropriate by the CHMP, since the results from these studies have provided a thorough

picture of the pharmacodynamic and pharmacokinetic profile of mipomersen as well as the data of safety pharmacology.

2.3.4. Toxicology

The toxicology programme of mipomersen includes repeat dose studies in mouse, rat and monkey, in vitro and in vivo genotoxicity studies, reproductive and developmental studies in mouse, rat and rabbit, carcinogenicity studies in mouse and rat, and special toxicity studies such as immunotoxicity in mouse and juvenile toxicology in rat. The non-clinical toxicology development is considered to be in accordance with the valid guidelines. Pivotal non-clinical toxicity studies were conducted in compliance with the GLP. Some non-GLP studies were conducted as well. Since these studies were exploratory, the absence of GLP compliance is not considered to compromise the overall scientific integrity of the experimental results.

Single dose toxicity

No separate single dose/acute toxicity studies were carried out. The acute toxicity of mipomersen was evaluated in mice, as part of the dose range finding study for the mouse micronucleus assay. This approach is in line with the current view that adequate information can be obtained from other sources than the specific single dose toxicity studies (EMA/CHMP/SWP/81714/2010). The maximum tolerated dose of mipomersen was 1200 mg/kg in mice, because of lethargy, irregular breathing and palpebral closure at higher doses.

Repeat dose toxicity

Repeat-dose toxicity studies with mipomersen were performed using a subcutaneous injection for time intervals of 3 and 6 months in mice, 13 weeks and 5 months in rats, and 5 weeks, 13 weeks, and 12 months in cynomolgus monkeys.

The major findings observed in repeat-dose toxicity studies were similar to the toxicity profile previously observed with other antisense oligodeoxynucleotides: poor local tolerance, increased coagulation time, complement activation, haematotoxicity, stimulation of the immune system, and uptake of the test article in kidney and liver with subsequent lesions. In both, subchronic and chronic toxicology studies, the systemic toxicities in mice, rats and monkeys were found to be dose-dependent and were generally observed at doses and exposures that exceed the intended clinical dose. The dose regimens were selected to provide continuous tissue exposure. In the chronic toxicology studies the dose regimen was once weekly for 6 months in mice and up to 1 year in monkeys.

In general, there were no mipomersen related changes in clinical signs or mortality or changes in body weights in mice and monkeys. No changes in cardiovascular function (ECG, blood pressure, or heart rate) were observed in monkeys. Mice administered 25 mg/kg/week, subcutaneously, showed minimal increases in organ weights and a presence of basophilic granules. At 75 mg/kg/week dose, mild increases in AST and ALT were observed in addition to presence of basophilic granules.

Rats administered 30 mg/kg/week subcutaneously presented increases in liver weight and mild increases in AST and ALT in females. In monkeys at 10 mg/kg/week and 30 mg/kg/week, there was a presence of basophilic granules and Kupffer cell hyperplasia/hypertrophy. Kidneys accumulated the highest concentrations of mipomersen and are potentially key target organs for toxicity in both, monkeys and rodents. In mice, the uptake of mipomersen in the renal proximal tubules was evident in the form of haematoxylin-staining basophilic granules. The toxicological significance of this accumulation is uncertain. Reversible lymphohistiocytic cell infiltrates were noted in the kidneys at ≥ 9 mg/kg/week, which are considered to be an inflammatory response accompanied by cytokine production. The distribution of mipomersen to proximal tubular epithelium in rats was similar to that in mice and monkeys. However, rats tend to be more sensitive to the increase in proteinuria possibly related to competition between mipomersen and low molecular weight proteins for reabsorption from filtrate or decrease in the capacity for uptake in tubular epithelium. There was a marked increase in TG and VLDL cholesterol in both high dose males and females at termination. Total cholesterol, HDL cholesterol and LDL cholesterol were also increase.

The liver is an organ with the highest oligonucleotide concentrations in all species studied. Unlike the kidney, oligonucleotide is distributed to all cell types in the liver, with the highest concentrations in Kupffer cells and lower concentrations in endothelial cells and hepatocytes. In mice, the treatment with ≥ 25 mg/kg/week mipomersen for 3 or 6 months showed increases in liver weight and serum transaminases, basophilic granulation in Kupffer cells, extramedullary haematopoiesis and lymphohistiocytic infiltrates, and this is attributed to the inflammatory effects of mipomersen. The effects on mice liver were partially or fully reversible. In the 13-week and 5-month toxicology studies, as well as in the 2-year carcinogenicity study in rats, increases in liver weights, basophilic granulation in Kupffer cells, vacuolation of sinusoidal cells, and various inflammatory effects at doses > 24 mg/kg/week for the 13 week study and at doses > 3 mg/kg/week in the 5 month study were observed.

In monkeys, there was a presence of basophilic granules in Kupffer cells and hyperplasia/hypertrophy in Kupffer cells at doses ≥ 3 mg/kg/week. In the absence of associated changes in hepatic function, Kupffer cell hyperplasia/ hypertrophy is of uncertain toxicological significance. In hyperlipidemic monkeys there were no increases in serum transaminases, indicating that there were no adverse effects of apoB inhibition on the liver. In these monkeys fed with a high-fat diet, there was evidence of fat accumulation in liver in all monkeys, including controls. Reversibility of observed hepatic effects was assessed in both mice and monkeys and it appears that these are reversible. There was no evidence of recurring toxicity. The toxicokinetic observations were consistent with apparent complete systemic availability following s.c. dosing compared to i.v. administration, rapid plasma clearance of mipomersen predominantly due to distribution to tissues rather than urinary elimination, and slow tissue clearance of either the intact drug or endonuclease-derived metabolites.

Lower levels of exposure in the mouse exhibit pathology similar to that seen at higher exposures in the monkey suggest that the mouse liver is more sensitive to hepatotoxicity than the primate liver. There was no evidence of hepatotoxicity in mice treated with ≤ 10 mg/kg/week of mipomersen for up to 6 months of and in monkeys treated with ≤ 30 mg/kg/week mipomersen for up to 1 year of treatment. The clinical dose regimen of 200 mg/week (3 mg/kg/week) is at least 3-fold and 10-fold lower than the NOAEL for functional liver pathology in mouse and monkey, respectively. Subcutaneous injection of 30 mg/kg of mipomersen in monkeys was associated with a Cmax of

approximately 50 μg/mL. The no-effect dose for complement activation was 10 mg/kg (Cmax approximately 30 μg/mL). These values are 2.5 to 10 times greater than the plasma Cmax ≤ 1 to 13 μg/mL observed after s.c. injection of 200 mg/week (3 mg/kg/week) in patients.

Acute and transient changes in plasma clotting times were observed in monkeys and were limited to an approximate 1.3-fold increase in activated partial thromboplastin time (aPTT) during the first four hours. No other clotting parameters were affected, and the effect was not observed in monkeys treated with lower. There was no evidence of sustained or progressive effects on aPTT with chronic administration in monkeys.

Acute to subchronic exposures to oligonucleotides have not produced alterations in haematopoiesis. Treatment of mice with some oligonucleotides has been associated with increases in circulating mononuclear cells, which is consistent with an inflammation-mediated increase in this cell type in peripheral tissues.

The toxicology studies with mipomersen showed a slight decrease in red blood cell count, haematocrit, and haemoglobin at doses ≥ 10 mg/kg/week administered for up to 6 months in mice. In rats and mice a slight increase of platelet count in males administered the higher dose were described (≥ 25 mg/kg/week). These doses represent approximately 3- to 10-fold multiples of the proposed clinical dose (3 mg/kg/week). Monkeys treated with ≤ 30 mg/kg/week of mipomersen showed platelet counts approximately 30% lower than controls after about 6 months of treatment. This decrease was transient. In the 12-month study, two animals died. One animal of the low dose group was attributed to sepsis and its death was not considered test article related. The cause of morbidity of the high dose monkey was the widespread haemorrhage secondary to severe thrombocytopenia and multifocal tissue necrosis, potentially treatment-related and resulting from local tissue anoxia and anaemia. An effect on platelets is included as a potential risk in the Risk Management Plan of mipomersen.

In mice, the increased spleen weight, multiorgan lymphohistiocytic cell infiltrate, and splenic extramedullary haematopoiesis were collectively regarded as inflammatory effects. These effects were typically mild, reversible, and evident mostly in mice treated with ≥ 44 mg/kg/week mipomersen for 13 weeks. Plasma MCP-1 was transiently increased from control levels at doses of 10 or 75 mg/kg/week on Day 1. These data demonstrated the limited scope of the inflammatory effects associated with chronic mipomersen treatment. Toxicology studies in rats showed treatment-related increased spleen weight, lymphoid hyperplasia in spleen and multiorgan lymphohistiocytic cell infiltrates, mostly in rats administered ≥ 24 mg/kg/week for 13 weeks and ≥10 mg/kg/week for 5 months. These findings were partially reversible. Furthermore dose-dependent increase in MCP-1 at approximately 48 hour post-dose after 5 months of treatment was detected. This increase is considered to be correlated with the increase in spleen weights and multi-organ lymphohistiocytic cell infiltrates.

In monkeys treated with 30 mg/kg/week mipomersen chronically, there were increases in spleen and lymph node weights and in total plasma IgG. These changes coincided with episodes of infections that occurred in individual monkeys in the 30 mg/kg/week dose group. However, a clear association to treatment could not be made. In addition, the increases in total plasma IgG and plasma C3 were also observed. These findings could have secondary effects on blood vessels through impair the innate immune surveillance and clearance of immune complex by the

complement pathway. Finally, in monkeys, local inflammation at the s.c. injection site skin was the most common manifestation of inflammatory effects and this was likely to be associated with high local concentrations of mipomersen.

The CHMP was of the opinion that further studies were not needed, since immunogenicity, including antibody formation, has been included as potential risk in the Risk Management Plan.

Measurement of Anti-Mipomersen Antibody (Ab): The potential antigenicity of mipomersen was assessed in the chronic toxicity study in monkeys and the immune function study in mice. In the mouse, there was no evidence of antigenicity. Potentially positive responses were observed in 5 monkeys, but these occurred randomly across dose groups, at scattered time-points, and were not dose-dependent. These results are not considered to be an evidence of an oligonucleotide-specific Ab response.

In vivo and in vitro immunotoxicology studies: Potential alterations of immune function and activation of mast cells were specifically addressed in an influenza host resistance study in mouse and an in vitro mouse mast cell degranulation assay. There were no effects on viral clearance, indicating that mipomersen does not impair antigen presenting or lymphocyte function in this model and no significant increases in histamine, cytokines or chemokines were measured at concentrations up to 300 µg/mL. According to the published literature, stimulation of the immune system is a class effect of antisense compounds. The acute effects include activation of the alternative complement pathway and inhibition of the intrinsic coagulation pathway. There seems to be a threshold blood concentration at which complement activation occurs. For mipomersen, the NOEL was 10 mg/kg/week in the 5-, 13-week and 12-month studies. The mean Cmax in these studies was approximately in the range of 20 – 30 µg/mL. For antisense drugs in general, the risk of complement activation has been greatly reduced by the use of slow or continuous intravenous infusion, which substantially lowers the maximum plasma concentration relative to bolus injection. However, Kynamro is intended to be for a subcutaneous injection and thus, the complement activation and immunogenicity, including antibody formation, are identified risks in the Risk Management Plan.

Genotoxicity

Standard genotoxicity studies were conducted with mipomersen, please see the below table.

Summary of Genotoxicity Studies

Test	Strain	Dose Range/Route	Cytotoxic and Genotoxic Effects
In Vitro			
Bacterial Mutagenicity	S. typhimurium strains TA1535, TA1537, TA98, TA100 E. coli strain WP2uvrA	Activated and Nonactivated: 156-5000 µg/plate [a,b]	No cytotoxic or genotoxic effects
Mouse Lymphoma Cell Gene Mutation Assay	L5178Y/TK +/- Mouse Lymphoma Cell	Activated and Nonactivated 1000-5000µg/mL	No cytotoxic or genotoxic effects
In Vivo			
Mouse micronucleus assay	Mouse, CD-1	0[c], 300, 600, 1200 mg/kg, CP[d] Single IV dose	No erythropoiesis inhibition: No increase in micronucleated PCE

Abbreviations: IV= intravenous, PCE = polychromatic erythrocytes
[a] Control = DMSO (dimethyl sulfoxide) for tester strain plates
[b] Positive controls = sodium azide, 9-aminoacridine hydrochloride, 2-nitrofluorene, N-ethyl-N-nitro-N-nitroguanidine, 2-anthramine
[c] Vehicle = phosphate buffered saline
[d] Positive control = cyclophosphamide monohydrate

In the bacterial mutagenicity test no positive mutagenic responses were observed with any of the tester strains in either the presence or absence of S9 activation. Under the conditions of in vitro L5178Y/TK+/- Mouse Lymphoma Cell Gene Mutation Assay study, mipomersen was concluded to be without a genotoxic potential. Mammalian Erythrocyte Micronucleus Assay evaluated the clastogenic potential of mipomersen as measured by its ability to induce micronucleated polychromatic erythrocytes in mouse bone marrow. No mortality was observed and under the conditions of the assay, a single intravenous administration of mipomersen at doses up to 1200 mg/kg did not induce increased incidence of micronucleated polychromatic erythrocytes in the bone marrow. The genotoxicity studies are considered appropriate by the CHMP and showed absence of mutagenic potential of mipomersen.

Carcinogenicity

The tumorigenicity potential of mipomersen and species-specific analogues was assessed in standard 2-year carcinogenicity studies in mice (GT-348-TX-1) and rats (GT-348-TX-2). For both species, exposure to mipomersen was assessed by determination of tissue concentrations of oligonucleotide in liver, kidneys, and spleen following up to 2 years of treatment. The doses of 5, 20, and 60 mg/kg/week were selected on the basis of toxicity, pharmacodynamic, and pharmacokinetic endpoints. The high dose of 60 mg/kg/week was considered to be a maximum tolerated dose (MTD) for a 2 year study.

In both, mouse and rat, there was no clear evidence of tumourigenic potential and only a few treatment-related increases in neoplastic lesions. In the rat, in the region of the subcutaneous sites, there was a statistically significant increased incidence of malignant fibrous histiocytoma at 10 and 20 mg/kg/wk mipomersen and an increase in malignant fibrosarcoma in females at 10 and 20 mg/kg/wk mipomersen. Rodents are particularly susceptible to development of sarcomas in the subcutaneous tissue by chronic tissue irritation and inflammation. This effect is not relevant for humans. The proposed SmPC would adequately reflect the findings from carcinogenicity studies, however; these are not expected to be relevant for humans.

Reproduction Toxicity

Reproductive and developmental toxicology studies were conducted in mice, rabbits and rats with the aim to evaluate the potential effects of mipomersen on fertility, pregnancy and foetal development, as well as pre- and post-natal development including maternal function. In mice, there was a slight maternal toxicity as indicated by reduced haemoglobin and haematocrit values, increase in platelet counts, and some slight changes in serum chemistry parameters. Maternal toxicity in rabbits was also evident. No effects on fertility or foetal development were observed in mice up to 87.5 mg/kg/week of mipomersen or in rabbits up to 52.5 mg/kg/week of mipomersen. There was a little or no accumulation of oligonucleotide in the foetus or the placenta. A poor uptake of oligonucleotides in placenta, with concentrations dose-dependent and exposition very low relative to target organs such as liver and kidney was reported. The NOAEL for fertility or foetal development in mice and rabbits was > 87 or 52 mg/kg/week, respectively, representing a greater than 15-fold safety margin for the anticipated therapeutic dose of 3 mg/kg/week. Subcutaneous administration of mipomersen to pregnant female rats and postpartum elicited maternal effects associated with accumulation of mipomersen in the spleen, liver and kidneys. Increased spleen weight and some changes in haematological parameters, increased liver weights and changes in plasma liver enzyme levels and increased plasma creatinine levels associated with impaired renal function were also described. The NOAEL for pre- and post-natal development in this study was considered to be 35 mg/kg/week, representing at least a 10-fold safety margin for the anticipated therapeutic dose of 3 mg/kg/week. The excretion of mipomersen and its metabolites via milk was not investigated. There was a slight decrease in the maternal function in the lactation period. This was accompanied by a decrease in body weight of the pups.

Mipomersen was subcutaneously administered to juvenile rats at doses up to 50 mg/kg/week for 10 weeks. The observed changes were similar to the observed in adults: increased spleen, kidney and liver weights, alterations in haematological parameters and others. Nevertheless, the level of marrow fat in the femoral and sternal marrow was notably lower with mipomersen in juvenile animals, which partially restored after cessation of treatment. It can neither be excluded that bone marrow and/or blood are targets of toxicity observed in juvenile animals only, nor that effects in juvenile animals are more pronounced.

Toxicokinetic data

The toxicokinetic profile of mipomersen was evaluated as part of the toxicity studies described above. The one-year study in cynomolgus monkeys evaluated the potential toxicity and toxicokinetic profile of mipomersen when administered by s.c. injection to monkeys twice weekly for two weeks followed by once weekly thereafter for 25 or 50 consecutive weeks. The toxicokinetic data demonstrated dose-dependent exposure in plasma and tissues of monkeys given mipomersen following s.c. administrations for 12 months. The toxicokinetics and tissue exposure data suggested that steady-state exposure was reached by 6 months, and the plasma and tissue elimination half-life was approximately 30 days. As it was commented above the primary effects of mipomersen after 12 months of dosing were limited to the 30 mg/kg/week dose group and included decreases in platelet count, a decrease in total complement factor C3, as well as minimal degenerative changes

and vacuolation in tubular epithelial cells in the kidney, most of which were recovered to baseline levels during a 6 month recovery period. There were no mipomersen related changes in liver function parameters and no significant changes in cholesterol related lipid parameters in serum.

Local Tolerance

There are no specific local tolerance studies with mipomersen. The local tolerance of the product was evaluated within the toxicology studies. In general, s.c. administration of mipomersen was well tolerated, however, there were some local findings due to the route of administration and the kind of product. Dermal perivascular mononuclear cell infiltrates, basophilic granule accumulation in dermal or histiocytes and mixed cell infiltrates in the dermis and tissue, as well as oedema and haemorrhage, fibrosis/fibroplasias in the s.c. injection sites were observed. These were more extensive with continued administration. Overall, the CHMP considered it acceptable to include the local tolerance testing within the toxicology studies. Mipomersen produced local irritation in s.c. and i.v. studies in all laboratory species. Moreover, pathological changes were evident at a dose-related trend. Regarding the increase in the incidence of hystiocytoma and fibrosarcoma observed in rats during the carcinogenicity study it should be taken into account that rodents are particularly susceptible to development of sarcomas in subcutaneous tissue in the presence of chronic tissue irritation and inflammation as occurred at injections sites in these investigations. This is not relevant for humans. The presented local tolerance data are considered sufficient.

Other toxicity studies

Antigenicity: An ELISA method was developed to detect antibodies (Abs) directed against mipomersen in in two chronic toxicology studies (6-month and 1-year in mice and monkeys, respectively) and in the influenza host resistance study in mice. In the mouse, there was no evidence of antigenicity. In the 54 tested monkeys, the majority of samples tested were negative for anti-mipomersen Ab. Potentially positive responses were observed in 5 monkeys, but these occurred randomly across dose groups, at scattered time-points, and were not dose-dependent. The potentially positive samples were further evaluated. Data from studies with other antisense oligonucleotides indicate that these compounds are not recognised by the adaptive immune system as a foreign antigen. Because of the low incidence and inconsistent time course, the results of the Ab assay in the chronic monkey study with mipomersen are not considered reflective of an oligonucleotide-specific Ab response.

Immunotoxicity: In the repeated dose studies the effects of mipomersen or its analogues on the immune system were related to inflammatory effects which are a consequence of activation of innate immune cells. The local inflammation at the injection side was the most common manifestation of these effects and was associated with high concentrations of mipomersen. Since data from studies with other antisense oligonucleotides indicate that these compounds are not recognized by the adaptive immune system as a foreign antigen, the potential antigenicity of mipomersen was assessed in the chronic toxicity study in monkeys and the immune function study in mice. In the mouse, there was no evidence of antigenicity. In monkeys the 5 positive responses were not dose-dependent and were not considered clear evidence of an oligonucleotide-specific Ab response.

In addition, evaluation of mipomersen in the Mouse Influenza Host Resistance Model to determine whether it exerts immunotoxicity was performed in the influenza host resistance model in female Balb/c mice. In this model, immunotoxicity is defined as impaired clearance of the infectious agent, influenza virus. Although there was a slight decrement in influenza-specific IgG response at 100 mg/kg/week in mice treated with mipomersen that might suggest some impairment in the function of helper T cells, B cells, or the antigen processing and presentation activity of macrophages, there was no effect on the net immune capability of the host to clear the infectious virus challenge. As noted in other repeat dose toxicity studies, dose levels ≥25 mg/kg/week were associated with inflammatory effects in mice, as increased spleen weight and increased plasma MCP-1, in addition to the inherent functional reserve of the immune system, may have contributed to normal viral clearance and net immune health. Thus, with no effect on viral clearance at any dose, mipomersen was not deemed immunotoxic in this host resistance model.

The CHMP concluded that taking into account the data provided in the above testing and from the repeated dose studies, as well as the recommendations of the ICH Topic S8 Guideline on Immunotoxicity, additional studies are not considered necessary.

Ecotoxicity / environmental risk assessment

During the environmental risk assessment (ERA), mipomersen PECsurfacewater value was found to be below the action limit of 0.01 µg/L. The compound is not a PBT substance as log Kow does not exceed 4.5. These results confirm the absence of risk to the environment. Therefore, mipomersen is not expected to pose a risk to the environment and to stop the environmental risk assessment in Phase I is acceptable.

Summary of main study results

Substance (INN / Invented Name): mipomersen sodium			
CAS-number (if available): 629167-92-6			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}		-3.5	not B
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	-3.5	not B
	BCF		not B
Persistence	DT50 or ready biodegradability		not P
Toxicity	NOEC or CMR		not T
PBT-statement :	PM		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default F_{pen}	1	µg/L	> 0.01 threshold: Y
refined F_{pen}		µg/L	< 0.01
Other concerns (e.g. chemical class)			none

2.3.5. Discussion on non-clinical aspects

An extensive non-clinical development program related to the requested indication has been carried out. The non-clinical toxicology development conducted with mipomersen provides a thorough profile of the product. In general, the studies are GLPs compliant and in accordance with the current requirements regarding the animal models, dosing regimen, time of treatment, route of administration. These studies identified the targets of mipomersen as well as its toxicity, which is similar to the known effects of ASOs which have been described so far and are available in the literature. No evidence of exaggerated pharmacological effects has been observed for mipomersen. Furthermore it has been demonstrated that it is highly unlikely that an oligonucleotide of 20 residues (as mipomersen) or greater would hybridize with a non-targeted mRNA. The studies performed with mipomersen confirmed this. In addition, on the basis of these non-clinical studies the applicant estimated an acceptable safe starting dose for humans based on the results observed.

Safety pharmacology studies did not reveal significant relevant findings. The safety pharmacology data of mipomersen were completed with data from a toxicology study in monkeys, which confirmed the lack of cardiac findings.

With regard to pharmacokinetics, there appears to be a possibility that mipomersen is excreted via milk and this may have an indirect effect on milk composition or milk production, or can accumulate in the mammary gland and thereby affect its function. An appropriate warning would be included in the proposed SmPC regarding this issue, since a risk to newborns/infants cannot be excluded and therefore mipomersen should not be used during breast feeding.

In relation with the toxicology development, it was observed that the principal target organs for mipomersen are the kidney, liver, mesenteric lymph nodes, spleen and bone marrow and that the target organs display the highest distribution of the compound, all exhibiting an histopathology reflective of cellular uptake. This issue would be highlighted in the proposed SmPC. In rats, increased BUN, decreased albumin and tendency for higher potassium in serum have been reported, and again the information would be included in the proposed SmPC.

Mipomersen was not found to be genotoxic and did not display significant adverse effects in reproductive toxicology and developmental studies.

Carcinogenicity studies in mouse and rat exhibited very few neoplastic lesions (not relevant for humans) and provided no clear evidence of tumourigenic potential.

2.3.6. Conclusion on the non-clinical aspects

The CHMP considered that in general, the non-clinical studies conducted with mipomersen were sufficient and provided an adequate overview of the non-clinical product profile. Appropriate justifications were provided for the absence of specific studies. The concerns raised during the evaluation were addressed either by means of submitting additional data and re-analyses, or by accepting appropriate risk minimisation activities and reflecting relevant findings in the proposed Product Information. The CHMP did not request any post-authorisation measures and non-clinical issues have been resolved.

2.4. Clinical aspects

2.4.1. Introduction

The clinical programme for mipomersen included 18 studies in healthy volunteers and patients. Of these, there were 4 phase III studies in HoFH and primary hypercholesterolaemic (HeFH and non-FH) patients. Data from 792 subjects exposed to at least one dose of mipomersen in clinical trials (733 with SC administration) were submitted originally. Mipomersen was administered over a dose range of 30 to 400 mg, given as either a single dose or multiple doses by subcutaneous (s.c.) or intravenous (i.v.) administration for up to 2 years. One study also evaluated a 500 mg oral dose of mipomersen.

It is to be noted, that in the view of the CHMP's negative opinion for Kynamro, the Product Information and Risk Minimisation Plan were not adopted and agreed by the CHMP. Thus, all references to these documents in the report are the proposed draft versions.

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study No. and Description	Population	Study Type (PK/ PD/ IMG)	Route	Subjects Treated (n)	Mipomersen Dosage	Treatment Duration	Mono or Add-on Therapy	Post-First Dose Time Points for PK/PD Measurements
Phase 1 Studies								
ISIS 301012-CS1 Phase 1 dose-ranging study	Healthy volunteers with hypercholesterol-aemia	PK PD	IV and SC	Mipo: 29 Placebo: 7	**Single Dose:** 50, 100, 200 and 400 mg with 3:1 ratio active to placebo in each cohort **Multiple Dose:** 50, 100, 200, and 400 mg with 4:1 ratio active to placebo in each cohort	3 weeks	Mono	Single Dose (SC): 0.5, 1, 1.5, 2, 2.25, 2.5, 3, 4, 6, 8, 12, 24 and 72 hours Multiple Dose (IV): Day 1 (pre-dose, 0.5, 1, 2, 2.25, 2.5, 3, 4, 6, 8, and 24 hours), Days 3 and 5 (pre-dose, 2 and 24 hours) Multiple Dose (SC): Days 8 and 15 (pre-dose), Day 22 (pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 and 72 hours)
MIPO3200309 Phase 1 relative bioavailability, PK, safety, and tolerability study of different SC dosing regimens with mipomersen	Healthy volunteers	PK	SC	Mipo: 63 Placebo: 21	**Multiple Dose:** **Regimen 1:** 30 mg mipomersen or placebo once daily **Regimen 2:** 70 mg mipomersen or placebo 3x/week **Regimen 3:** 200 mg mipomersen or placebo once weekly	3 weeks	Mono	1, 2, 3, 4, 6, 8, 12 hours following first and last dose, and 48 hours following last dose, and on Days 22 (200 mg only), 28, 35, 49, 77, 105

Phase 2 Studies								
ISIS 301012-CS3 Phase 2 dose-loading and maintenance regimen study	Subjects with mild hypercholesterol-aemia	PK PD IMG	SC	Mipo: 40 Placebo: 10	**Multiple Dose**: 4 doses of 200 mg administered over 11 days followed by 100 mg (n=10) or 200 mg (n=10) qow for 11 weeks OR 200 mg, 300 mg, or 400 mg administered qw for 13 weeks (n=10 each per dose cohort); 4:1 ratio active to placebo in each cohort	13 weeks	Mono	Pre-dose on Days 4, 8, 15, 22, 36, 50, 64, 78, and 85 Day 14: 72 hours Day 85: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48 and 72 hours, and on Days 86, 87, 88, 92, 99, 115, 145, 175, 205, 235, and 265
ISIS 301012-CS4 Phase 2 dose-ranging study	Subjects with polygenic hypercholesterol-aemia on stable simvastatin or atorvastatin	PK	SC	Mipo: 59 Placebo: 15	**Multiple Dose**: 4 doses of 30, 100, 200 mg, 300 mg, or 400 mg over 12 days then once a week for 3 weeks with 4:1 ratio active to placebo in each cohort (Cohorts A-E) **Multiple Dose (Extended)**: 200 mg and 300 mg qod x 3 Doses, then once weekly x 12 weeks; 4:1 ratio active to placebo (Cohorts F and G)	5-13 weeks	Add-on	Cohorts A - E: Pre-dose on Days 2, 4, 8, 10, 12, 15, 22, 29, 36, 43, 59, 87, 115, 143, 171, 199, 227, and 255 Cohorts F and G: Pre-dose on Days 1, 3, 5, 8, 15, 22, 29, 43, 57, 71, 85, 92, 115, 143, 171, 199, 227, and 255
ISIS 301012-CS8 Phase 2 dose-escalation add-on therapy study	Patients with homozygous familial hypercholesterol-aemia	PK IMG	SC	Mipo: 9	**Multiple Dose**: 4 doses of 50 mg (n=3), 100 mg, or 200 mg 11 days then once a week for 4 weeks (Cohorts A-C) **Multiple Dose (Extended)**: 4 doses of 300 mg (n=4) over 11 days then once a week for 11 weeks	6-13 weeks	Mono	Cohorts A-C: Pre-dose on Days 8, 15, 22, 29, and Weeks 7, 11, 15, 19, with serial 24-hour blood sampling on Day 36 Cohort D: Pre-dose on Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, 85, and Weeks 15, 19, 23, 27, with serial 24-hour blood sampling on Day 85
ISIS 301012-CS9 Phase 2 dose-escalation add-on therapy study	Patients with heterozygous familial hypercholesterol-aemia	PK IMG	SC	Mipo: 36 Placebo: 8	**Multiple Dose**: 4 doses of 50 mg (n=8), 100 mg (n=8), 200 mg (n=11) followed by 4 weekly doses with a 4:1 ratio active to placebo in each cohort (Cohorts A-C) **Multiple Dose (Extended)**: 4 doses of 300 mg (n=9) administered over 11 days then once a week for 11 weeks; 4:1 ratio active to placebo (Cohort D)	6-13 weeks	Add-on	Cohorts A-C: Pre-dose on Days 8, 15, 22, 29, and Weeks 7, 11, 15, 19, with serial 24-hour blood sampling on Day 36. Cohort D: Pre-dose on Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, 85, and Weeks 15, 19, 23, 27, with serial 24-hour blood sampling on Day 85
ISIS 301012-CS10 Phase 2 study to determine the effect of apoB reduction on liver TG content	Subjects with hyperlipidemia	PK PD	SC	Variable on cohort	**Multiple Dose**: 6 doses of 200 mg mipomersen over 3 weeks in healthy volunteers (n=9) (Cohorts A and D); 200 mg mipomersen or placebo once weekly x 12 weeks in HeFH patients (n=20, active: placebo=1:1) (Cohort E)	3-12 weeks	Mono	Cohort A and D: Pre-dose on Days 8, 22 and Weeks 4, 8, 12 16. Cohort E: Pre-dose on Days 8, 22, 26, 29, 43, 57, 71, 85 99, 113, 141, 169, 197, and 225 Cohort G: Days 8, 15, 29, 43, 57, 71, 85, 99, 120, 148, 176, 190, 204, 218, 246, 274, 302, 329, 358, 372, 400, 442, and 498
Phase 3 Studies								
ISIS 301012-CS5 Phase 3 placebo-controlled study in HoFH	Patients with homozygous familial hypercholesterol-aemia	PK IMG	SC	Mipo: 34 Placebo: 17	**Multiple Dose**: 200 mg mipomersen or placebo once weekly; Pediatric and adult patients <50 kg received 160 mg of active or placebo.	26 weeks	Add-on	Pre-dose on Days 1, 15, 29, 57, 85, 113, 141, 176, 190, 246, and 344
MIPO3500108 Phase 3 placebo-controlled study in severe hypercholesterolaemia (not on apheresis)	Patients with severe hypercholesterol-aemia on maximally tolerated lipid lowering regimen	PK IMG	SC	Mipo: 39 Placebo: 19	**Multiple Dose**: 200 mg mipomersen or placebo once weekly	26 weeks	Add-on	Pre-dose on Days 1, 15, 29, 43, 57, 85, 113, 141, 176, 190, 218, 274, and 344
ISIS 301012-CS7 Phase 3 placebo-controlled study in HeFH	Patients with heterozygous familial hypercholesterol-aemia	PK IMG	SC	Mipo: 83 Placebo: 41	**Multiple Dose**: 200 mg mipomersen or placebo once weekly	26 weeks	Add-on	Pre-dose on Days 1, 15, 29, 57, 85, 113, 141, 176, 190, 218, 274, and 344
ISIS 301012-CS12 Phase 3 placebo-controlled study in high risk hypercholesterolaemia	Patients at high risk for coronary heart disease	PK IMG	SC	Mipo: 105 Placebo: 53	**Multiple Dose**: 200 mg mipomersen or placebo once weekly	26 weeks	Add-on	Pre-dose on Weeks 1, 3, 5, 9, 13, 17, 21, 26, 30, 34, 38, 42, 46, and 50
Open-Label Extension Studies								
ISIS 301012-CS17 Phase 2 open-label extension study for patients who participated in ISIS 301012-CS8 or ISIS 301012-CS9	Patients with familial hypercholesterol-aemia	PK IMG	SC	Mipo: 21	**Multiple Dose**: 200 mg mipomersen once weekly or every other week	Up to 156 weeks	Mono or Add-on	Pre-dose on Weeks, 1, 4, 8, 12, 16, 20, 28, 36, 44, 52, 60, 68, 76, 85, 94, and 104 Year 3 Weeks 1, 8, 16, 24, 33, 42, and 52

ISIS 301012-CS6 Phase 3 open-label extension study for patients who participated in ISIS 301012-CS5, ISIS 301012-CS7, or MIPO3500108	Patients with familial hypercholesterol-aemia	PK IMG	SC	Mipo: 141	**Multiple Dose**: 200 mg mipomersen once weekly	104 weeks	Add-on	Pre-dose on Weeks 1, 5, 9, 13, 17, 21, 26, 32, 39, 45, 52, 58, 64, 70, 76, 83, 90, 97, 104, 112, 120, and 128
Other Studies								
ISIS 301012-CS101 Phase 1 proof-of-concept study to evaluate an oral formulation	Healthy volunteers with hypercholesterol-aemia	PK PD	IV and Oral	Mipo: 42	Multiple Dose: Oral Cohorts (n = 36) Single-dose IV (200 mg mipomersen or placebo) followed by 31 oral doses: placebo capsules (n = 6), Sodium caprate capsules (n = 6) or 500 mg mipomersen + sodium caprate capsules (n = 24) IV Cohort (n = 6) mipomersen: 100 mg. IV on Days 1 and 6 followed by six 200-mg IV doses over 4 weeks	6 weeks	Mono	Cohorts A-D: 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12 hours and 24 hours (Days 4 and 44), and Days 10, 26, 45, 55, 69, 97, and 125 Cohort E: 1, 2, 2.5, 3, 4, 6, 8, 12 hours and 24 hours (Days 2 and 40), and Days 11, 20, 31, 55, 69, 97, and 125
ISIS 301012-CS2 Phase 1 drug-drug PK interaction study	Healthy volunteers	PK PD	IV	Mipo: 20	**Multiple Dose**: 4 doses of 200 mg IV on Days 4, 6, 8 and 11 (Cohort A: simvistatin) or on Days 8, 10, 12 and 15 (Cohort B: ezetimibe), 40 mg simvistatin on Days 1 and 11, 10 mg ezetimibe on Days 1 and 15	2 weeks	Mono (DDI)	PK: 0.5, 1, 1.5 (simvastatin only), 2, 2.5 (mipomersen and simvastatin), 3, 4, 6, 8, 10 (simvastatin only), 12, 24 hours, and 36, 48, 60 and 72 hours (ezetimibe only) PD: Baseline and Day 40
MIPO2900509 Phase 1 drug-drug interaction study on warfarin	Healthy volunteers	PK PD	SC	Mipo: 16	**Multiple Dose**: 4 doses of 200 mg SC on Days 8, 10, 12 and 14, single doses of oral warfarin 25 mg on Days 1 and 14	4 days	Mono (DDI)	PK: 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 18, 24 hours, and 48, 72, 96, 120, 144 hours (warfarin only) on Days 1, 12 and 14 PD: 1, 2, 4, 8, 12, 24, 48, 72, 96, 120, and 144 hours on Days 1-7 and Days 14-20
MIPO2800209 Phase 1 thorough ECG study	Healthy volunteers	PK PD	IV and SC	Mipo: 60 (only 58 included in PK analysis)	**Single Dose**: 200 mg IV and 200 mg SC mipomersen, 400 mg moxifloxacin (positive control), and placebo control	2 days	Mono	1, 2 , 2.5, 3, 3.5, 4, 5, 6, 8, 10, 14, 18, and 22.5 hours
ISIS 301012-CS301 Phase 1 study to investigate injection site reactions	Healthy volunteers	PK	SC	Mipo: 60	**Single Dose**: 200 mg (n=30), 300 mg (n=10), or 400 mg (n=20)	1 day	Mono	6, 24 and 48 hours

qow=every other week; PK=pharmacokinetic, PD=pharmacodynamic, IMC=immunogenicity

2.4.2. Pharmacokinetics

The pharmacokinetics of mipomersen was examined in healthy volunteers and in subjects with primary hypercholesterolemia, including HoFH and HeFH. In phase III trials, PK samples were collected sparsely. In selected studies, preliminary PK/PD analyses were also completed. Population PK modelling and exploratory graphical population PK/PD analysis using a nonlinear mixed effect modelling approach were conducted using pooled data from phase 1-3 studies. Employed analytical methods were fully validated and comparable.

Absorption

Following the subcutaneous administration, the mean Tmax of mipomersen was typically 3-4 hours. In study ISIS 301012-CS1, which was a Phase 1, placebo-controlled study to assess the safety, tolerability, PK, and PD of mipomersen, the absolute plasma bioavailability of mipomersen following SC administration ranged from 54% to 78% in comparison to IV infusion. Plasma concentrations decreased more slowly from Cmax following SC injection, when compared to IV infusion. Absolute plasma bioavailability of mipomersen following SC administration ranged from 54% to 78% in comparison to IV infusion and was independent of dose in study ISIS 301012-CS1, which included 36 healthy volunteers with mild hypercholesterolaemia. Considering the SC injection site, the mean

and median Cmax after upper arm injection is approximately 45% higher than abdomen, while mean and median AUC after upper arm injection is approximately 20% higher than abdomen. These differences are similar in magnitude to the observed inter-subject variability in mipomersen PK parameters (~20-50%) and therefore do not warrant dosing recommendation. Plasma PK parameters were similar following the first and last SC injection. Maximum plasma concentrations were dose-dependent over the studied SC dose range, but were typically about 5-fold lower in comparison to equivalent IV infusion doses. There was little or no apparent increase of peak plasma levels with repeated versus single dose administration of mipomersen, indicating little or no plasma accumulation.

Following oral administration, the oral bioavailability of mipomersen was low, with mean values ranging from 1.1% to 1.9%. Therefore, the oral formulation of mipomersen was not considered for further development.

Distribution

Mipomersen has a rapid mean distribution plasma half-life of approximately 0.67 to 1.67 hours after IV administration and 2 to 5 hours after SC injection. Population PK analysis using a nonlinear mixed effect modelling approach has shown that the plasma concentration-time profiles of mipomersen are generally well-described by a two compartment model with first order elimination from the central compartment. Binding to albumin, α2-macroglobulin, and α1-acid glycoprotein was 95.87% at the lowest concentration (1 µg/mL) and 84.81% at the highest concentration (4556 µg/mL) tested, indicative of the high capacity for plasma proteins to non-specifically bind mipomersen. Mipomersen has a phosphorothioate backbone, which confers a greater resistance to enzymatic hydrolysis and a greater affinity for protein and cell binding. This is likely to be the cause of the inflammatory effects observed in rodents and the injection site reactions and constitutional effects seen in some patients treated with mipomersen. A potential relationship of the tight binding to proteins and cells and CV events, mediated by its proinflammatory effect and the induction of proteinuria cannot be ruled out at this stage (see section Clinical safety). Based on in vitro studies using cell models it was determined that mipomersen was not a substrate for the P-gp transporter. Preclinical studies in mice, rats and rabbits showed low concentrations of mipomersen were measured in placental tissue and oligonucleotide concentrations in placenta were dose-dependent. No exposure was measured in foetal kidney and fetal liver, suggesting that mipomersen does not readily cross the placenta.

Elimination

A minimal amount of urinary excretion of parent compound (<5% of administered dose) within the first 24 hours after dosing can be observed for 50 mg to 400 mg mipomersen administered by IV or SC route. The percentage of urinary excretion appeared to be dose- and route- dependent. Excretion of chain-shortened metabolites was evident in urine. Based on data from 15 studies (including four Phase 3 studies), with 133 healthy volunteers and 491 patients with hypercholesterolaemia, the clearance of mipomersen decreased over time from 3.63 L/h on the first day of dosing to 2.08 L/h after one year of dosing. The effect on renal function was small; over the range of CrCL values in the present database (42.2 to 273 mL/min) clearance ranged from 3.49 L/h to 3.76 L/h, thus a 9% change. Disease type had no effect on mipomersen clearance. For volume of

distribution, only route of administration was found to be predictive of variability in volume of distribution. Eleven mipomersen metabolites were identified in human urine. Extrapolation of the non-clinical metabolism data is reasonable since the human metabolite profile appears very similar to that of other investigated species. Mipomersen is metabolised in tissues by endonuclease hydrolysis and subsequently the substrates for additional metabolism by exonuclease hydrolysis and phosphatase hydrolysis. Cytochrome P450 is not involved in the metabolism of mipomersen.

Dose proportionality and time dependencies

Mipomersen exposure increases with dose, in an approximately dose-proportional manner across the studied dose range of 30 mg to 400 mg. In two other studies, mipomersen exposure increased with the dose, but a clear dose proportional relationship was not observed. Nevertheless, a strict dose proportionality analysis is limited by relatively small sample sizes in most of the studies when there is considerable inherent PK inter-subject variability for mipomersen.

Following s.c. administration of 30 mg to 200 mg doses of mipomersen sodium, mipomersen was absorbed rapidly to the systemic circulation, with Cmax typically observed at 2 hours to 4 hours post dose. After reaching Cmax, mean plasma concentrations of mipomersen declined in a multi-phasic fashion with time for all dose levels. The plasma PK parameters were similar following the first and last SC injection. The clearance of mipomersen was found to be time dependent due to a decay in clearance over time. Most subjects approach steady state at 6 months treatment, but in 21% of the subjects concentrations continue to rise after this period.

Plasma trough concentrations were generally dose-dependent, increasing with increased dose. C_{trough} gradually increased up to day 92, which is consistent with the long terminal elimination half-life.

Special populations

A population analysis using a non-linear mixed-effect modelling approach was conducted. Patient intrinsic factors, including age, gender, body weight, race, liver function and renal function were evaluated. Mipomersen clearance was found to be affected by creatinine clearance and patient gender, but not in a clinical significant level. The effect of impaired renal function was relatively small but patients with renal impairment were not included in the population analysis. While there does not appear to be any difference between patients with moderate renal insufficiency in PK or efficacy, no data on severe renal insufficiency are available. Since mipomersen undergoes urinary excretion and increases the risk for proteinuria, it should be contraindicated in severe renal insufficiency and should be used with caution in patients with mild to moderate renal insufficiency. This would be reflected in the SmPC. The effect of gender is low, with mipomersen clearance being approximately 6% lower in females than males. Age was not identified as a relevant covariate, in the population PK study. Approximately 10% of the patients were over 65 years of age. No PK data are available on the use of mipomersen in patients with liver function disorders. The SmPC would indicate that the effects of hepatic impairment on mipomersen PK have not been studied and that mipomersen is contraindicated in patients with significant hepatic dysfunction. This is agreed by the CHMP. Demographic factors do not have an effect on mipomersen PK, and therefore, no dose adjustment based on these factors is necessary.

Pharmacokinetic interaction studies

A total of three in vitro studies were conducted to evaluate the induction, inhibition and substrate potential of mipomersen with human cytochrome P450 (CYP450) enzymes. It was shown that all enzyme activities evaluated had less than 10% inhibition and dose-dependent inhibition was not observed. Therefore, mipomersen is not considered an inhibitor of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 isoforms. Mipomersen has a low potential to induce CYP1A2, CYP2B6, and CYP3A4 enzymes in plated cultures of cryopreserved human hepatocytes. Finally, it was observed that CYP450 enzymes do not contribute to the metabolism of mipomersen. Two dedicated in vivo drug-drug interactions studies conducted in healthy volunteers evaluated the potential for drug interactions between mipomersen and two oral hypolipidemic agents (simvastatin and ezetimibe), and between mipomersen and warfarin. Study ISIS 301012-CS2 showed that although modest changes in PK parameters were observed for simvastatin, its metabolite, simvastatin acid and ezetimibe, upon co-administration of mipomersen, the changes were not deemed clinically relevant. In study MIPO2900509, the co-administration of mipomersen with warfarin did not result in a PK interaction or a PD interactions.

In covariate analysis, co-administration with HMG CoA reductase inhibitors, lipid modifying agent (ezetimibe), nicotinic acid and derivatives vasopressors, selective beta blocking agents, ACE inhibitors, and platelet aggregation inhibitors (excluding heparin) was not found to alter the clearance of mipomersen.

2.4.3. Pharmacodynamics

Mechanism of action

Mipomersen is a first-in-class apolipoprotein B synthesis inhibitor, which binds to a specific segment of the mRNA coding region for apo B, thus inhibiting the synthesis of this target. In humans, apo B-100 is the principal apolipoprotein associated with very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL) and low density lipoprotein (LDL), comprising approximately 30% to 95% of the proteins in these lipoproteins. Apo B-100 is also a principal component of lipoprotein (a) (Lp[a]), which consists of apolipoprotein (a) covalently bound to the apo B component of an LDL-like particle. Low density lipoprotein cholesterol (LDL-C), apo B and Lp(a) are key risk factors for atherosclerosis.

Primary and Secondary pharmacology

The primary pharmacodynamic (PD) effects of mipomersen include inhibitory effects on apoB. Correlation between mipomersen plasma trough concentrations and apoB levels were investigated in studies ISIS 301012-CS1 in healthy volunteers and ISIS 301012-CS3 in nonfamilial hypercholesterolaemia patients.

In study ISIS 301012-CS1, the total tissue exposure, represented by trough plasma concentrations measured ≥ 72 hours post-dose was highly correlated with serum apo B protein levels in healthy volunteers. Significant reduction of apo B from baseline for the 200 mg treatment group was

achieved from multiple dose phase day 15 to post-dose phase day 58, which is consistent with the slow elimination of mipomersen in plasma. A direct correlation was achieved between the plasma concentrations and the response measures (serum apo B, LDL-C, and TC levels) 17 days after last treatment. Study ISIS 301012-CS3 used an inhibitory sigmoidal Emax model, an exploration of the relationship between inhibition of serum apo B and Ctrough of mipomersen on Day 99 or 78. The estimated 50% of maximum drug-induced effect (EC50) value was determined as 10 ng/mL ± 1.9 ng/mL.

Study MIPO2800209 was a Phase 1, randomised, double-blind, single-site, crossover study in healthy subjects to determine if mipomersen sodium 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. On average, the total plasma exposure of mipomersen was approximately 1.25-fold higher after the IV infusion compared with the SC injection of mipomersen, while the peak plasma exposure of mipomersen was approximately 3.8-fold higher after the IV infusion compared with the SC injection. Median time to reach Cmax (Tmax) was 3.6 hours in the 200-mg SC mipomersen treatment group and 2.1 hours (end of infusion) in the 200-mg IV mipomersen treatment group. The effect of mipomersen on cardiac repolarization using the QTcF interval showed no signal. There was no signal of an effect of mipomersen on heart rate, atrioventricular conduction, or cardiac depolarization. There were no new clinically relevant morphological changes or an indication of a QT/QTc prolonging effect of mipomersen sodium following single SC and IV doses of 200 mg.

The effect of 200 mg mipomersen sodium on lipoprotein particle number and size was assessed in each of the four Phase 3 studies. Since there is one molecule of apoB-100 per lipoprotein particle, inhibition of apoB-100 synthesis is expected to reduce VLDL and LDL particle numbers. Treatment with mipomersen results in decreases in LDL particle number, in increases in HDL particle number and in preferential reductions in the smallest particles of VLDL and LDL. Evaluation of the relationships between observed mipomersen Cmin and laboratory values shows a general decrease in many lipid measurements, e.g. LDL-C and VLDL-C decrease with increasing Cmin. There is a slight reduction in Apo B with increasing Cmin but data are sparse. Total cholesterol initially decreases with increasing Cmin, then shows a plateau at Cmin of approximately 200 ng/mL. There is a very weak trend towards increasing ALT and increasing AST with increasing Cmin.

Evaluation of the relationships between selected AEs (elevated ALT, elevated AST, elevated alkaline phosphatase, flu-like symptoms, injection site reactions, and steatosis) and mipomersen exposure showed no relationship except for steatosis, which occurred at higher AUC values (AUC > 50 ug*hr/L). However, no trend was observed between the incidence of steatosis and increased Cmin values. Therefore, given the relative incidence of steatosis and the overlapping values of AUC for subjects with and without steatosis, this trend should be interpreted with caution.

2.4.4. Discussion on clinical pharmacology

Absolute plasma bioavailability of mipomersen following SC administration ranges from 54% to 78% in comparison to IV infusion and is independent of dose. However, the absolute plasma bioavailability values likely underestimate the expected complete absorption of mipomersen after SC dosing. Following SC injection, Cmax is reached between 3-4 hours. Plasma concentrations

decreased more slowly from Cmax following SC injection, when compared to IV infusion, indicating continued absorption of mipomersen after achievement of Cmax. Terminal elimination half-life is approximately 23 to 31 days over a dose range of 50 mg to 200 mg following 22 days of s.c. treatment with mipomersen sodium. The oral bioavailability of an oral formulation of mipomersen and sodium caprate was low and the oral formulation of mipomersen was not developed further. The CHMP considered the analytical methods used for the detection of mipomersen sufficient.

Mipomersen has a relatively rapid mean distribution plasma half-life after IV or SC administration and is rapidly and broadly distributed to tissues, with the kidney and liver containing the highest concentrations. The pharmacologic activity is related to tissue concentrations. Mipomersen clearance decreases over time from 3.63 L/h after the first dose to 2.07 L/h after 1 year of dosing, and it shows a high binding to human plasma proteins (≥ 90%). Mipomersen has a phosphorothioate backbone, which is a widely used modification in antisense oligonucleotides. This substitution has only a relatively small effect on the oligonucleotide structure, but this disadvantage is outweighed by a greater resistance to enzymatic hydrolysis. A more significant change is the greater affinity of the phosphorothioate linkages for protein binding. Theoretically, a tight binding to charged residues in proteins on cell surfaces (hepatocytes, renal tissue) could occur. A potential linkage to other safety findings, i.e. pro-inflammatory effect, adverse events on liver or proteinuria, cannot be ruled out. Mipomersen is mainly excreted in urine as the parent drug and total oligonucleotide during the first 24 hours post administration. This suggests that the majority of the administered dose is extensively distributed in the body tissues. In the population PK analysis, mipomersen clearance was found to decrease with time and this effect would be expected to result in progressively increasing AUC and Cmin values. Mipomersen is metabolised by endonuclease hydrolysis and metabolites include oligonucleotides ranging from 5-base to 14-base residues. CYP450 enzymes do not contribute to the metabolism of mipomersen. Mipomersen exposure increases with dose in an approximately dose-proportional manner across the studied dose range of 30 mg to 400 mg. There was no indication of time-dependent pharmacokinetics.

Within-subject variability of mipomersen is low and there did not appear to be a difference in weight or age between the high and low in the examined individuals. The Cmax was not routinely monitored in the phase 3 studies and is therefore not well-characterised in these patients. The PK/PD analysis using pooled data suggests that values greater than 200 ng/mL are not associated with any additional increase in lipid-lowering activity. In approximately 21% of patients, a presumed higher accumulation of mipomersen in tissues is expected. There is a significant overlap between the decrease in clearance and the appearance of immunogenicity. Therefore, the decay in clearance overtime may be due to relatively high affinity protein binding of mipomersen to specific antibodies.

The PK profile of mipomersen is consistent among healthy volunteers and patients with hypercholesterolaemia, including those who received mipomersen in combination with stable lipid lowering therapies. Mipomersen plasma exposure increases with dose, and exhibits an approximate dose-proportionality across the studied dose range of 30 mg to 400 mg.

Mipomersen's mechanism of action is related to the inhibition of apoB synthesis, thus leading to decrease in synthesis of LDL, IDL and VLDL. Low density lipoprotein cholesterol, apo B and Lp(a) are key risk factors for atherosclerosis. It is believed that a reduction in LDL-C irrespective of the mechanism of action to reduce LDL-C is associated to a reduction in cardiovascular morbidity and

mortality. However, the effect of mipomersen on cardiovascular morbidity and mortality is yet to be established.

There is only scarce information on the use of mipomersen in special populations. While there does not appear to be any difference between patients with moderate renal insufficiency in PK or efficacy, no data on severe renal insufficiency are available. Since mipomersen undergoes urinary excretion and increases the risk for proteinuria, it should be contraindicated in severe renal insufficiency and should be used with caution in patients with mild to moderate renal insufficiency, this would be reflected in the SmPC. No data with mipomersen are available in patients with hepatic impairment. The SmPC wording would therefore include the contraindication of mipomersen in patients with significant hepatic dysfunction.

Weight and race are not significant covariates for mipomersen exposure in the PK analysis. Mipomersen clearance is 6% lower in females than males. The information regarding age was very scarce and the CHMP requested information on age subgroups in the PK analyses. The response clarified that in the population PK datasets, there are only 7 patients <18 years old, and 26 patients >70 years old. There does not appear to be a substantial age-effect on the plasma trough concentrations of mipomersen and in the population PK analysis age does not seem to be an influential factor on the PK of this substance. There are no clinical data on the use of mipomersen in pregnant women and appropriate SmPC wording would be implemented.

Data on PK/PD interactions with mipomersen are limited. Based on in vitro data, the potential of mipomersen to inhibit or induce the CYP-mediated metabolism of other compounds seems low. In the in vitro studies, statins were not displaced by mipomersen in human plasma and there was no significant displacement of mipomersen binding by either atorvastatin or simvastatin. Mipomersen is unlikely to be involved in drug-drug interactions with the P-gp transporter. Additional data from the population PK analysis, although limited, suggest that coadministration with HMG CoA reductase inhibitors, ezetimibe, nicotinic acid and derivatives vasopressors, selective beta blocking agents, ACE inhibitors, and platelet aggregation inhibitors (excluding heparin) does not alter the PK of mipomersen.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology programmes provides an evidence for mipomersen's effect of lowering the apo-B and LDL-C levels. A dose dependent effect was observed up to the 200 mg dose of mipomersen sodium. The studies were limited to healthy volunteers and dosing is shorter than in the phase III trials. The CHMP noted that attempts were made to develop an oral dose; however, the observed oral bioavailability was too low and the further studies were not conducted. The relationship between plasma concentration and effect is of limited value in terms of dose finding. The pharmacokinetic and pharmacodynamics profile of mipomersen, including the metabolism and drug-drug interactions, were appropriately characterised and the Product Information would include adequate statements about the recommended use of mipomersen or its restriction in special populations. The clinical pharmacology programme is satisfactory and the CHMP did not consider that there is a need for any additional measures.

2.5. Clinical efficacy

In order to support the originally proposed indication for treatment of patients with heterozygous and homozygous hypercholesterolaemia, four dose-ranging studies and two pivotal placebo-controlled phase 3 studies were submitted.

Initial phase 2 dose-ranging studies included ISIS 301012-CS3, which enrolled subjects with mild hypercholesterolaemia not on lipid-lowering therapy, and the ISIS 301012-CS4 trial, which enrolled patients with primary hypercholesterolaemia on stable statin therapy. These placebo-controlled studies included doses ranging from 50 mg in CS3, or 30 mg in CS4, to 400 mg in both studies, with treatment durations of 5 to 13 weeks. Later phase 2 studies included subjects diagnosed with HoFH or HeFH on lipid-lowering therapy (ISIS 301012-CS8 and ISIS 301012-CS9).

Two pivotal placebo-controlled phase 3 studies were conducted to demonstrate the efficacy of mipomersen in the target population: ISIS 301012-CS5 (in patients with HoFH; N=51) and MIPO3500108 (in patients with severe HeFH; N=58). Supportive data from patients with HeFH and coronary artery disease and from patients with hypercholesterolaemia at high risk of cardiovascular events were provided from the phase 3 studies ISIS 301012-CS7 and ISIS 301012-CS12, respectively. All of these phase 3, randomised, multicentre, double-blind, placebo-controlled studies were designed to evaluate the safety and efficacy of mipomersen sodium, 200 mg SC once weekly, added on to stable lipid-lowering therapy and low-fat diet for 26 weeks. All of these studies utilised 2:1 (mipomersen:placebo) randomisation. The long-term efficacy of mipomersen is further supported by data from the open-label, on-going extension studies ISIS 301012-CS6 and ISIS 301012-CS17.

It is acknowledged that during the evaluation, the applicant proposed limiting the indication of mipomersen to homozygous hypercholesterolaemia patients, however, the below sections describe the entire clinical efficacy programme as it was submitted. The proposed restricted indication was:

Kynamro is an apolipoprotein B (apo B) synthesis inhibitor indicated as an adjunct to maximally tolerated lipid-lowering medicines and diet to reduce low density lipoprotein-cholesterol (LDL-C) in adult patients with homozygous familial hypercholesterolaemia (HoFH).

Summary of main clinical studies with mipomersen

Study No. Phase Role	**Design Dose, Route, Regimen Duration**	**Study objective, Primary endpoint**	**Patients: Diagnosis No. planned No. analysed**	**Demography: Gender (M/F) Median age (range)**	**Study Dates Number of Study Centres Location**
Pivotal studies					
ISIS 301012-CS5 Phase 3	Randomised, double-blind, placebo-controlled 200 mg mipomersen (160 mg for patients weighing <50 kg) or placebo weekly SC for 26 weeks	Efficacy and safety, % change in LDL-C from baseline to PET, placebo vs. mipomersen	HoFH Planned: 50 Analysed: 51 (17 placebo, 34 mipomersen)	41.2%/58.8% placebo; 44.1%/55.9% mipomersen 33.0 years (12-53 years) placebo; 30.4 years (14–53 years) mipomersen	06 Sep 2007 - 25 Mar 2009 Nine study centres in 7 countries (Brazil, Canada, Singapore, South Africa, Taiwan, United States, UK)
MIPO3500108 Phase 3	Randomised, double-blind, placebo-controlled 200 mg mipomersen or placebo weekly SC for 26 weeks	Efficacy and safety, % change in LDL-C from baseline to PET, placebo vs. mipomersen	Severe hypercholesterolaemia[a] Planned: 51 to 75 Analysed: 58 (19 placebo; 39 mipomersen)	36.8%/63.2% placebo; 46.2%/53.8% mipomersen 52 years (18-66 years) placebo; 51 years (21-77 years) mipomersen	27 Jan 2009 – 14 Oct 2010 Twenty-six study centres in 6 countries (Canada, Czech Republic, Germany, South Africa, United Kingdom, and United States)
Supportive Studies					
ISIS 301012-CS7 Phase 3	Randomised, double-blind, placebo-controlled 200 mg mipomersen or placebo weekly SC for 26 weeks	Efficacy and safety, % change in LDL-C from baseline to PET, placebo vs. mipomersen	HeFH Planned: 100 to 125 Analysed: 124 (41 placebo; 84 mipomersen)	68.3%/31.7% placebo; 60.2%/39.8% mipomersen 56 years (47–62 years) placebo; 55 years (51–63 years) mipomersen	14 July 2008 – 18 May 2010 26 sites (19 in the US and 7 in Canada)

ISIS 301012-CS12 Phase 3	Randomised, double-blind, placebo-controlled 200 mg mipomersen or placebo weekly SC for 26 weeks	Efficacy and safety, % change in LDL-C from baseline to PET, placebo vs. mipomersen	High-risk HC Planned: 180 Analysed: 158 (53 placebo; 105 mipomersen)	55.8%/44.2% placebo: 49.5%/50.5% mipomersen 59 years (37–79 years) placebo; 60 years (36-81 years) placebo	24 Nov 2008 – 20 Oct 2010 43 study centers in the US

HeFH=heterozygous familial hypercholesterolaemia; HoFH=homozygous familial hypercholesterolaemia; LDL-C=low density lipoprotein cholesterol; PET=primary efficacy timepoint, defined as the post-baseline visit closest to 14 days after the last dose of study treatment for which LDL-C was assessed. [a] *The patient population from MIPO3500108 is the same population now designated as the severe HeFH population, although this terminology was not used in the protocol.*

2.5.1. Dose response studies

Phase 2 dose-loading study in non-familial hypercholesterolaemia patients (ISIS 301012-CS3): Study ISIS 301012-CS3 was a phase 2, placebo controlled, dose ranging study to assess the safety, tolerability, PK, and PD of varying loading and maintenance dosing regimens of mipomersen administered as monotherapy to hypercholesterolemic subjects. A total of 50 hypercholesterolemic subjects were enrolled in this study: 10 subjects received placebo, 8 subjects received mipomersen sodium 100 mg QOW, 8 subjects received 200 mg QOW, 8 subjects received 200 mg QW, 8 subjects received 300 mg QW, and 8 subjects received 400 mg QW. Dosing was stopped early for the 400 mg cohort (after the 10th dose, day 64) because apo B values had fallen below the limits of detection in 4 of 8 subjects on active treatment. The pairwise treatment comparison between mipomersen 100 mg QOW and placebo for median percent change in LDL-C was not statistically significant, while the pairwise treatment comparisons between mipomersen sodium 200 mg QOW and placebo, 200 mg QW and placebo, 300 mg QW and placebo, and 400 mg QW and placebo were all statistically significant. Similar results regarding mipomersen dose were obtained for the pairwise treatment comparison between mipomersen and placebo for median percent change in apo B. Treatment with mipomersen at all dose levels resulted in median percent reductions in TC, non-HDL-C, TG, VLDL-C, lipoprotein(a). No changes in HDL-C were observed.

In conclusion, this study met its primary objective by demonstrating mipomersen-associated, dose-dependent reductions in LDL-C from baseline to week 15 and by reaching statistical and clinical significance in the mipomersen sodium 200 mg QOW and higher groups compared with placebo. In addition, reductions were seen in all apo B-containing lipoproteins as well as a range of additional lipid parameters including TC, non-HDL-C, Lp(a), TG, VLDL-C, apo B/apo A1 ratio, LDL-C/HDL-C ratio, and TC/HDL-C ratio.

Phase 2 dose-ranging study in hypercholesterolaemia patients on stable statin therapy (ISIS 301012-CS4): Study ISIS 301012-CS4 was a phase 2, placebo controlled, dose-ranging study to assess the safety and PD of mipomersen treated hypercholesterolemic patients on stable statin therapy. A total of 74 patients were enrolled and in the 5-week cohorts, 62 patients received study drug: 13 received placebo, 8 received mipomersen sodium 30 mg, 8 received 100 mg, 16 received 200 mg, 8 received 300 mg, and 9 received 400 mg. In the 13-week cohort, 12 patients received study drug: 2 received placebo and 10 received mipomersen sodium 200 mg extended. The study met its efficacy objective by demonstrating that mipomersen treatment in patients on stable statin therapy resulted in a statistically significant reduction in LDL-C from baseline to the primary efficacy time point compared with placebo. The administration of mipomersen to patients with hypercholesteremia on stable statin therapy for 5 weeks and for 13 weeks produced

dose-dependent and prolonged reductions in apo B-containing atherogenic lipoproteins, including LDL-C, with clinically meaningful reductions seen with mipomersen sodium doses of 200 mg, 300 mg, and 400 mg.

Phase 2 Open-label Dose-escalation Study in HoFH Patients on Lipid-lowering Therapy (ISIS 301012-CS8): Study ISIS 301012-CS8 was a phase 2, open-label, dose-escalation study to assess the safety and efficacy of mipomersen add-on therapy in HoFH patients. A total of 9 patients were enrolled in this study in three cohorts (n = 3 in each): cohort A (50 mg/week), cohort B (100 mg/week), and cohort C (200 mg/week) and were dosed for 6 weeks. Since the apo B and LDL-C reductions observed after 5 weeks in this open-label study were limited, and since mipomersen was well-tolerated in the HoFH patients, a 13-week cohort (cohort D, 300 mg/week) was added to better assess the target and LDL-C reduction potential in this refractory population. All patients in the 300 mg/wk (n=4), 13-week treatment cohort had participated earlier in either the 50 mg (n=2) or 100 mg (n=2) cohort and had undergone a washout period ≥5 half-lives prior to enrolling in the 300 mg/wk cohort. Mipomersen was administered to by SC injection.

Treatment with mipomersen sodium 50 mg, 100 mg, and 200 mg in the 6-week cohorts was associated with moderate and variable reductions in LDL-C, with no dose response evident. Three patients received apheresis. Similarly, the changes in apo B, TC, non-HDL-C, TG, and HDL-C permitted no clear conclusions about the efficacy of these doses when administered according to the protocol schedule during a 6-week treatment period. In the 13-week cohort, which included patients who had each been previously treated in one of the 6-week cohorts, clinically meaningful reductions in LDL-C were observed in 3 of the 4 patients, although the fourth patient, which received apheresis, did not show such meaningful reductions from baseline. Definitive conclusions about the efficacy response to mipomersen in patients with HoFH are hampered by the small sample sizes in this study and the fact that 3 patients received apheresis.

Phase 2 Open-label Dose-escalation Study in HeFH Patients on Lipid-lowering Therapy (ISIS 301012-CS9): Study ISIS 301012-CS9 was a phase 2, placebo controlled, dose-escalation study to assess the safety, efficacy, and PK of mipomersen as add-on therapy in HeFH patients. A total of 44 patients on stable concomitant lipid-lowering therapy were enrolled into the study to receive mipomersen (at either 50, 100, 200, or 300 mg) or placebo (4 active:1 control). The 50, 100, and 200 mg cohorts were treated for 6 weeks and the 300 mg cohort was treated for 13 weeks. Study drug was administered by SC injection. Reductions in the primary efficacy parameter LDL-C from baseline appeared to be generally dose-related for the 6-week cohorts. Percent change in LDL-C was similar the 50 mg group and the 100 mg group. The median percent change in LDL-C from baseline was -6.3% for the placebo group, -9.5% for the mipomersen sodium 50 mg group, -8.6% for the mipomersen 100 mg group, and -15.1% for the mipomersen sodium 200 mg group. Treatment comparisons between each of the mipomersen dose groups and the placebo group for percent change in LDL-C were not statistically significant. Treatment with mipomersen sodium 200 mg for 6 weeks resulted in statistically significant percent reductions from baseline to the PET in the secondary efficacy parameters apo B, TC, and non-HDL-C. Furthermore, the treatment comparison between the mipomersen sodium 200 mg group and the placebo group for percent change in apo B was statistically significant. For the 13-week cohort, the median percent change in LDL-C from baseline to the PET was -0.6% for the placebo group and -37.2% for the mipomersen sodium 300 mg group. The percent change in LDL-C from baseline to the PET for the mipomersen sodium 300 mg group was statistically significant. Treatment with 300 mg for 13 weeks resulted in significant

percent reductions in the secondary efficacy parameters apo B, TC, non-HDL-C and in the tertiary efficacy parameters Lp(a), and LDL-C/HDL-C ratio from baseline to the PET.

In summary, administration of mipomersen to patients with HeFH or severe hypercholesterolemia on stable lipid-lowering therapy for 6 weeks and for 13 weeks resulted in reductions in LDL-C from baseline that appeared to be dose related. Treatment with 200 mg was associated with a significant LDL-C-lowering effect of approximately 15% from baseline. This was accompanied by reductions in apo B level.

2.5.2. Main studies

Title of Study

Study 301012-CS5: A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of ISIS 301012 as Add-on Therapy in Homozygous Familial Hypercholesterolemia Subjects.

Study MIPO3500108: A Prospective Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of Mipomersen in Patients With Severe Hypercholesterolemia on a Maximally Tolerated Lipid-Lowering Regimen and Who are Not on Apheresis.

The above two phase 3 studies are considered the main pivotal studies for the claimed indication.

Methods

Study Participants

The main characteristics of study participant in both pivotal studies are summarised on the table below.

	ISIS 301012-CS5 (N=51)	MIPO3500108 (N=58)
Diagnosis	HoFH	Severe hypercholesterolaemia/ Severe HeFH[a]
Screening lipid levels	Fasting LDL-C ≥130 mg/dL (≥3.4 mmol/L) and TG <350 mg/dL (<4.0 mmol/L)	Fasting LDL-C ≥300 mg/dL (≥7.8 mmol/L), or fasting LDL-C ≥200 mg/dL (≥5.1 mmol/L) in the presence of CAD, and TG <350 mg/dL (<4.0 mmol/L)
Comorbidities	[none required]	Coronary artery disease required if fasting LDL-C ≥200 mg/dL (≥5.1 mmol/L) but <300 mg/dL (<7.8 mmol/L)[b]
Lipid-lowering regimen	Stable low-fat diet and stable lipid-lowering regimen prior to screening	Stable low-fat diet and stable, maximally tolerated lipid-lowering regimen, including statin therapy
Demographic and other baseline characteristics	Male or female ≥12 years, Tanner stage >2; body weight ≥40 kg	Male or female ≥18 years
Other	No apheresis within eight weeks of screening	No apheresis within 12 weeks of screening

HoFH, homozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides

[a] As discussed in m2.7.3, the patient population from MIPO3500108 is the same population now designated as the Severe HeFH population, although this terminology was not used in the

protocol
[b] The majority of patients had CHD or other clinical atherosclerotic disease at baseline

Notable exclusion criteria in both studies included significant hepatic or renal disease, recent major cardiovascular event (MI, PCI, CABG, CVA, unstable angina or acute coronary syndrome within 24 weeks before initiating treatment, presence of a clinically significant arrhythmia, poorly controlled diabetes, uncontrolled hypertension or clinically significant hepatic or renal disease or Gilbert's syndrome), congestive heart failure, recent LDL aphaeresis, elevated TG (>350 mg/dL [>4.0 mmol/L]), or other significant laboratory abnormalities.

Major differences in exclusion criteria across the phase 3 studies included the exclusion of patients with diabetes mellitus from ISIS 301012-CS7, and the exclusion of patients under the age of 18 in MIPO3500108, ISIS 301012-CS7, and ISIS 301012-CS12 (ISIS 301012-CS5 allowed patients over the age of 12, as long as Tanner stage >2). As a result, there is limited clinical experience with mipomersen in elderly (aged >65) patients; minimal clinical experience in children aged <18; and no clinical experience in children <12. Statins were not a required part of therapy in ISIS 301012-CS5, as, owing to their lack of functional LDLr, HoFH patients do not always respond to statins.

Treatments

The pivotal Phase 3 studies (ISIS 301012-CS5 and MIPO3500108) were randomised, double blind, placebo-controlled, parallel-group studies designed to determine the effects of 26 weeks of mipomersen therapy on LDL-C levels in patients not reaching target lipid goals on current lipid-lowering therapy. The studies consisted of a ≤4-week screening period, 26 weeks of treatment, and a 24-week post-treatment follow-up period (unless patients enrolled into an open-label extension study). The 26-week treatment duration was based on the elimination half-life of mipomersen, so that the efficacy endpoint could be evaluated when drug tissue levels were expected to be ≥90% of steady-state values. The majority of patients in both studies were also receiving additional second- and third-line lipid-lowering therapies. All patients (including patients receiving placebo) were required to maintain a stable, low-fat diet, and were counseled to follow the NCEP ATP III Therapeutic Lifestyle Changes (TLC) approach (including regular physical activity and weight management), or a similar approach depending on local guidelines, throughout the course of the studies. The baseline therapy is considered optimal or according to current standard of care.

In both studies, mipomersen sodium was administered as 200 mg/1 mL solution once weekly for 26 weeks as SC injections in the outer area of the upper arm, abdomen, or thigh. The comparator was a matching volume of placebo.

Objectives

The main objective of the studies was to compare the safety and efficacy of 26 weekly subcutaneous injections of mipomersen against placebo in treating severely hypercholesterolemic patients who were on a maximally tolerated lipid-lowering regimen and who were not on apheresis. Taking into account the originally proposed therapeutic indication for mipomersen, the objectives of the phase 3 studies are considered appropriate.

Outcomes / endpoints

Primary endpoint: The primary efficacy parameter in the phase 3 studies was the percent change in LDL-C from baseline to the primary efficacy time point (PET; the post-baseline visit closest to 14 days after the last dose of study treatment for which LDL-C is assessed). Reduction in LDL-C was used as the primary efficacy endpoint across all safety and efficacy studies in the mipomersen clinical development program.

Secondary endpoints: Secondary efficacy parameters included percent changes from baseline to PET in apo B, non-HDL-C, and TC levels, and tertiary efficacy parameters included percent change in TG, Lp(a), VLDL-C, LDL/HDL ratio, apo A-I, and HDL-C. Overall, these assessments allow an overview of the effects of mipomersen on lipoprotein metabolism that is consistent with its targeted mechanism of action inhibiting apo B synthesis, with consequences on apo B and components of apo B containing lipoproteins: VLDL, IDL, LDL and Lp(a).

With respect to other efficacy endpoints, changes in triglycerides, total cholesterol and HDL-cholesterol were considered acceptable by the CHMP. Other lipid parameters, like apolipoprotein A-I, apolipoprotein B, and lipoprotein (a) were also studied. There parameters are in general consistent with those reflected in the CHMP "NfG on lipid lowering agents CPMP/EWP/3020/03" and "Draft Guidance on lipid lowering agents EMA/CPMP/3020/2003".

Sample size

Based upon prior clinical study experience with mipomersen, it was estimated that the standard deviation of the percent change in LDL-C is approximately 22%. With 15 patients in the control group and 30 patients in the mipomersen-treated group, this study would have at least 80% power to detect a 20-percent point difference between the 2 treatment groups. The pivotal studies (ISIS301012-CS5 and MIPO3500108) were designed to have at least 80% power, with additional patients to allow for patient withdrawals and potential exclusions from analysis sets (51 randomised in ISIS301012-CS5 and 58 randomised in MIPO3500108). Power calculation to detect a statistical difference in the treatment effect is considered appropriate.

Randomisation

Eligible patients were randomised in a 2:1 ratio using an Interactive Voice Response System (IVRS) to receive mipomersen SC once weekly or placebo SC once weekly, respectively.

Blinding (masking)

Laboratory analyses for lipid data were performed at a central laboratory and results were not available to the subjects, investigators, study staff, or the sponsor until the study was unblinded after database lock. Because mipomersen treatment resulted in a higher level of injection site reactions (ISRs) than placebo, it is possible that investigators, study staff, or subjects may have surmised whether subjects were treated with mipomersen or placebo. However, since the efficacy results were not available until after database lock, there was no potential for direct bias in the efficacy results as a result of these assumptions.

Statistical methods

The primary analysis of efficacy parameters was the assessment of percent change from baseline to the primary efficacy timepoint compared between treatment groups. Both, the 2-sample t-test and the Wilcoxon rank sum test were assessed for the comparison between treatment groups. Changes within treatment groups were assessed using the Wilcoxon signed rank test. Additional descriptive tabulations of categories of percent change from baseline to the PET were provided by treatment group. For analyses at each follow-up visit, if multiple values were recorded during a visit window, the average of all assessments was used to provide the most robust estimate of a patient's lipid profile during that period of the study. The secondary efficacy endpoints and the tertiary efficacy endpoints (percent changes in TG, Lp(a), VLDL-C, LDL-C/HDL-C ratio, apo A1, and HDL-C from baseline at the PET) were analysed in a similar manner as the primary endpoint.

Results

Participant flow

The participant flow in the two pivotal trials is described in the table below. A total of 73 patients received mipomersen and 36 patients received placebo in the 2 pivotal Phase 3 studies. There was an imbalance in the percentage of patients who discontinued treatment: mipomersen arms 17.6% in ISIS301012-CS5 and 30.8% in MIPO3500108 versus placebo 0% in ISIS301012-CS5 and 5.3% in MIPO3500108, respectively. The imbalance was mainly due to discontinuations due to AEs.

	Study Number			
	CS5 (HoFH)		MIPO35 (Severe HeFH)	
	Placebo N=17	Mipo N=34	Placebo N=19	Mipo N=39
Randomised, n	17	34	19	39
Treated, n (% of randomised)	17 (100.0)	34 (100.0)	19 (100.0)	39 (100.0)
Completed treatment, n (% of randomised)	17 (100.0)	28 (82.4)	18 (94.7)	27 (69.2)
Enrolled in open-label extension study	16 (94.1)	23 (67.6)	3 (15.8)	6 (15.4)
Completed follow-up, n (% of randomised)	0 (0.0)	5 (14.7)	15 (78.9)	19 (48.7)
Discontinued follow-up, n (% of randomised)	1 (5.9)	0 (0.0)	0 (0.0)	2 (5.1)
Withdrawal by patient	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued treatment, n (% of randomised)	0 (0.0)	6 (17.6)	1 (5.3)	12 (30.8)
AE or SAE	0 (0.0)	4 (11.8)	1 (5.3)	8 (20.5)
Physician decision	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)
Withdrawal by patient	0 (0.0)	1 (2.9)	0 (0.0)	2 (5.1)
Other	0 (0.0)	1 (2.9)	0 (0.0)	1 (2.6)
Protocol non-compliance	0 (0.0)	1 (2.9)	0 (0.0)	1 (2.6)
Completed follow-up, n (% of randomised)	0 (0.0)	1 (2.9)	0 (0.0)	9 (23.1)
Discontinued follow-up, n (% of randomised)	0 (0.0)	5 (14.7)	1 (5.3)	3 (7.7)
Other	0 (0.0)	1 (2.9)	1 (5.3)	0 (0.0)
Protocol non-compliance	0 (0.0)	1 (2.9)	0 (0.0)	1 (2.6)
Withdrawal by patient	0 (0.0)	3 (8.8)	0 (0.0)	2 (5.1)

Recruitment

The phase 3 studies were conducted in nine countries: Study ISIS 301012-CS5 was conducted at nine study centres in seven countries (Brazil, Canada, Singapore, South Africa, Taiwan, United States, and the UK). Study MIPO3500108 was conducted at 26 study centres in six countries (Canada, Czech Republic, Germany, South Africa, United States, and the UK). Both studies were conducted between 2007 and 2010.

Conduct of the study

Study ISIS 301012-CS5: There were 3 amendments to the original protocol, dated 18 July 2005. Amendment 1 included several modifications in the study design, such as in the inclusion/exclusion criteria, stratification, etc. These modifications correspond to the final protocol as described previously. No patients were enrolled into the study under the original protocol or Amendment 1. Amendment 2 prolonged study period from 13 to 26 weeks and assessment of primary endpoint from 15 to 28 weeks. Amendment 3 was a change in study sponsor.

Study MIPO3500108: There were 2 amendments to the original protocol. Amendment 1 simplified the study design to include a single LDL-C entry criterion for patients with coronary artery disease. Amendment 2 to the protocol allowed inclusion of patients with other atherosclerotic diseases (PAD, symptomatic carotid artery disease, or AAA) who met similar LDL-C entry criteria as those with CHD.

Baseline data

Baseline levels were well-matched between treatment groups within each study as summarised in the table below. In both studies, mean baseline LDL-C levels were high for both treatment groups, reflective of the population under study. The mean baseline LDL-C values qualify these patients to undergo apheresis in many countries.

Demographics and Baseline Characteristics (Safety Set)

	Study Number			
	CS5 (HoFH)		MIPO35 (Severe HeFH)	
	Placebo N=17	Mipo N=34	Placebo N=19	Mipo N=39
Median age, years (range)	38 (12–53)	27 (14–53)	52 (18 - 66)	51 (21 - 77)
Sex, % male	41.2%	44.1%	36.8%	46.2%
Race				
White	76.5%	73.5%	84.2%	84.6%
Asian	17.6%	23.5%	0	2.6%
Black	5.9%	2.9%	5.3%	5.1%
Multiple	0	0	10.5%	2.6%
Other	0	0	0	5.1%
Median BMI, kg/m^2 (Q1, Q3)	26.4 (23.1, 29.6)	25.4 (21.6, 29.5)	29.7 (26.1, 33.8)	28.0 (24.8, 31.0)
Mean Baseline LDL-C	400.2 mg/dL (10.37 mmol/L)	438.9 mg/dL (11.37 mmol/L)	249.4 mg/dL (6.46 mmol/L)	276.1 mg/dL (7.15 mmol/L)
Median Baseline TG	92 mg/dL (1.04 mmol/L)	91 mg/dL (1.03 mmol/L)	139 mg/dL (1.57 mmol/L)	125 mg/dL (1.41 mmol/L)

BMI, body mass index; HeFH, Heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesteroaemia; LDL-C, low density lipoprotein cholesterol; TG, triglycerides.

Numbers analysed

All efficacy parameters were assessed on the Per-Protocol Set (PPS) and Full Analysis Set (FAS), with the latter being the basis for the primary efficacy analysis. The FAS, which represented the practically-feasible intent-to-treat (ITT) population as delineated in ICH Guideline E9, consisted of the subset of the safety data with a valid baseline and at least one post-baseline LDL-C measure. The PPS consisted of the subset of the FAS with no significant protocol deviations that would be expected to bias the patient's efficacy assessments. It is appropriate to consider the ITT population as the population being the basis for efficacy evaluation. The impact of the larger proportion of patients discontinuing in the mipomersen group dilutes the effect and is therefore considered by the CHMP the most conservative approach.

Outcomes and estimation

Primary efficacy endpoint (change in LDL-C level)

The primary efficacy results from the pivotal studies (ISIS 303012-CS5 and MIPO3500108) show that treatment with mipomersen resulted in a decline of 24.7% to 35.9% in LDL-C levels at PET versus baseline. This approximately corresponds to a reduction by 21% to 48% when corrected with placebo in studies CS5 and MIPO35, respectively as summarised in the table below. The treatment differences compared with placebo were statistically significant in both studies (p <0.001).

Percent Change in LDL Cholesterol from Baseline to the Primary Efficacy Time Point (Gravimetric Units) – Full Analysis Set

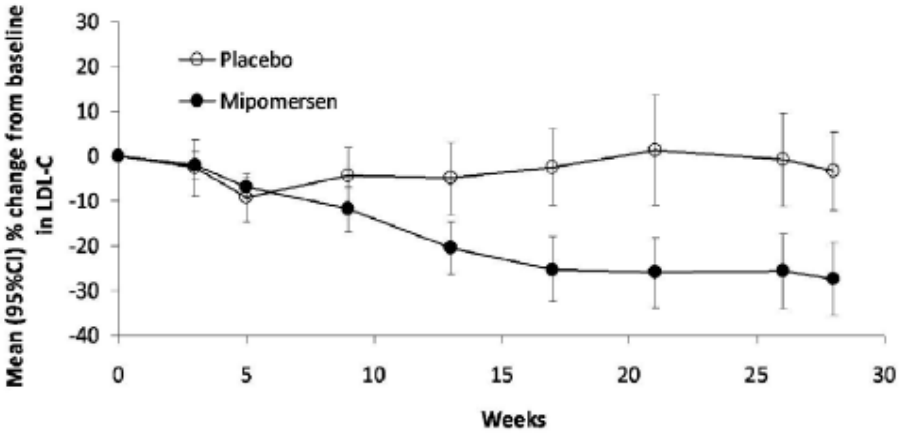
	STUDY NUMBER					
	CS5 (HoFH)			MIPO35 (Severe HeFH)		
	Placebo N=17	Mipo N=34	p	Placebo N=18	Mipo N=39	p
Mean (SD) LDL-C at baseline, mg/dL	400.2 (141.5)	438.9 (138.6)		249.4 (84.3)	276.1 (72.1)	
Mean (SD) LDL-C at PET, mg/dL	388.2 (150.5)	326.2 (121.3)		263.9 (102.0)	174.9 (82.8)	
Mean (SD) % change from baseline to PET	-3.3 (17.06)	-24.7 (19.85)	<0.001	12.5 (46.87)	-35.9 (24.71)	<0.001

p-values are from 2-sample t-test
HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia; LDL-C, low density lipoprotein cholesterol; PET, primary efficacy timepoint, SD, standard deviation

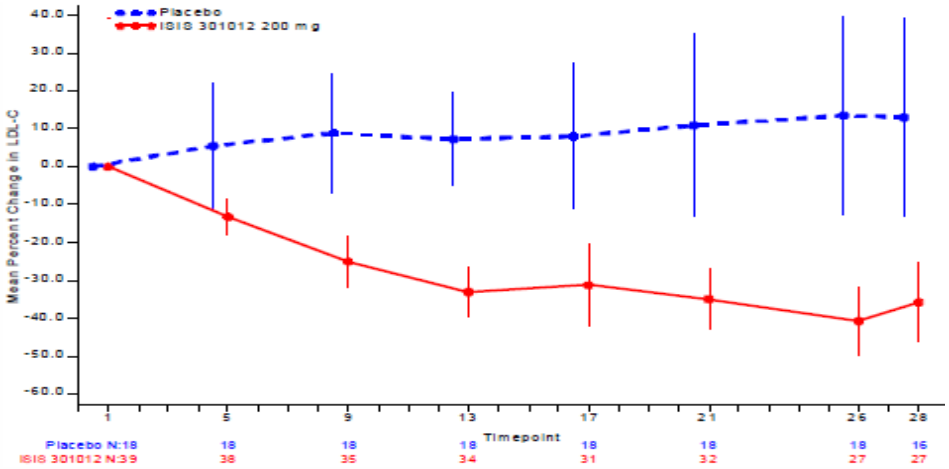
The figure below shows the mean percent change in LDL-C over time in ISIS 301012-CS5 (a) and MIPO3500108 (b), respectively. In ISIS 301012-CS5, a progressive decrease in LDL-C levels was observed in the mipomersen group over approximately the first 16 weeks of treatment. From week 17 to week 28, the LDL-C levels remained generally stable. In the mipomersen group of MIPO3500108, the observed decrease in LDL-C levels was generally progressive from baseline to week 26. From week 26 to week 28 (2 weeks after the last dose of study drug), a slight increase in LDL-C was observed. In the placebo group, LDL-C level increased slightly from baseline to end of follow-up at week 28.

Mean Percent Change in LDL Cholesterol in Patients from Studies Study ISIS 301012-CS5 (a) and MIPO03500108 (b) – Full Analysis Set

a) Study ISIS 301012-CS5



b) Study MIPO3500108



Lipid response categories

As indicated in the table below, approximately 59% and 79% of patients in the mipomersen groups of ISIS 301012-CS5 and MIPO3500108, respectively, had at least a 15% decrease in lipid levels from baseline to PET, compared with only 24% (ISIS 301012-CS5) or 17% (MIPO3500108) of patients in the placebo groups. Four (11.8%) patients in the mipomersen group in ISIS 301012-CS5 and 10 (25.6%) in MIPO3500108 had a >50% decrease in lipid levels from baseline to PET; no patients in either placebo group had a >50% decrease. Some increases in LDL-C were noted, primarily in the placebo groups (47.1% of placebo patients in ISIS 301012-CS5 and 55.6% in MIPO3500108, as compared with 5.9% and 7.7% of mipomersen-treated patients, respectively).

Categories of Lipid Response
(Percent Change From Baseline to the Primary Efficacy Time Point) – Full Analysis Set

	STUDY NUMBER			
	CS5 (HoFH)		MIPO35 (Severe HeFH)	
	Placebo N=17	Mipo N=34	Placebo N=18	Mipo N=39
Increase	8 (47.1)	2 (5.9)	10 (55.6)	3 (7.7)
0% to 5% decrease	1 (5.9)	2 (5.9)	4 (22.2)	3 (7.7)
>5% to 10% decrease	2 (11.8)	3 (8.8)	1 (5.6)	1 (2.6)
>10% to 15% decrease	2 (11.8)	7 (20.6)	0 (0.0)	1 (2.6)
>15% to 20% decrease	2 (11.8)	3 (8.8)	0 (0.0)	4 (10.3)
>20% to 25% decrease	1 (5.9)	3 (8.8)	0 (0.0)	1 (2.6)
>25% to 30% decrease	0 (0.0)	3 (8.8)	1 (5.6)	1 (2.6)
>30% to 35% decrease	1 (5.9)	3 (8.8)	0 (0.0)	3 (7.7)
>35% to 40% decrease	0 (0.0)	2 (5.9)	1 (5.6)	2 (5.1)
>40% to 45% decrease	0 (0.0)	1 (2.9)	1 (5.6)	4 (10.3)
>45% to 50% decrease	0 (0.0)	1 (2.9)	0 (0.0)	6 (15.4)
>50% decrease	0 (0.0)	4 (11.8)	0 (0.0)	10 (25.6)

Secondary and tertiary endpoints

Statistically significant percent reductions with mipomersen compared to placebo were observed for the secondary efficacy variables apo B, TC, and non HDL-C from baseline to PET.

Secondary Efficacy Results (Gravimetric Units) – Full Analysis Set

	STUDY NUMBER					
	CS5 (HoFH)			MIPO35 (Severe HeFH)		
	Placebo N=17	Mipo N=34	p	Placebo N=18	Mipo N=39	p
Apolipoprotein B-100, mean (SD)						
Apo B at baseline (mg/dL)	259.2 (84.4)	283.1 (78.4)		182.8 (48.6)	202.1 (49.1)	
Apo B at PET (mg/dL)	252.6 (85.0)	205.4 (70.0)		193.7 (54.2)	126.8 (49.6)	
% change in Apo B from baseline to PET	-2.5 (12.56)	-26.8 (17.04)	<0.001	11.4 (36.80)	-35.9 (22.95)	<0.001
Total cholesterol, mean (SD)						
TC at baseline (mg/dL)	460.5 (132.0)	502.4 (144.5)		320.6 (87.2)	356.8 (77.0)	
TC at PET (mg/dL)	452.1 (144.6)	389.7 (125.3)		341.5 (100.5)	251.5 (82.2)	
% change in TC from baseline to PET	-1.98 (14.82)	-21.20 (17.69)	<0.001	11.13 (34.74)	-28.31 (20.43)	<0.001
Non HDL-C, mean (SD)						
non-HDL-C at baseline (mg/dL)	418.9 (144.5)	464.3 (145.4)		277.5 (88.3)	305.6 (78.3)	
non-HDL-C at PET (mg/dL)	409.1 (156.6)	345.8 (126.6)		296.7 (103.8)	198.1 (85.3)	
% change in non-HDL-C from baseline to PET	-2.90 (16.32)	-24.50 (19.17)	<0.001	14.17 (47.75)	-33.95 (23.80)	<0.001

p-values are from 2-sample t-test
Apo B, apolipoprotein B; HDL-C, high density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia; PET, primary efficacy timepoint; TC, total cholesterol

Statistically significant percent reductions in Lp(a) were noted in mipomersen-treated patients compared to placebo-treated patients, as was the case for reductions in LDL-C/HDL-C ratio from

baseline to PET. Reductions in TG and VLDL-C were also observed, but were not consistently statistically significant. Changes in apo A-I were not statistically significant or clinically meaningful. Statistically significant increase in HDL-C was observed in ISIS 301012-CS5 but not in MIPO3500108

Ancillary analyses

Comparison of Efficacy Results in Subpopulations

Effect of gender: Regression analyses were performed to assess the impact of the following demographic and baseline characteristics: baseline LDL-C value, age, gender, and race (White or Non-White). In study ISIS 301012-CS5, results of the linear regression analyses showed homogeneity across the factors measured (baseline LDL-C value, age, sex, and race), with no appreciable confounding relationships. No trends were evident for the relationship of endpoint LDL-C (i.e., LDL-C response) with baseline LDL-C, TG, concomitant lipid-lowering therapy, and genotype. In study MIPO3500108, the effect of treatment on LDL-C was influenced by gender. There was a more pronounced effect in females than in males, though a significant mipomersen reduction in LDL-C was also observed among males. For females, the mean percent change in LDL-C from baseline to the PET was -43.6% for the mipomersen group and +29.9% for the placebo group; the percent change from baseline to the PET for female patients in the mipomersen group was statistically significant. For males, the mean percent change in LDL-C from baseline to the PET was -27.0% for the mipomersen group and -14.7% for the placebo group; the percent change from baseline to the PET for male patients in the mipomersen group was statistically significant.

Results in elderly patients: Ten patients in the pivotal trials were aged 65 or older, all from MIPO3500108 (2 placebo-treated and 8 mipomersen-treated patients). Of the 8 mipomersen-treated patients, one discontinued due to an AE after one week of study treatment, another demonstrated a change in LDL-C of -0.7% at PET, and the other six had changes in LDL-C ranging from -30.8 to -70.0% at PET. Due to the small numbers of elderly patients in these studies, no clear conclusion can be drawn at this time regarding differences in efficacy in elderly patients as compared with the general population. The proposed SmPC would acknowledge the limited data in this population.

Results in paediatric patients: The inclusion criteria of ISIS 301012-CS5 allowed the enrolment of children aged 12 years and over. Of the 51 randomised patients, 7 were adolescents, 3 of whom were randomised to mipomersen and 4 to placebo. Although a dose adjustment was allowed for patients below 50 kg (to 160 mg mipomersen once weekly), all of the mipomersen-treated children in ISIS 301012-CS5 were above 50 kg (range, 55 to 61 kg; aged between 14 and 16 years), so all were treated with 200 mg mipomersen sodium once weekly. During ISIS 301012-CS5, mipomersen resulted in changes in LDL-C from -30.8% to -62.0% in the 3 mipomersen-treated adolescent patients. The percent change in LDL-C in the 4 placebo-treated patients ranged from -7.9% to 43.1%. After week 28, the 7 adolescent patients from ISIS 301012-CS5 enrolled in an open label extension (ISIS 301012-CS6). The 3 patients who were receiving mipomersen in ISIS 303012 CS5 continued to receive 200 mg mipomersen sodium once weekly. The percent change in LDL-C as of their last dose of mipomersen ranged from -35.9% to 3.9% in these 3 patients. The 4 placebo patients from ISIS 301012-CS5 were assigned to receive mipomersen sodium at 200 mg once weekly (3 patients) or 160 mg once weekly (1 patient at 45.8 kg; 13 years of age) in ISIS 301012-CS6. Changes in LDL-C in these patients as of their last dose of mipomersen ranged from -42.1% to 11.2%). There is insufficient information to conclude that data in children show a similar pattern of efficacy and safety to that seen in adults. The proposed SmPC would acknowledge the insufficient data in children and no recommendation of use in this population.

Summary of main studies

The following table summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Efficacy for pivotal trials

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment.

Title: ***RADICHOL I: A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of ISIS 301012 as Add-on Therapy in Homozygous Familial Hypercholesterolemia Subjects***			
Study identifier	ISIS 301012-CS5		
Design	Randomised, double-blind, placebo-controlled		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		26 weeks ≤ 4-week screening period 24-week post-treatment follow-up period (with the exception of patients who enrolled in the open-label extension study, ISIS 301012-CS6).
Hypothesis	Superiority		
Treatments groups	experimental		200 mg mipomersen (160 mg for patients weighing <50 kg) weekly SC for 26 weeks
	control		placebo weekly SC for 26 weeks
Endpoints and definitions	Primary endpoint	LDL-C	Percent reduction in LDL-C from baseline at the primary efficacy time point (PET). The PET was defined as the post-baseline visit closest to 14 days after the last dose of study treatment for which LDL-C was assessed (i.e., 2 weeks after the last dose for patients who did not complete the 26 weeks of treatment, or week 28 for patients who completed the treatment period).
	Secondary	apo B, total cholesterol, non-HDL-C,	Percent reduction from baseline at the PET
Database lock	25 March 2009		
Results and Analysis			
Analysis description	**Primary Analysis (change in mean LDL-C)**		
Analysis population and time point description	Modified ITT (FAS: the Full Analysis Set included all randomized patients who received at least 1 injection of the study drug, and had a valid baseline and at least 1 post-baseline measurement). Time point: PET		
Descriptive statistics	Treatment group	mipomersen	placebo

and estimate variability	Number of subject	34	17
	Mean (SD) **LDL-C** at baseline, mg/dl	438.9 (138.6)	400.2 (141.5)
	Mean (SD) **LDL-C** at PET, mg/dl	326.2 (121.3)	388.2 (150.5)
Effect estimate per comparison	Mean (SD) **LDL-C change** from baseline to PET, %	-24.7 (19.85)	-3.3 (17.06)
	p-value*	**< 0.001**	
Analysis description	**Secondary analysis 1 (change in mean Apo B)**		
Analysis population and time point description	Same as primary analysis		
Descriptive statistics and estimate variability	Treatment group	mipomersen	placebo
	Number of subject	34	17
	Mean (SD) **Apo B** at baseline, mg/dl	283.1 (78.4)	259.2 (84.4)
	Mean (SD) **Apo B** at PET, mg/dl	205.4 (70.0)	252.6 (85.0)
Effect estimate per comparison	Mean (SD) **Apo B change** from baseline to PET, %	-26.8 (17.04)	-2.5 (12.56)
	p-value*	**< 0.001**	
Analysis description	**Secondary analysis 2 [change in mean Total Cholesterol (TC)]**		
Analysis population and time point description	Same as primary analysis		
Descriptive statistics and estimate variability	Treatment group	mipomersen	placebo
	Number of subject	34	17
	Mean (SD) **TC** at baseline, mg/dl	502.4 (144.5)	460.5 (132.0)
	Mean (SD) **TC** at PET, mg/dl	389.7 (125.3)	452.1 (144.6)
Effect estimate per comparison	Mean (SD) **TC change** from baseline to PET, %	-21.20 (17.69)	-1.98 (14.82)
	p-value*	**< 0.001**	
Analysis description	**Secondary analysis 3 (change in mean non-HDL-C)**		
Analysis population and time point description	Same as primary analysis		
Descriptive statistics and estimate variability	Treatment group	mipomersen	placebo
	Number of subject	34	17
	Mean (SD) **non-HDL-C** at baseline, mg/dl	464.3 (145.4)	418.9 (144.5)
	Mean (SD) **non-HDL-C** at PET, mg/dl	345.8 (126.6)	409.1 (156.6)
Effect estimate per comparison	Mean (SD) **non-HDL-C** from baseline to PET, %	-24.50 (19.17)	-2.90 (16.32)
	p-value*	**< 0.001**	

Title: ***A Prospective, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of Mipomersen in Patients With Severe Hypercholesterolemia on a Maximally Tolerated Lipid-Lowering Regimen and Who are Not on Apheresis***			
Study identifier	MIPO3500108		
Design	Randomised, double-blind, placebo-controlled		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		26 weeks ≤ 4-week screening period 24-week post-treatment follow-up period (with the exception of patients who enrolled in the open-label extension study, ISIS 301012-CS6).
Hypothesis	Superiority		
Treatments groups	experimental		200 mg mipomersen weekly SC for 26 weeks
	control		placebo weekly SC for 26 weeks
Endpoints and definitions	Primary endpoint	LDL-C	Percent reduction in LDL-C from baseline at the primary efficacy time point (PET). The PET was defined as the post-baseline visit closest to 14 days after the last dose of study treatment for which LDL-C was assessed (i.e., 2 weeks after the last dose for patients who did not complete the 26 weeks of treatment, or week 28 for patients who completed the treatment period).
	Secondary	apo B, total cholesterol, non-HDL-C,	Percent reduction from baseline at the PET
Database lock	14 October 2010		

Results and Analysis

Analysis description	**Primary Analysis (change in mean LDL-C)**		
Analysis population and time point description	Modified ITT (FAS: the Full Analysis Set included all randomized patients who received at least 1 injection of the study drug, and had a valid baseline and at least 1 post-baseline measurement). Time point: PET		
Descriptive statistics and estimate variability	Treatment group	mipomersen	placebo
	Number of subject	39	18
	Mean (SD) **LDL-C** at baseline, mg/dl	276.1 (72.1)	249.4 (84.3)
	Mean (SD) **LDL-C** at PET, mg/dl	174.9 (82.8)	263.9 (102.0)
Effect estimate per comparison	Mean (SD) **LDL-C change** from baseline to PET, %	-35.9 (24.71)	12.5 (46.87)
	p-value*	**< 0.001**	
Analysis description	**Secondary analysis 1 (change in mean Apo B)**		
Analysis population and time point description	Same as primary analysis		

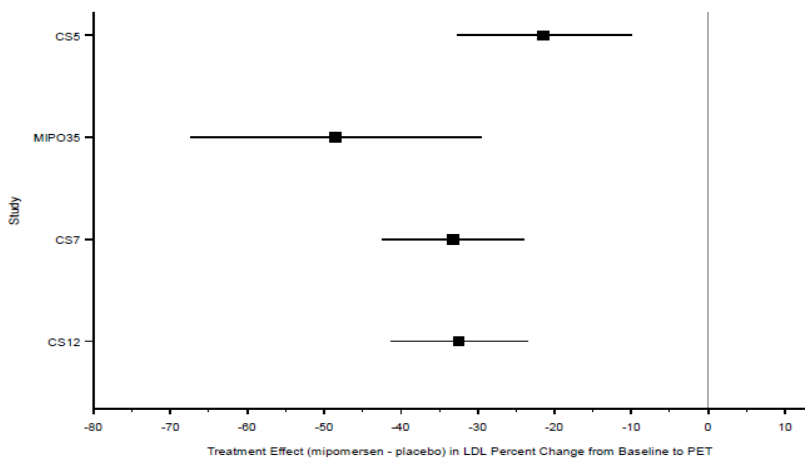
Descriptive statistics and estimate variability	Treatment group	mipomersen	placebo
	Number of subject	39	18
	Mean (SD) **Apo B** at baseline, mg/dl	202.1 (49.1)	182.8 (48.6)
	Mean (SD) **Apo B** at PET, mg/dl	126.8 (49.6)	193.7 (54.2)
Effect estimate per comparison	Mean (SD) **Apo B change** from baseline to PET, %	-35.9 (22.95)	11.4 (36.80)
	p-value*	**< 0.001**	
Analysis description	**Secondary analysis 2 [change in mean Total Cholesterol (TC)]**		
Analysis population and time point description	Same as primary analysis		
Descriptive statistics and estimate variability	Treatment group	mipomersen	placebo
	Number of subject	39	18
	Mean (SD) **TC** at baseline, mg/dl	356.8 (77.0)	320.6 (87.2)
	Mean (SD) **TC** at PET, mg/dl	251.5 (82.2)	341.5 (100.5)
Effect estimate per comparison	Mean (SD) **TC change** from baseline to PET, %	-28.31 (20.43)	11.13 (34.74)
	p-value*	**< 0.001**	
Analysis description	**Secondary analysis 3 (change in mean non-HDL-C)**		
Analysis population and time point description	Same as primary analysis		
Descriptive statistics and estimate variability	Treatment group	mipomersen	placebo
	Number of subject	39	18
	Mean (SD) **non-HDL-C** at baseline, mg/dl	305.6 (78.3)	277.5 (88.3)
	Mean (SD) **non-HDL-C** at PET, mg/dl	198.1 (85.3)	296.7 (103.8)
Effect estimate per comparison	Mean (SD) **non-HDL-C** from baseline to PET, %	-33.95 (23.80)	14.17 (47.75)
	p-value*	**< 0.001**	

*Both the 2-sample t-test and the Wilcoxon rank sum test were obtained for the comparison between treatment groups. If the Kolmogorov-Smirnov test of normality was not statistically significant ($p>0.05$), then the mean and the 2-sample t-test were used. Otherwise, the median and the Wilcoxon rank sum test were utilized.

Analysis performed across trials (pooled analyses and meta-analysis)

The treatment effect of mipomersen (the effect in mipomersen-treated patients minus the effect in placebo-treated patients) was consistent across all four phase 3 studies. Ancillary analyses show that the lipid-lowering effect was consistent across different geographic regions, as shown in the figure below.

LDL-C Percent Change from Baseline to PET Treatment Effects (difference between mipomersen and placebo) and 95% CI for phase 3 clinical studies—full analysis set



Clinical studies in special populations

Statin-Intolerant Patients: Randomised, double-blind, placebo-controlled, single-centre phase 2 study (ISIS 301012-CS19) was conducted in order to assess the safety and efficacy of mipomersen administration in high-risk statin-intolerant patients (patients unable to tolerate any dose of a statin due to any form of side effects, with the exception of clinically significant ALT elevations). This study has been recently completed. Patients were randomised in a 2:1 manner to receive either mipomersen 200 mg SC (n=22) or placebo (n=12) for 26 weeks, followed by a 24-week follow-up period. Discontinuations were similar between the treatment groups: 2/12 placebo patients (17%) and 5/22 mipomersen patients (22.7%) discontinued, 4 due to AEs and 1 due to ineligibility. Significant reductions in lipid parameters were seen with mipomersen treatment; the mean percent reductions from baseline in LDL-C and apo B were consistent with, but generally greater than, those observed during the 26-week, double blind treatment periods of the index studies.

Supportive studies

Two additional phase 3 studies and two open-label extension studies are included as supportive of the pivotal studies in the submitted dossier and are described and discussed below.

Study ISIS 301012-CS7: RADICHOL II: A Randomized, Double-Blind, Placebo-Controlled Study to Assess Efficacy and Safety of mipomersenas Add-on Therapy in Heterozygous Familial Hypercholesterolemia Subjects With Coronary Artery Disease

This was an international, multicenter study conducted in a total of 26 study centres in the US and Canada and included 124 patients (84 on mipomersen and 41 on placebo). Ten (8.1%) patients, all in the mipomersen group, discontinued treatment during the treatment period.

Weekly treatment with 200 mg mipomersen sodium for 26 weeks in patients with HeFH and CAD resulted in a significant mean percent reduction in LDL-C from baseline to the PET compared to placebo treatment (-28.0% versus 5.2%; p<0.001). Levels of LDL-C were progressively reduced during the 26-week treatment period. The treatment effect was influenced by gender. There was a more pronounced effect in females, although the effect in males was still statistically significant. Statistically significant percent reductions with mipomersen compared to placebo were observed for the secondary efficacy variables apo B, TC, and non HDL-C, and for the tertiary variables TG, Lp(a), VLDL-C, and LDL-C/HDL-C ratio, while there was a statistically significant increase in apo A1 in the mipomersen group. There were no clinically meaningful changes in HDL-C in either treatment group.

Study ISIS 301012-CS12: A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of ISIS 301012 (mipomersen) as Add-on Therapy in High Risk Hypercholesterolemic Patients

This study was conducted at 43 study centres in the US. Once weekly treatment with mipomersen sodium 200 mg for 26 weeks in hypercholesterolaemic patients on a maximally tolerated dose of a statin and at high risk of CHD events, including patients with CHD or a CHD risk equivalent, resulted in significant mean percent reductions in LDL-C from baseline to the PET compared to placebo treatment (mean percent change in LDL-C: mipomersen -36.9% vs. placebo -4.5%). Levels of LDL-C were progressively reduced through the first 17 weeks of treatment and remained relatively stable thereafter. Results of the linear regression analyses showed that the effect of treatment on LDL-C was dependent on gender and age. There was a more pronounced effect in females and in patients with age above the median. Significant percent reductions with mipomersen compared to placebo were observed for the secondary efficacy variables apo B, TC, and non HDL-C, and for the tertiary variables TG, Lp(a), VLDL-C, and LDL-C/HDL-C ratio. There were no meaningful changes in HDL-C in either treatment group. In patients with diabetes, the mean percent change in LDL-C was -40.5% in the mipomersen group and -4.9% in the placebo group. In patients without diabetes, the mean percent change in LDL-C was -32.4% in the mipomersen group and -4.0% in the placebo group.

Study ISIS 301012-CS6: An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 301012 in Patients with Familial hypercholesterolemia or Severe Hypercholesterolemia (Data through cut-off date of 30 November 2011)

An ongoing, open-label, extension study (ISIS 301012-CS6) is evaluating the safety and efficacy of extended dosing with mipomersen in 141 patients with FH or severe hypercholesterolemia on concomitant lipid-lowering therapy who had previously completed study ISIS 301012-CS5, MIPO3500108, or ISIS 301012-CS7. In ISIS 301012-CS6, some patients consented to 1 year of treatment while others consented to 2 years of treatment. Because this study is ongoing, and patients enrolled at different times, the numbers of patients providing measurements in the second year of treatment were smaller than in the first year and varied at each time point. Baseline measurement of lipid parameters was defined as the last value prior to receiving mipomersen in ISIS 301012-CS6 for patients who had received placebo in their index study or who had last received mipomersen ≥6 months prior to receiving mipomersen in ISIS 301012-CS6. The total discontinuation rate was 56.0%. A differential withdrawal rate in patients who consented to 1 year treatment (73% of patients (29 of 40) discontinued prior to completing 1 year), and patients who consented 2 year treatment (48% (48 of 101 patients) discontinued prior to completing 2 years) was observed. Data on withdrawals were provided separately for patients with severe and non-severe hypercholesterolemia. Patients with severe hypercholesterolemia, which is likely to be considered the target population, showed a high rate of withdrawals [62% (34 of 56)]. Patients with non-severe hypercholesterolemia treated with mipomersen also had a 52% withdrawal rate (45 of 86 patients). The vast majority of these withdrawals were due to adverse reactions (see tables below).

Study ISIS 301012-CS6
Patient Disposition by Treatment Group in Index Studies
All Enrolled Patients with Severe Hypercholesterolemia

	Placebo (N=23)	ISIS 301012 200 mg QW (N=33)	Total (N=56)
Enrolled, n	23	33	56
Never treated, n (% of enrolled)	0 (0.0)	1 (3.0)	1 (1.8)
Treated, n (% of enrolled)	23 (100.0)	32 (97.0)	55 (98.2)
Completed up to 2 years of initial treatment, n (% of treated)	9 (39.1)	12 (37.5)	21 (38.2)
Completed follow-up, n (% of treated)	6 (26.1)	8 (25.0)	14 (25.5)
Discontinued follow-up, n (% of treated)	2 (8.7)	1 (3.1)	3 (5.5)
ADVERSE EVENT OR SAE	0 (0.0)	1 (3.1)	1 (1.8)
OTHER	2 (8.7)	0 (0.0)	2 (3.6)
Continuing follow-up, n (% of treated)	1 (4.3)	3 (9.4)	4 (7.3)
Discontinued prior to completing up to 2 years of initial treatment, n (% of treated)	14 (60.9)	20 (62.5)	34 (61.8)
ADVERSE EVENT OR SAE	13 (56.5)	15 (46.9)	28 (50.9)
PREGNANCY	0 (0.0)	1 (3.1)	1 (1.8)
WITHDRAWAL BY SUBJECT	1 (4.3)	4 (12.5)	5 (9.1)
Completed follow-up, n (% of treated)	13 (56.5)	16 (50.0)	29 (52.7)
Discontinued follow-up, n (% of treated)	1 (4.3)	4 (12.5)	5 (9.1)
ADVERSE EVENT OR SAE	1 (4.3)	0 (0.0)	1 (1.8)
WITHDRAWAL BY SUBJECT	0 (0.0)	2 (6.3)	2 (3.6)
OTHER	0 (0.0)	2 (6.3)	2 (3.6)
Continuing follow-up, n (% of treated)	0 (0.0)	0 (0.0)	0 (0.0)

Study ISIS 301012-CS6
Patient Disposition by Treatment Group in Index Studies
Enrolled Patients with Non-Severe Hypercholesterolemia

	Placebo (N=35)	ISIS 301012 200 mg QW (N=51)	Total (N=86)
Enrolled, n	35	51	86
Never treated, n (% of enrolled)	0 (0.0)	0 (0.0)	0 (0.0)
Treated, n (% of enrolled)	35 (100.0)	51 (100.0)	86 (100.0)
Completed up to 2 years of initial treatment, n (% of treated)	14 (40.0)	25 (49.0)	39 (45.3)
Completed follow-up, n (% of treated)	4 (11.4)	5 (9.8)	9 (10.5)
Discontinued follow-up, n (% of treated)	5 (14.3)	12 (23.5)	17 (19.8)
OTHER	5 (14.3)	12 (23.5)	17 (19.8)
Continuing follow-up, n (% of treated)	5 (14.3)	8 (15.7)	13 (15.1)
Discontinued prior to completing up to 2 years of initial treatment, n (% of treated)	19 (54.3)	26 (51.0)	45 (52.3)
ADVERSE EVENT OR SAE	15 (42.9)	19 (37.3)	34 (39.5)
LACK OF EFFICACY	1 (2.9)	1 (2.0)	2 (2.3)
PHYSICIAN DECISION	1 (2.9)	1 (2.0)	2 (2.3)
WITHDRAWAL BY SUBJECT	2 (5.7)	5 (9.8)	7 (8.1)
Completed follow-up, n (% of treated)	12 (34.3)	19 (37.3)	31 (36.0)
Discontinued follow-up, n (% of treated)	5 (14.3)	5 (9.8)	10 (11.6)
ADVERSE EVENT OR SAE	2 (5.7)	0 (0.0)	2 (2.3)
PHYSICIAN DECISION	1 (2.9)	1 (2.0)	2 (2.3)
WITHDRAWAL BY SUBJECT	2 (5.7)	3 (5.9)	5 (5.8)
OTHER	0 (0.0)	1 (2.0)	1 (1.2)
Continuing follow-up, n (% of treated)	2 (5.7)	2 (3.9)	4 (4.7)

As seen in other phase 3 studies, a progressive decrease in LDL-C levels was observed during the first 21 weeks of treatment. From week 21 to week 156, LDL-C levels were generally stable. For patients who discontinued treatment, by 24 weeks post-dose, mean percent change in LDL-C from baseline was 1.1%. The numbers of patients who provided measurements in the second year of treatment and post-treatment follow-up period were smaller than in the first year of treatment and varied at each time point.

The retention rate with mipomersen in HoFH patients was 8% at 3 years (3 out of 38). A total of 63% (24 out of 38) withdrew treatment and 29% patients (11 of 38) completed their consent for the first or second year and did not consent a second or third year of treatment. The most common causes leading to discontinuation were adverse events (19 of 24; 79%), including FLS (7 of 24; 29%), ISR, (3 of 24; 13%), FLS and ISR (1 of 24; 12%), increased transaminases (5 of 24; 15%), depression (1 of 24; 4%), urticaria (1 of 24; 4%), and nausea (1 of 24; 4%). The vast majority of withdrawals were due to intolerability. However, despite measures to milder FLS and ISRs, final result was a 63% withdrawal rate due to AEs after 2 years. Therefore, withdrawal rates are not

expected to decrease in standard practise overtime. The reasons beyond withdrawal of consent in the remaining 29% of patients remain unclear, but it may comprise logistical reasons as well as perceived lack of efficacy or tolerability.

Study ISIS 301012-CS17: An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 301012 in Subjects with Familial Hypercholesterolemia (Data through cut-off date of 07 May 2010)

The ISIS 301012-CS17 was an open-label extension study for patients who had previously received treatment in ISIS 301012-CS8 or ISIS 301012-CS9. Patients received 200 mg mipomersen sodium SC either weekly (N = 16) or every other week (N = 5), for up to 2 years. In the patients who received 200 mg weekly, the mean baseline LDL-C was 203.8 mg/dL (5.3 mmol/L). At Week 52, the mean percent change was -22.0% (95% CI, -33.2% to -10.8%). At Week 104, the mean percent change was -29.8% (95% CI, -43.4% to -16.2%). Withdrawal rate at 2 years in patients on mipomersen 200 mg OW were 56.3% (25% due to AEs).

2.5.3. Discussion on clinical efficacy

Four dose-ranging studies (N = 177 treated subjects) and two pivotal placebo-controlled Phase 3 studies (N = 109 total patients) are the main studies to support the efficacy of mipomersen in the requested indication.

Design and conduct of clinical studies

Dose-finding trials: Two phase 2 dose-ranging studies (ISIS 301012-CS3 and ISIS 301012-CS4) included mipomersen doses ranging from 50 mg in CS3, or 30 mg in CS4, to 400 mg in both studies, with treatment durations of 5-13 weeks. Mipomersen produced dose-dependent reductions in circulating concentrations of apo B, accompanied by reductions in LDL-C and non-HDL-C. Results from these studies led to selection of a 200 mg weekly dose for the phase 3 studies, by showing a substantial PD effect at this dose level (>30% reduction in LDL-C after 13 weeks of treatment). A third phase 2 study (ISIS 301012-CS8) failed to show a dose response of mipomersen. However, these results are hampered by the small sample sizes. In this study, mipomersen did not show a significant effect on LDL change in 3 patients on LDL apheresis.

Pivotal studies: Studies ISIS 301012-CS5 (in patients with HoFH; N=51) and MIPO3500108 (in patients with severe HeFH; N=58) were submitted to support the indication requested. The pivotal studies were designed to compare the safety and efficacy of 26 weekly SC injections of 200 mg mipomersen sodium versus placebo in severely hypercholesterolemic patients who were on a maximally tolerated lipid-lowering regimen and who were not on apheresis. After the primary endpoint, patients began a 24-week of safety follow-up period. The treatment period and follow-up period durations (26 and 24 weeks, respectively) were roughly 5 times the $t_{1/2}$ of mipomersen. Randomisation and double-blinding were used to minimise the bias.

Inclusion criteria were acceptable for patients with HoFH and severe HeFH. With respect to exclusion criteria, the CHMP noted that some important populations were excluded, e.g. significant hepatic or renal disease, recent major cardiovascular event, congestive heart failure, recent LDL apheresis, elevated TG. In order to obtain sufficient CV endpoints to allow a meaningful estimate of CV risk, phase 2 and 3 programmes should have included patients at higher risk of cardiovascular events, such as patients with relatively advanced disease, elderly patients, and patients with some degree of renal impairment. Trial ISIS301012-CS5 allowed patients over the age of 12, while in MIPO3500108, patients under the age of 18 were excluded.

This issue is of utmost importance in the case of mipomersen, a medicinal product with a completely novel mechanism of action aimed to target a rather vulnerable population at particular high CV risk.

The analysis of CV AEs and MACE present many limitations as it was not prospectively defined, not defined according to current standards and not independently adjudicated. This inadequate quality of the evaluation, along with the limited sample size and duration of the follow-up, is a major drawback of the dossier for the proper assessment of the effect on CV mortality of mipomersen.

In addition, changes in triglycerides, total cholesterol, HDL-cholesterol and in other lipid parameters, like apolipoprotein A-I, apolipoprotein B, and lipoprotein (a) were also studied. These parameters are in general consistent with those recommended by guidelines on investigation of lipid lowering agents as asupportive evidence of the effect in the lipids profile.

In terms of the methods used for evaluation, the CHMP considered the sample size calculation, definition of populations, as well as the sensitivity of analyses appropriate. The methods used for laboratory assessment of lipid parameters are endorsed. The study amendments are considered to be sufficiently justified and seem adequate.

A total of 73 patients received mipomersen and 36 patients received placebo in the 2 pivotal Phase 3 studies submitted. The HoFH population in ISIS 301012-CS5 was generally younger and had higher baseline LDL-C and TG levels and lower BMI than the HeFH population of MIPO3500108. Baseline levels were well-matched between treatment groups within each study. In both studies, mean baseline LDL-C levels were high for both treatment groups, reflective of the population under study. In pivotal trials, nearly all patients were on high levels of statins, often in combination with other lipid-lowering drugs. However, in MIPO3500108, only 24 (41.4%) patients were on the maximal allowed dose of statin therapy with or without other lipid-lowering medications.

The primary efficacy results from both pivotal studies show that treatment with mipomersen resulted in a statistically significant decline of 24.7% to 35.9% in LDL-C levels at PET versus baseline. This corresponds to a reduction by 21% to 48% with mipomersen when corrected with placebo in studies CS5 and MIPO35, respectively. In absolute terms, it corresponds to a placebo-corrected reduction with mipomersen by -100 to -114 mg/dl LDL-C at PET versus baseline studies CS5 and MIPO35, respectively, which may be considered of clinical relevance. In relative terms, prospective primary and secondary prevention studies with statins have shown reduction in cardiovascular events and mortality when LDL cholesterol concentration is reduced. This effect remains to be confirmed for the case of mipomersen given the uncertainties on whether the effects of mipomersen on CV risk factors other than LDL-C level might counteract the expected benefit. In addition, clinical data from special population (patients with hepatic and renal disorders) are scarce. The effect on LDL-C was evident after 9 weeks of treatment and maintained at least 2 weeks after the last dose of study medication (week 28). Approximately 70% of patients in the mipomersen groups of pivotal trials had at least a 15% decrease in LDL-C levels from baseline to PET in comparison with approximately 20% of patients in the placebo groups. In general, sensitivity analyses conducted are robust and support the results of the primary analysis on change in LDL-C. Results on the primary efficacy endpoint by geographic region were consistent. Statistically significant percent reductions with mipomersen compared to placebo were also observed for secondary efficacy variables apo B, TC, and non HDL-C from baseline to PET. The beneficial effects in terms of reductions in LDL-C appeared to be sustained over time in patients who tolerated the drug up to 2 years. However, the benefits of mipomersen at the population level are significantly affected by its poor tolerability (60-70% of patients discontinued at 2 years mainly due to side effects including FLS, ISR and liver toxicity), markedly decreasing the rate of patients that may benefit from the lipid-lowering effect of the drug in the long-term, which is considered a major concern.

Efficacy data and additional analyses

The effect on LDL-C in elderly and pediatric patients seems to be in line with those in the overall population, but the number of patients (10 or less subjects in each special population) is very scarce to draw definitive conclusions on mipomersen's efficacy and safety in these populations. Patients

with significant hepatic or liver disease were excluded from pivotal trials. The use of mipomersen should be contraindicated in patients with significant hepatic disease and in patients with severe renal insufficiency.

Two additional phase 3 supportive studies examined the treatment with 200 mg mipomersen sodium once weekly and this resulted in significant decreases in LDL-C by approximately 30% compared to placebo in patients with HeFH and CAD or high risk hypercholesterolemic patients.

An on-going, open-label, extension study (ISIS 301012-CS6) is evaluating the safety and efficacy of extended dosing with mipomersen in 141 patients with FH or severe hypercholesterolemia on concomitant lipid-lowering therapy who had previously completed other study with mipomersen. In the pivotal studies, there was an imbalance in the percentage of patients who discontinued treatment: mipomersen arms 17.6% in ISIS301012-CS5 and 30.8% in MIPO3500108 versus placebo 0% in ISIS301012-CS5 and 5.3% in MIPO3500108, respectively. The imbalance was mainly due to discontinuations due to adverse events (AEs). In line with pivotal studies, treatment withdrawals in long-term extension study ISIS 301012-CS6 are significant (between 50-70%). On-treatment analysis for LDL-C levels in study CS6 shows maintenance of the lipid-lowering effect in patients completing 2 years of therapy.

Withdrawal rates: Mipomersen treatment is associated with a high rate of discontinuations. In total, 79 of 141 patients (56%) who enter study CS6 discontinued treatment, of which 78% (62/79) was due to adverse events. In the originally intended target population of high risk FH patients (severe HeFH and HoFH), analyses show that the discontinuation rate is even higher 34/56 (61.8%) of which 28 are due to adverse events. FLS (23.4%), ISR (9.2%) and elevated liver transaminases (10.6%) are the most common adverse events leading to discontinuation during the 2 years period, of which ISR discontinuation seems to decrease over time in contrast to FLS discontinuations.

Although some patients may potentially benefit from mipomersen treatment due to its LDL-C lowering effect, more than half of the patients will not benefit from mipomersen treatment as they prematurely discontinue, most of the time (80%) due to adverse events. Due to this disappointing safety profile and poor tolerability, adherence to treatment with mipomersen is seriously compromised, thus significantly limiting the number of patients that may potentially have a cardiovascular benefit due to LDL-C reduction for a disease that needs life-long treatment.

Even in case of the potentially more motivated HoFH patients, the retention rate was only 8% at 3 years (3 of 38 patients), with 63% (24 of 38 patients) withdrawing due to adverse events and 29% (11 of 38) who did only consented for one or two years of additional treatment.

Additional expert consultation

Due to the uncertainties of mipomersen use in terms of its safety in patient diagnosed with heterozygous and homozygous familial hypercholesterolaemia, the CHMP requested the opinion of additional experts with clinical experience in treatment of lipid disorders, hepatic and cardiovascular disease. Since the main questions to be addressed in this consultation relate to the CHMP's concerns of clinical safety of mipomersen and its potential for adverse drug reactions, the details of the expert consultation and its outcome are discussed in the Clinical Safety section.

Assessment of paediatric data on clinical efficacy

There were 7 paediatric patients involved in the clinical trials with mipomersen. In light of the limited information from children, their treatment cannot be recommended. The agreed Paediatric Investigation Plan (PIP) includes a waiver for children up to 12 years of age and a deferral till 2019 for children between 12 and 18 years. The SmPC would specify that mipomersen is intended for use

in adult patients. The SmPC would also acknowledge the insufficient data in children and no recommendation of use in this population.

2.5.4. Conclusions on the clinical efficacy

Treatment with mipomersen results in a statistically significant decline of 24.7% and 35.9% in LDL-C levels at PET versus baseline in patients with HoFH and severe HeFH on top of statins, respectively. This approximately corresponds to a reduction by 21%and 48% with mipomersen when corrected with placebo (for HoFH and HeFH, respectively). In absolute terms, it corresponds to a placebo-corrected reduction with mipomersen by -100 and -114 mg/dl in LDL-C at PET versus baseline, which may be considered of clinical relevance. Approximately 70% of patients in the mipomersen groups of pivotal trials had at least a 15% decrease in LDL-C levels from baseline to PET in comparison with approximately 20% of patients in the placebo groups. Statistically significant percent reductions with mipomersen compared to placebo were observed for the secondary efficacy variables apo B, TC, and non HDL-C from baseline to PET. In general, sensitivity analyses conducted are robust and support the results of the primary analysis on change in LDL-C. No differences on the lipid-lowering effect were found between geographic regions. However, based on data from pivotal studies and OLE CS6 study, withdrawal rates may be as high as 50%-70% at two years and mainly due to mipomersen treatment intolerability, thus, significantly decreasing the rate of patients that may benefit from the lipid-lowering effect of the drug in the long-term. Even in the most severe and motivated HoFH population, the retention rate was only 8% at 3 years (3 of 38 patients), with 63% (24 of 38 patients) withdrawing due to adverse events and 29% (11 of 38) completed their consent for the first or second year and did not consent for a second or third year of treatment. Thus, the high overall withdrawal rate with mipomersen after 2-3 years, even in the restricted HoFH population, remains a major concern, thus severely limiting the number of patients that may obtain a potential benefit from its lipid-lowering effect. Given that withdrawals are mainly due to intolerance, it is unlikely that retention rates may be improved in a less selected population in standard practice. Limited data suggest that the exposure and the effect of mipomersen might be dramatically reduced in patients undergoing apheresis. Although not available on widespread basis, apheresis is accepted as an effective treatment in severe hypercholesterolemia. It is also anticipated that in a large number of patients, particularly those with HoFH, mipomersen might be insufficient to reach the target of blood lipid parameters making necessary to maintain apheresis. Further investigation is needed to determine whether mipomersen is able to reduce the requirements for apheresis, and if both treatment can coexist in a given patient and under what conditions. In the meantime, concomitant use cannot be recommended in this point in time.

2.6. Clinical safety

In order to evaluate the clinical safety profile of mipomersen, tree main datasets are provided:

- Phase 2 pooled studies (three phase 2 supportive studies),
- Phase 3 pooled studies (two pivotal phase 3 studies and two supportive phase 3 studies),
- Long term safety data (study ISIS 301012-CS6, an on-going long term open label study).

Phase 2 pooled studies provide supporting data on dose escalations of mipomersen in patients with HoFH, severe HeFH, and hypercholesterolemia on lipid-lowering therapy. Phase 3 pooled studies were composed of 4 phase 3 studies 2-arm, double-blind, randomized 2:1, placebo controlled, which compared a weekly SC 200mg dose of mipomersen in patients with HoFH (n=51), severe HeFH (n=58), HeFH (n=124) and high risk HC (n=158) on lipid-lowering therapy (LLT). The on-going, OLE study included patients with FH on concomitant LLT, who had previously completed treatment in any Study ISIS 301012-CS5, ISIS 301012-CS7, or MIPO3500108.

Patient exposure

In clinical studies, a total of 733 subjects (502 patients and 231 healthy volunteers) were exposed to at least 1 SC injection of mipomersen. Exposure of subjects receiving mipomersen *via* an alternative route of administration is not included. The below table summarises cumulative mipomersen SC exposure for all subjects up to October 2010. During the evaluation, the CHMP noted that further data from extension studies were provided, but the overall safety picture as provided in the table below does not change substantially.

Cumulative Exposure to SC Mipomersen – Patients and Healthy Volunteers

Duration (Months)	Dose (mg/week)						
	30 or 50 (n)	100 (n)	200 (n)	300 (n)	400 (n)	800 (n)	Total (Any Dose)*
0-3	35	34	266	36	46	17	419
> 3-6	0	1	140	3	0	0	139
> 6-12	0	1	79	0	0	0	76
> 12-18	0	3	58	0	0	0	59
> 18	0	0	35	0	0	0	40
Total (Any Duration)	35	39	578	39	46	17	733
Subject-years of Exposure							288.8

Cumulative Exposure to 200 mg/week SC Mipomersen - All Patients

200 mg/week SC - Patients	
Cumulative Exposure (Months)	N
≥ 6*	242
Patient-years	225.2
≥ 12	102
Patient-years	147.0
≥ 18	36
Patient-years	65.8
≥ 24	10
Patient-years	20.7

Most patients were Caucasians (85%). The CHMP noted that the EU contribution to the clinical database is limited. Only 7 children, 3 of them treated with the test drug, have been included in the clinical programme. When considering the pooled 6-month phase 3 studies, the mean exposure to study drug 167.8 days for patients in the placebo group (59.2 patient-years) and 146.1 days for patients in the mipomersen group (104.4 patient-years). This difference is due to the higher rate of treatment interruptions among mipomersen treated patient.

Adverse events

The on-treatment adverse events (AEs) observed in the phase 3 placebo-controlled studies by treatment group are presented in the table below.

Overview of On-Treatment Adverse Events for Pooled Phase 3 Placebo-Controlled Studies

Placebo	(N=129)	Mipomersen (N=261)
Patients with On-Treatment AEs	109 (84.5)	249 (95.4)
Related AEs	73 (56.6)	239 (91.6)
Mild AEs	51 (39.5)	72 (27.6)
Moderate AEs	52 (40.3)	134 (51.3)
Severe AEs	6 (4.7)	43 (16.5)
AEs Leading to Discontinuation	3 (2.3)	47 (18.0)
Patients with On Treatment SAEs	7 (5.4)	21 (8.0)
Related SAEs	0 (0.0)	3 (1.1)
Mild SAEs	0 (0.0)	2 (0.8)
Moderate SAEs	3 (2.3)	10 (3.8)
Severe SAEs	4 (3.1)	9 (3.4)
SAEs Leading to Discontinuation	1 (0.8)	4 (1.5)
On-Treatment Deaths	1 (0.8)	0 (0.0)

As many as 73/129 patients suffering from at least 1 AEs in the placebo group were considered to have a treatment-related AEs. The number of AEs per patient is higher with mipomersen than with placebo, indicating a significant issue with tolerability, which persists over time, leading to up to 60% of treatment discontinuations along the clinical programme (phase III and extension studies).

The following table shows the treatment-emergent adverse events (≥5% of patients) at the patient level occurring 0-6 months and > 6 months after the start of mipomersen treatment in the OLE study.

Summary of Treatment-Emergent Adverse Events (≥5% of Patients in Either Subgroup) by System Organ Class and Preferred Term for Adverse Events Occurring 0-6 Months and >6 Months After the Start of Mipomersen – Safety Set

System Organ Class Preferred Term	Adverse Events Occurring 0-6 Months After Mipomersen (N = 141) n (%)	Adverse Events Occurring >6 Months After Mipomersen (N = 141) n (%)
Patients with events	135 (95.7)	122 (86.5)
Cardiac disorders	12 (8.5)	14 (9.9)
Angina pectoris	5 (3.5)	7 (5.0)
Gastrointestinal disorders	39 (27.7)	39 (27.7)
Abdominal pain	3 (2.1)	9 (6.4)
Diarrhea	10 (7.1)	7 (5.0)
Nausea	17 (12.1)	13 (9.2)
Vomiting	5 (3.5)	8 (5.7)
General disorders and administration site conditions	127 (90.1)	110 (78.0)
Chills	8 (5.7)	12 (8.5)
Fatigue	19 (13.5)	21 (14.9)
Influenza-like illness	22 (15.6)	33 (23.4)
Injection site discoloration	32 (22.7)	23 (16.3)
Injection site discomfort	10 (7.1)	3 (2.1)
Injection site edema	10 (7.1)	4 (2.8)
Injection site erythema	91 (64.5)	60 (42.6)
Injection site hematoma	62 (44.0)	31 (22.0)
Injection site hemorrhage	10 (7.1)	6 (4.3)
Injection site induration	12 (8.5)	11 (7.8)
Injection site inflammation	8 (5.7)	5 (3.5)
Injection site nodule	6 (4.3)	10 (7.1)
Injection site pain	79 (56.0)	58 (41.1)
Injection site papule	7 (5.0)	1 (0.7)
Injection site pruritus	34 (24.1)	14 (9.9)
Injection site rash	11 (7.8)	5 (3.5)
Injection site reaction	5 (3.5)	9 (6.4)
Injection site recall reaction	13 (9.2)	9 (6.4)
Injection site swelling	15 (10.6)	19 (13.5)
Injection site warmth	10 (7.1)	8 (5.7)
Pain	7 (5.0)	5 (3.5)
Pyrexia	15 (10.6)	9 (6.4)
Hepatobiliary disorders	3 (2.1)	9 (6.4)
Hepatic steatosis	3 (2.1)	7 (5.0)
Infections and infestations	52 (36.9)	52 (36.9)
Nasopharyngitis	12 (8.5)	16 (11.3)
Sinusitis	4 (2.8)	10 (7.1)
Upper respiratory tract infection	10 (7.1)	6 (4.3)
Urinary tract infection	9 (6.4)	7 (5.0)
Investigations	32 (22.7)	39 (27.7)
Alanine aminotransferase increased	15 (10.6)	12 (8.5)
Aspartate aminotransferase increased	9 (6.4)	15 (10.6)
Musculoskeletal and connective tissue disorders	36 (25.5)	35 (24.8)
Arthralgia	8 (5.7)	8 (5.7)
Back pain	6 (4.3)	9 (6.4)
Myalgia	13 (9.2)	15 (10.6)
Pain in extremity	7 (5.0)	4 (2.8)
Nervous system disorders	31 (22.0)	34 (24.1)
Headache	18 (12.8)	21 (14.9)
Tremor	0 (0.0)	7 (5.0)
Respiratory, thoracic and mediastinal disorders	17 (12.1)	30 (21.3)
Cough	6 (4.3)	7 (5.0)
Dyspnea	1 (0.7)	9 (6.4)
Oropharyngeal pain	6 (4.3)	8 (5.7)

If a patient had >1 event within a particular System Organ Class or Preferred Term, he/she was counted only once for that System Organ Class or Preferred Term. Patient percentages were based on the total number of treated patients.
A patient could have been included in both subgroups if he/she had a particular event occurring 0 to 6 months

Cardiovascular events: There were more patients with cardiac (9.2% vs. 6.2%) and vascular (11.1% vs. 5.4%) disorders in the mipomersen-treated group than in the placebo group, respectively. When aggregating PT related to coronary artery disease (angina pectoris, coronary artery disease, acute myocardial infarction, acute coronary syndrome, angina unstable, myocardial ischemia, prinzmetal angina), more patients had AEs in the mipomersen treated group than in the placebo group (7.6%, 20/261 vs. 4.6%, 6/129). In addition, more AEs of hypertension have been reported in the mipomersen group vs. placebo (6.5%, 17/261 vs. 3.1%, 4/129, respectively). Acute dose-dependent post-dose elevations in hsCRP were observed in several studies with mipomersen treatment. HsCRP is considered a modest contributor to the absolute CV risk estimations for individual patients. Overall, the analysis of CV AEs and MACE presents many limitations and should be interpreted with utmost caution, since it was not prospectively defined, not defined according to current standards, not independently adjudicated, of limited duration of the follow-up and in a small sample size. However, data on CV safety is a matter of real concern in a clinical setting where the absolute risk of MACE is particularly high. Thus, in the intended target population for mipomersen, the annual rate of CV events may range between 5%-10% and over 10% in the HoFH.

The below table shows a post-hoc analysis of the incidence of CV morbidity in the pivotal studies ISIS 301012-CS5 and MIPO3500108, where morbidity is expressed in terms of individual event types, MACE (includes acute myocardial infarction, stroke or CVA, unstable angina, PCI, and CABG), and overall CV morbidity. There is an increase in CV events in pivotal trials with mipomersen versus placebo by 13.7%, which increases to 21.5% per year when the events are adjusted by duration of exposure. The increase is consistent for MACE (12.3% absolute increase) and hypertension (8.1% increase) as well as for other events analysed (acute myocardial infarction, stroke/CVA, PCI, CABG) in this high CV risk population (mean baseline LDL-C levels in the two pivotal trials were 7 and 10.4 mmol/L, respectively).

Incidence of Cardiovascular Morbidity in Phase 3 Pivotal trials Population

Pooled Studies ISIS 301012-CS5 and MIPO3500108
Incidence of Cardiovascular Morbidity
Safety Set

	Placebo (N=36)		ISIS 301012 (N=73)	
	n (%)	Events/100 patient-years	n (%)	Events/100 patient-years
Acute myocardial infarction	0	0	1 (1.4)	1.9
Stroke or CVA	0	0	2 (2.7)	3.9
Unstable angina	0	0	1 (1.4)	2.0
PCI	0	0	3 (4.1)	6.0
CABG	0	0	2 (2.7)	4.0
Pulmonary embolism	0	0	0	0
Deep vein thrombosis	0	0	0	0
Transient ischemic attack	0	0	0	0
Hypertension	0	0	4 (5.5)	8.1
Major cardiac event (MACE)	0	0	6 (8.2)	12.3
Cardiovascular morbidity	0	0	10 (13.7)	21.5

This imbalance is less apparent when two additional phase 3 supportive studies, including patients with a lower CV risk (LDL-C between 3.2 to 3.8 mmol/L) are added to the analysis (mipomersen

18.8% vs. placebo 10.1%). The absolute adjusted increase is mainly at the expense of hypertension (12.0 vs. 4.4%); while a small increase is seen for MACE (6.6% vs. 5.4%).

Analysis of SAEs leading to hospitalisation, including CV SAEs, was provided on request of the CHMP. Overall, there were 18 CV events leading to hospitalisation with mipomersen (~ 8.1 events per 100 pt per year) and only 3 CV events leading to hospitalisation with placebo (~ 3 events per 100 pt per year):

- Hospitalisations due to cardiac events: mipomersen 14 events vs placebo 3 events (6 events per 100 pt per year vs. 3.3 events per 100 pt per year)
- Hospitalisations due to vascular disorders (hypertension) (mipomersen 2 events vs placebo 0 events; 1.1 events per 100 pt per year vs. 0 events per 100 pt per year)
- Hospitalisations due to cerebrovascular accident: mipomersen 1 event vs placebo 0 events (0.5 events per 100 pt per year vs. 0 events per 100 pt per year) and
- Hospitalisations due to pulmonary embolism: mipomersen 1 event vs placebo 0 events (0.5 events per 100 pt per year vs. 0 events per 100 pt per year).

Although this analysis should be interpreted with caution, due to its post-hoc nature and the limited numbers of events, the data suggest an increase in clinically relevant CV events with mipomersen. However, it is not proven whether any differences in CV events could be driven by a chance. Thus, the analyses of CV risk markers could suggest no differences between mipomersen-treated and placebo-treated patients in the pivotal studies with regards to blood pressure, chronic hsCRP levels, or renal function parameters. However, the results are inconclusive due to low numbers, unequal baseline values, and inconsistencies between studies or between datasets considered.

Hepatic effects: Throughout the clinical development programme, study protocols identified exclusion criteria for patients at a particular risk for hepatic effects; therefore, there is a lack of clinical evidence of the mipomersen treatment effects on this population.

Mipomersen inhibits the translation of the apo B-100 protein, the principal apolipoprotein of LDL and its metabolic precursor, very low density lipoprotein (VLDL). Consequently, triglycerides can accumulate in liver cells leading to steatosis that may affect hepatic safety in terms of inflammation and subsequent fibrosis and cirrhosis. Throughout the clinical development programme, hepatic safety was important and the study protocols included exclusion criteria for patients at particular risk for hepatic effects, safety stopping rules (based on AST, ALT and total bilirubin elevations), and guidance for close monitoring of potential hepatic effects, including standard laboratory testing for serum transaminases and imaging for hepatic fat by MRI.

In a minority of patients, persistent increases in serum transaminases were observed: 8.4% of mipomersen treated patients experienced ALT levels ≥3 x ULN on at least two consecutive occasions at least seven days apart. Finding in pooled phase 2 studies results were consistent with those from pooled phase 3 studies, which showed that increases in ALT, AST, liver function test abnormal and hepatic enzyme increased occurred more frequently in the mipomersen treatment group compared to the placebo group (24.5%, 64/261 vs. 4.6%, 6/129, respectively). Overall, 76% (199/261) of patients had at least 1 ALT result that was abnormal compared to 38% (49/129) in the placebo group. A total of 22 (11%) mipomersen-treated patients experienced ALT levels ≥3 x ULN on at least 2 consecutive occasions at least 7 days apart following initial dosing. Results for the AST test analyses were consistent with results for the ALT test analyses although the incidence was smaller, as shown in the below table.

Liver Function Test Analyses for Pooled Phase 3 Placebo-Controlled Studies

Parameter	Statistic	Placebo (N=129)	Mipomersen (N=261)
ALT maximum	Incidence rate, n (%)		
	> ULN and < 2 x ULN	42 (32.6)	95 (36.4)
	≥2 x ULN and < 3 x ULN	6 (4.7)	61 (23.4)
	≥3 x ULN and < 5 x ULN	1 (0.8)	31 (11.9)
	≥5 x ULN and < 8 x ULN	0 (0.0)	6 (2.3)
	≥8 x ULN	0 (0.0)	6 (2.3)
ALT	≥3 x ULN, two consecutive results (at least 7 days apart), n (%)	0 (0.0)	22 (8.4)
AST maximum	Incidence rate, n (%)		
	> ULN and < 2 x ULN	49 (38.0)	124 (47.5)
	≥2 x ULN and < 3 x ULN	4 (3.1)	27 (10.3)
	≥3 x ULN and < 5 x ULN	1 (0.8)	19 (7.3)
	≥5 x ULN and < 8 x ULN	0 (0.0)	4 (1.5)
	≥8 x ULN	0 (0.0)	3 (1.1)
AST	≥3 x ULN, two consecutive results (at least 7 days apart), n (%)	0 (0.0)	11 (4.2)

ALT = alanine aminotransferase (SGPT), AST = aspartate aminotransferase (SGOT), ULN = upper limit of normal range.

The OLE study results showed ALT increased (18%), AST increased (16%), hepatic enzyme increased (3%), liver function test abnormal (2%), and transaminases increased (0.7%). Twenty two (15.6%) patients experienced increases in ALT and AST that met protocol-defined monitoring/safety rules for liver chemistry; for 8 (5.7%) of these patients, dosing with mipomersen was stopped. As in pooled phase 3 studies, increases in ALT ≥3 x ULN and < 5 x ULN were more frequent than increases in ALT ≥5 x ULN and < 8 × ULN, and increases in ALT ≥8 x ULN. An amendment to the OLE protocol allowed for the mipomersen dose to be held or decreased to 100 mg/week for a subset of patients who met protocol-defined monitoring rules.

Hepatic fat measurements: In selected Phase 3 studies (ISIS 301012-CS7 and ISIS 301012-CS12), hepatic fat fraction was assessed with MRI at baseline and week 28/early termination. Overall current data showed that hepatic steatosis and increases in liver fat fraction are more frequent in the mipomersen treatment group. There is a trend correlating change in liver fat fraction and elevations in ALT values. The liver fat fraction was observed to return to near baseline following cessation of mipomersen treatment. Beyond six months, hepatic fat generally stabilised, and in some patients even reversed, despite on-going mipomersen treatment. However, long term data are inconclusive. In the OLE study, the number of patients with available data at baseline, week 26, week 52, and week 72 is small to draw firm conclusions regarding long-term effects on liver fat accumulation with mipomersen treatment. Nevertheless, there is a trend showing an increase in liver fat fraction over time.

Hepatic biopsy findings: Liver biopsies were not included as part of the study protocols; however, in the course of the clinical programme, five patients had liver biopsies for medical indications. Baseline biopsies were available for these patients and all had increases in hepatic fat on magnetic resonance spectroscopy or MRI, and four of five had elevations in ALT ≥3 x ULN. Results of liver biopsy confirm the presence of liver fat and show mild signs of inflammation without significant liver fibrosis. The signs of inflammation may indicate an underlying inflammatory/immunological mechanism in addition to the direct hepatic adverse effects produced by mipomersen. In addition,

monitoring the long term progress of these patients should be of major importance since the duration of current studies was not sufficient to monitor the potential development of liver fibrosis.

Injection site reactions: Local injection site reactions (ISRs) were the most commonly observed AEs associated with mipomersen. Eighty-four (84 %) and 99% of patients in the pooled phase 3 studies and OLE study reported ISRs, respectively. The most frequent ISR AEs were injection site erythema, pain, haematoma, pruritus, swelling, and discolouration. Of those mipomersen patients who discontinued study treatment due to an AE (n=47), 21 patients discontinued due to general disorders and administration site conditions, and 32 patients due to ISRs.

The nature of the ISR has not been properly discussed. Considering the local and systemic safety findings, including skin reactions, FLS, immunologic findings, consumption of complement (C3 fraction), and 65% of patients showing mipomersen antibodies, a contributing effect of immunologically mediated damage to the ISRs cannot be completely excluded.

Renal effects: Renal and urinary disorders were more frequent in the mipomersen treatment group than in placebo group (6.1% vs. 4.7%, respectively) in the pooled phase 3 studies. Nine (9%) of patients reported renal and urinary disorders in the OLE study. Laboratory parameters showed that no fluctuations in serum creatinine, GFR or BUN were observed in either treatment group over the 28/ET week treatment period in the Phase 3 pooled analyses. However, urine parameters of albuminuria, proteinuria, ACR, individual cases of increases in beta-2 microglobulin, showed an increase in the mipomersen treatment group at 28/ET week compared to placebo group. Importantly, proteinuria was observed in 9% of patients in the mipomersen treatment group.

Flu-like symptoms: In the pooled phase 3 studies, more patients had flu-like symptoms (FLS) in the mipomersen-treated group than in the placebo group. These included mainly fatigue, influenza like illness, pyrexia and chills. The OLE study showed consistent results when compared to pooled phase 3 studies. When analysing AEs by SOC > 6 months after the start of mipomersen, all except for pyrexia and arthralgia showed increased frequencies compared to 0-6 months after mipomersen. Therefore, there is no tolerance over time for FLS.

Inflammatory and immunological effects: Acute, dose-dependent post-dose elevations in hsCRP with mipomersen treatment were observed in several studies. In addition, based on the pooled analysis of phase 3 studies, more patients in the mipomersen treatment group showed shifts in CRP from baseline to end of treatment compared to placebo. However, the chosen thresholds were not appropriate to assess the CV risk and/or other inflammatory conditions. In addition, patients with high CRP values were not additionally monitored until a stable baseline value was seen. Therefore, the submitted data may underestimate the real behaviour of the CRP in patients receiving mipomersen treatment. Decreases in C3 were seen in some conditions, such as cirrhosis, glomerulonephritis, hepatitis and bacterial infections. Correlation of the C3 levels decreases with any clinical AEs remains to be evaluated. Finally, a 65% of patients were positive to mipomersen antibodies. According to the data provided, efficacy does not appear to be affected. The long-term safety consequences remain unknown. Antibody formation might induce complement consumption, although not to a significant extent, and formation of immune-complexes can be detected in up to 30% of patients with antibodies. There seems to be an association between antibody detection and the presentation FLS. However, no clear relationship is observed with ISR, since this reaction is more likely mediated locally by cells.

Neoplasms: Overall, there were 22 neoplasms in mipomersen-treated subjects and 2 neoplasms in placebo subjects. According to the applicant, neither the incidence nor the prevalence of malignant neoplasms was higher than expected in the target population. In particular, neoplasms were not systematically evaluated throughout the studies and no particular pattern in type of neoplasia was observed. Definite conclusions are difficult to make as baseline examinations were not consistently made, as well as the follow up and examination during the study could have been different. This all adds to the uncertainty of a potential association. The sometimes short-term duration between exposure and a newly found neoplasm renders an association in most cases unlikely, although a tumour unmasking effect cannot be ruled out. Further studies are deemed necessary.

Serious adverse event / deaths / other significant events

More on-treatment SAEs in the mipomersen treatment group compared to the placebo group (8% vs. 5.4%) were reported in the pooled phase 3 studies. Twenty (20%) of patients reported SAEs during the OLE study (till 31 October 2010). In addition, there is an increase in frequency of SAEs >6 months after the start of mipomersen compared to 0-6 months after mipomersen (13.5% vs. 6.4%, respectively), which would support the assumption that no tolerance to mipomersen-induced toxic effects can be developed. Cardiac disorders were the most frequently reported SAEs, followed by nervous system disorders in the OLE study. Both, the cardiovascular and CNS disorders increased in frequency over time. Although the effect on cardiovascular events was explained as being due to the medical history of the patient population, the CHMP could not consider this as certainty. Death rates in mipomersen clinical trials are low and similar between mipomersen (3 of 749; 0.40%) and placebo (1 of 221; 0.45%). Of 3 deaths reported with mipomersen, two were due to myocardial infarction. However, the report of a death due to hepatic failure possibly-related to mipomersen was of concern, but other potential causal factors were found, which, to some extent alleviate the initial concern A causality relationship is difficult to establish because the enrolled population is at high risk of events.

Laboratory findings

For laboratory findings, see above analysis of adverse events by organs and systems or syndromes.

Safety in special populations

Regarding the analyses by subgroups (gender, age, diabetes mellitus), the AE profile was similar to those presented in a general population. Special caution should be taken in patients ≥ 65 years of age due to a higher incidence of hypertension, peripheral oedema and hepatic steatosis in mipomersen treated patients compared to the placebo group or the lower age groups. There is only limited or no data in children, patients with pre-existing hepatic disease or pre-existing renal disease, patients with acute cardiovascular events, pregnant or lactating women and patients with genetic polymorphisms.

Safety related to drug-drug interactions and other interactions

Two dedicated drug-drug interaction studies were conducted in healthy volunteers evaluating the potential for drug interactions between mipomersen and two oral hypolipidaemic agents (simvastatin and ezetimibe), and mipomersen and warfarin. No clinically relevant pharmacokinetic interactions between mipomersen and the 3 investigated test drugs (simvastatin, ezetimibe, and warfarin) were observed. Additionally, the coadministration of mipomersen with warfarin did not result in a pharmacodynamic interaction as determined by INR, aPTT and PT. However, this data is scarce and a warning about the limited information on the use mipomersen with ethanol,

acetaminophen and other hepatotoxicity drugs was requested by the CHMP to be reflected in the SmPC. In addition, a contraindication would be included in the SmPC to state that mipomersen should not be used in patients with alcohol and/or acetaminophen consumption.

Discontinuation due to adverse events

The AEs that led to an early treatment discontinuation by SOC and PT for the pooled phase 3 studies and the open label study are presented in the table below. During the phase 3 studies, 18% of patients treated with mipomersen discontinued treatment as compared to placebo. The time pattern of drug discontinuation shows that AEs leading to treatment interruption were evenly occurring during the period of follow-up.

Adverse Events Resulting in Study Discontinuation 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 (%)	**3 (2.3)**	**47 (18.0)**
Cardiac disorders	**1 (0.8)**	**1 (0.4)**
Acute myocardial infarction	1 (0.8)	0 (0.0)
Cardiogenic shock	1 (0.8)	0 (0.0)
Palpitations	0 (0.0)	1 (0.4)
Gastrointestinal disorders	**0 (0.0)**	**6 (2.3)**
Abdominal pain upper	0 (0.0)	2 (0.8)
Constipation	0 (0.0)	2 (0.8)
Nausea	0 (0.0)	2 (0.8)
Vomiting	0 (0.0)	1 (0.4)
General disorders and administration site conditions	**1 (0.8)**	**21 (8.0)**
Injection site pain	0 (0.0)	8 (3.1)
Injection site erythema	0 (0.0)	6 (2.3)
Injection site pruritus	0 (0.0)	6 (2.3)
Fatigue	1 (0.8)	3 (1.1)
Chills	0 (0.0)	3 (1.1)
Injection site discoloration	0 (0.0)	3 (1.1)
Injection site swelling	0 (0.0)	3 (1.1)
Influenza like illness	0 (0.0)	2 (0.8)
Chest pain	0 (0.0)	1 (0.4)
Injection site hematoma	0 (0.0)	1 (0.4)
Injection site induration	0 (0.0)	1 (0.4)
Injection site rash	0 (0.0)	1 (0.4)
Injection site recall reaction	0 (0.0)	1 (0.4)
Injection site urticaria	0 (0.0)	1 (0.4)
Injection site warmth	0 (0.0)	1 (0.4)
Non-cardiac chest pain	0 (0.0)	1 (0.4)
Pain	0 (0.0)	1 (0.4)
Pyrexia	0 (0.0)	1 (0.4)
Hepatobiliary disorders	**0 (0.0)**	**5 (1.9)**
Hepatic steatosis	0 (0.0)	3 (1.1)
Hepatic function abnormal	0 (0.0)	1 (0.4)
Liver tenderness	0 (0.0)	1 (0.4)
Infections and infestations	**0 (0.0)**	**1 (0.4)**
Influenza	0 (0.0)	1 (0.4)
Investigations	**1 (0.8)**	**16 (6.1)**
Alanine aminotransferase increased	0 (0.0)	9 (3.4)
Aspartate aminotransferase increased	0 (0.0)	6 (2.3)
Liver function test abnormal	0 (0.0)	4 (1.5)
Hepatic enzyme increased	0 (0.0)	2 (0.8)
Blood creatinine increased	1 (0.8)	0 (0.0)
Blood urea increased	1 (0.8)	0 (0.0)
Platelet count decreased	0 (0.0)	1 (0.4)
Musculoskeletal and connective tissue disorders	**0 (0.0)**	**4 (1.5)**
Myalgia	0 (0.0)	2 (0.8)
Pain in extremity	0 (0.0)	2 (0.8)
Musculoskeletal pain	0 (0.0)	1 (0.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0 (0.0)**	**1 (0.4)**
Non-small cell lung cancer	0 (0.0)	1 (0.4)
Nervous system disorders	**1 (0.8)**	**3 (1.1)**
Lethargy	0 (0.0)	2 (0.8)
Headache	1 (0.8)	0 (0.0)
Presyncope	0 (0.0)	1 (0.4)
Restless legs syndrome	1 (0.8)	0 (0.0)
Psychiatric disorders	**0 (0.0)**	**1 (0.4)**
Depression	0 (0.0)	1 (0.4)
Renal and urinary disorders	**0 (0.0)**	**1 (0.4)**
Chromaturia	0 (0.0)	1 (0.4)
Skin and subcutaneous tissue disorders	**0 (0.0)**	**4 (1.5)**
Rash	0 (0.0)	2 (0.8)
Pruritus	0 (0.0)	1 (0.4)
Urticaria	0 (0.0)	1 (0.4)

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

Considering the withdrawal rate of phase III plus extension studies, the retention rate on treatment of patients with mipomersen for 2 years is around 40%. This is a critical aspect for a drug that is supposed to be administered during a life time.

Mipomersen treated patients who discontinued due to an AE, the major reasons were elevated ALT and AST levels (6.1% of mipomersen-treated patients), ISRs (5.0%) and flu-like symptoms (2.7%). The main reasons for discontinuation in the open-label studies were: flu-like symptoms (FLS) (23.4%), injection site reactions (ISRs) (9.2%), abnormal liver function tests such as elevated ALT or AST (7.1%). This occurred at a constant rate.

Post marketing experience

There is no post marketing experience with mipomersen since at the time of the evaluation this product has not been marketed.

2.6.1. Discussion on clinical safety

The submitted safety data were obtained from patients with HoFH as well as HeFH. The main safety database consists of approximately 250 patients from the pooled phase 3 dataset treated with the finally selected dose, of them only 100 treated for a period of 12 months. This is questionable for a target population that includes HeFH, even if only the “severe” subset of this condition were to be considered. Most patients are Caucasians (85%); with few being Black (25), Asiatic (9) and Hispanic/Latin (23). Only a minority of the enrolled population is European (total number 58, of them 39 in mipomersen). Seven children and adolescent patients were included in the studies, of them only 3 received mipomersen and 4 were assigned to placebo group. In HoFH, the paediatric, in particular the adolescent target population is deemed critical. From a safety point of view, the paediatric dataset is insufficient.

Some long-term data (>12-month) from mipomersen treated patients were provided, mostly from the uncontrolled study OLE. Interestingly, when analysing the exposure data from the pooled phase 3 set it can be observed that mean exposure to mipomersen (146 days) was notably shorter than that for placebo (168 days). This data may suggest poor treatment tolerance. The high rate of withdrawals, which does not decrease over time, is fully consistent with this observation.

Mipomersen is poorly tolerated. Overall, 95% of patients in phase 3 studies presented at least one AE. Fully consistent with this data, total exposure to mipomersen in phase 3 studies is lower than to placebo, reflecting treatment discontinuation. Discontinuations due to adverse events were frequent and mostly related to ISR, FLS and liver enzyme elevations; 47 (18.0%) patients in the mipomersen group and three (2.3%) patients in the placebo group discontinued during the phase 3 studies. In the open-label long-term extensions 54 (38.3%) for study CS6 and 13 (61.9%) patients in study CS17 discontinued study drug during the first 2 years of treatment. Tolerability does not seem to improve over time, and the rate of withdrawals during the extension phase was even higher than during phase 3 studies, even considering that only patients tolerating the drug at the end of the phase 3 studies entered the extension phase.

Cardiovascular events: It is unclear whether in a population with such a high CV risk, the imbalance in CV MACEs should be considered as a safety concern or as a lack of efficacy. The inconsistencies in the numbers of MACEs between phase 3 pivotal studies and overall phase 3 studies in mipomersen treated patients, casts doubts on whether the drug is exerting the supposed protective effect. As discussed in the efficacy section, the current CHMP guidelines acknowledge the LDL-C

value as a possible surrogate for clinical efficacy for lipid lowering agents providing that there is no suspicion of a detrimental effect on CV outcomes. It is difficult to accept that in this target population, the analysis of MACE has been only undertaken on a retrospective basis, with no pre-definition of MACE according to accepted standards, and no pre-specified adjudication of events.

Furthermore, these findings were not sufficiently addressed by the applicant and the imbalance was considered to be by chance in population where MACE can be regarded as naturally occurring. Analyses of CV risk markers suggested no differences between mipomersen-treated and placebo-treated patients in the pivotal studies CS5 and MIPO35 with regards to blood pressure, chronic hsCRP levels, or renal function parameters. However, the results are inconclusive due to low numbers, unequal baseline values, and inconsistencies between studies or datasets. At present, it remains uncertain whether potential negative effects, in particular inflammatory effects, immunological reactivity, increase in blood pressure and renal toxicity (as shown by proteinuria) on other cardiovascular risk factors may counteract the potential beneficial effect on CV outcome due to reduction in LDL-C.

Hepatotoxicity: Liver changes were assumed to be associated with the on-target mechanism of mipomersen. Reversibility of increased transaminase in liver fat fraction after discontinuation of treatment was observed. Hepatic steatosis in mipomersen-treated patients most likely occurs in patients whose livers do not adapt rapidly to the reduction in triglyceride export. There is no known threshold at which hepatic steatosis or liver fat fraction results in inflammation and progressive liver disease, and there is no evidence to indicate that the clinical consequences or natural history of fatty liver due to the metabolic syndrome/insulin resistance are equivalent to fatty liver results from the inhibition of VLDL secretion. The on-treatment accumulation of fat in the liver varied amongst patients. In some patients who had an increased liver fat, extended treatment with mipomersen was associated with liver fat stabilization, or decrease. Measures to minimize the risk of developing steatohepatitis, which may become the precursor to long-term liver fibrosis and cirrhosis were proposed, e.g. avoiding treatment with mipomersen in inappropriate patients, monitoring ALT levels during treatment, and withdrawal of mipomersen if needed. Although the CHMP agreed that these are necessary, some concerns remained:

- No clear predictors for patients at risk for hepatic adverse events were identified. The only identified marker for elevated transaminase levels was a better treatment response in terms of LDL-C reduction.
- The observed higher levels of transaminase were not linked to a higher fat fraction, and might therefore probably also not directly predictive of hepatotoxic effects.
- Data on the liver fat fraction were provided at several time points and these indicate some reversibility in fat fraction, although there is no full return to baseline after treatment discontinuation. The mechanism and variability of increase in liver fat remains unexplained. It addition, it is not clear whether mipomersen induced liver fat fraction can eventually result in liver fibrosis. Although most patients return to near baseline in liver fat fraction, it cannot be ruled out that for certain patients liver fat fraction increase is permanent. For these patients it remains unpredictable if they develop hepatosteatitis and further hepatic fibrosis.

Thus, the CHMP questioned whether a maximal effect (plateau) is observed in ALT/AST levels in the individual patients. Whether patients ALT or AST levels reached a plateau cannot be solved based on the current data, due to stopping rules, where patients with ≥8xULN single or ≥5xULN confirmed elevated transaminases were taken off mipomersen therapy. Reinitiating therapy was possible in a number of patients without recurrence of elevated transaminase levels. This lead to treatment discontinuation in 7.1% patients because of hepatic AEs. Although in the majority of patients the ALT and AST levels return to (near) baseline, in the minority this may not be the case. The risk for those patients in terms of hepatic damage remains unclear.

Neoplasms: Overall, there were 22 neoplasms in mipomersen-treated subjects and 2 neoplasms in placebo subjects. Importantly, in the pooled analysis of AEs in the 6 month phase 3 studies, there were more patients with neoplasms (n=10; 3.8%) in the mipomersen group compared with the placebo group (n=0). This imbalance is of a major concern, although it is acknowledged that no clear explanation is apparent. Neoplasms were not systematically evaluated throughout the studies and no particular pattern in type of neoplasia was observed. Definite conclusions are difficult to make as baseline examinations and examination during the study were not conducted consistently. The CHMP believes that this adds to the uncertainty of a potential association. The sometimes short-term duration between exposure and a newly found neoplasm renders the association to be unlikely, although a tumour unmasking effect cannot be ruled out. With the available database, no new analyses are expected to provide further clarification. However, this is a critical risk and would need be considered and evaluated in the post-marketing setting.

Renal damage: Animal data and proteinuria observed in 9% of patients suggest that mipomersen may induce glomerular or tubular renal damage. Therefore, renal complications cannot be ruled out and the implied mechanism should be further elucidated, as well as its impact on vascular disorders (e.g. hypertension).

Immunological/inflammatory effects: Mipomersen is associated with a high incidence of adverse reactions, flu-like symptoms, short term effect on inflammatory markers (hsCRP) and slight decrease on C3. Mipomersen may be immunogenic and antibodies have been detected in 65% of subjects. In addition, C3 consumption was more pronounced in patients with antibody formation. However, the consequences of these findings are unclear. Only for higher hsCRP more cardiac disorders were found, however, numbers were very small. Slightly lower C3 values were observed, but without signs of complement activation. The clinical significance is unknown. Discontinuation rate seems not to be associated with antibody formation, neither does the increase in ALT/AST level, renal events, injection site reactions, and flu-like symptoms. Antibody positive patients seem to have a slightly higher hsCRP level, but the clinical meaning of this relationship is unclear.

In the view of the above described concerns, an oral explanation was held during the CHMP in September 2012 and the remaining major objections were addressed by the applicant. The applicant also proposed to restrict the indication of mipomersen to the HoFH patients only, based on the claim of an unmet medical need in this group of patients, who would benefit from a new LDL-cholesterol lowering drugs in order to reduce their high cardiovascular risk with a high probability to die at a young age of ischemic heart disease. The existing therapy such as statins and non-medical therapy (LDL-apheresis) do not satisfactory address this condition. Due to the proposal for indication restriction, the Committee requested further clarifications and information on the risks, how these could be minimised in HoFH patients treated with mipomersen, and how the withdrawal of these patients from the treatment due to AEs can be addressed should the product be placed on the market. In the written responses, additional analyses were also provided regarding CV hospitalisations of during phase 3 trials, showing numerically more CV hospitalisations with mipomersen (18 CV hospitalisations; 8.1 events per 100 pt per year) than with placebo (3 CV hospitalisations; 3 events per 100 pt per year). Thus, a favourable benefit-risk of mipomersen in the HoFH patients could not be agreed by the CHMP, due to the lack of a scientific proof.

The proposed studies for post-authorisation phase (mainly MIPO38) were in CHMP's view not sufficiently detailed, and were poorly defined with respect to sample population and sample size calculation, CV endpoints in addition to MACE, such as blood pressure measurements after subcutaneous administration or CV hospitalisations. The CHMP considered it unlikely that a study with only 240 patients would alleviate most of the major concerns raised by the Committee. Notwithstanding the above considerations, the critical issue is that the uncertainties on relevant safety concerns cannot be clarified at this time so as to allow a fair assessment of the efficacy and safety balance. The CHMP did not consider the overall response adequate and maintained their concerns regarding the safety signals observed with mipomersen. Furthermore, the CHMP questioned whether the studies proposed could adequately solve the concerns in an acceptable

timeframe during post-authorisation, so that a possible harm to the patients could be avoided. The CHMP was of the opinion that the additional clinical data to answer the major relevant uncertainties should be provided prior to authorisation, in agreement with the conclusions of the clinical experts.

Additional expert consultations

Due to the uncertainties of mipomersen use in terms of its effect and its safety in patient diagnosed with heterozygous and homozygous familial hypercholesterolaemia, the CHMP requested the opinion of additional experts with clinical experience in treatment of lipid disorders, hepatic and cardiovascular disease. Thus, an ad-hoc expert group meeting was constituted and a meeting was held in order to answer the following questions:

1. *Although the beneficial effects in terms of reductions in LDL-C appear to be sustained over time, only 20-30% of patients appear to tolerate long-term treatment with mipomersen (more than 2 years). Injection site reactions, hepatotoxicity and flu-like symptoms are the adverse reactions more commonly resulting in treatment discontinuation. So far, patients at particular risk for developing intolerance to this treatment have not been identified and therefore there is no possibility to minimize the exposure to a drug with a rather worrying safety profile that is intended for life-long administration. Considering the safety profile of the drug and its poor tolerability, the experts are requested to discuss whether there is an identified population for whom the benefits of mipomersen (LDL-C reduction) clearly outweigh the risks identified and potential. Separate consideration should be given to patients with Homozygous Familial Hypercholesterolemia (HoFH) and to patients with Heterozygous forms of Familiar Hypercholesterolemia (HeFH).*

2. *Hepatotoxicity, with liver enzyme elevations and steatosis, is a major limiting factor of mipomersen safety. Fat accumulation in the liver (triglycerides) associated to the decrease in ApoB occurs as a direct consequence of the pharmacological effect of this drug and is correlated with its effect on blood lipid levels. The long-term hepatic safety is not known. From the limited evidence available, it is not clear whether these effects are completely reversible in the long-term for all patients. The expert advice is requested on the following issues:*

    a. *To discuss whether there might be a risk to develop progressive and non-reversible liver damage as a consequence of persistent liver steatosis and, if so, the potential contribution of the proinflammatory and immunologic reactions observed in patients treated with mipomersen.*

    b. *To comment on appropriate measures to minimise this risk, including e.g. close monitoring of liver parameters, serial scanning, among others, and to discuss on whether patients at risk could be identified at a stage where reversibility might still be expected.*

Due to the nature of the questions and a direct interlinking between the topics raised in both CHMP questions, the experts discussed these topics concurrently. In addition, in light of the assessment of the latest data submitted by the applicant, the Rapporteurs asked the experts to express their opinion on the cardiovascular risks identified with the use of mipomersen.

In order to identify whether there is a specific group of patients that would receive a better benefit from mipomersen treatment, the experts suggested to discuss separately the B/R for each patient group proposed in the indication: the HoFH patients, the severe HeFH patients, and the group of statin intolerant patients. It is to be noted that HoFH condition is rare and more severe that the

HeFH. It was, however, noticed that the clinical analyses submitted by the applicant do not distinguish between these sub-groups.

The following aspects were considered relevant to each of the three patient groups:

- *The lack of a measurable reduction in cardiovascular endpoints and cardiovascular symptoms - or even a trend towards it - following the observed LDL-C lowering effect*

One of the key concerns of the experts is the missing evidence of the cardiovascular disease (CVD) benefits of mipomersen, which would be expected from a medicinal product that lowers LDL-C levels substantially. Given the extremely high global cardiovascular risk in HoFH and the high risk in HeFH patients, while it might have been difficult to demonstrate clear reductions in major adverse cardiovascular disease endpoints (MACEs) due to the limited number of individuals and the short periods of follow-up, the experts would have expected a clear tendency towards a relief of CVD symptoms such as angina pectoris or in the rate of hospital admissions for CVD causes. The applicant should have the relevant data on file because hospital admissions are recorded as adverse events. Considering the lack of clinical data, it seemed questionable whether a patient tolerating mipomersen and exhibiting a decrease in LDL-C would also experience a real benefit. In addition, this was put into question since the decrease in LDL-C might be be counter-balanced by unresolved side effects, some of which may immediately be relevant for vascular function and atherosclerosis development (i.e. inflammatory reaction, increase in C-reactive protein, proteinuria, hypertension). The experts were of the opinion that even if the positive clinical effect of LDL-C reduction had been demonstrated, the evidence of clinical efficacy regarding the reduction of CVS risks has not been shown and that the long-term benefit of mipomersen remained uncertain.

- *Adverse effect of mipomersen treatment on liver*

The experts noted that there is limited data available on the exact effect of mipomersen on the liver. The doubts of hepatotoxicity, fat accumulation, and possible development of cirrhosis remain and the treated patients would need to be strictly monitored for their liver enzyme levels and detection of fatty liver using imaging techniques. Also, many patients with hepatic fat accumulation can develop significant fibrosis prior to enzyme level increases. Therefore, given the results seen with mipomersen treatment, patients would also have to undergo regular liver biopsies. This recommendation shall be included in the SmPC of mipomersen. In general, the experts suggested that biopsies should be performed every 2 years and after ALT levels increase significantly (e.g. 1.5 times over the upper limit of normal population range) or if the liver content of MRI measured fat increases. There was, however, no consensus on the need to conduct liver biopsy at the baseline.

One of the exclusion criteria in the conducted clinical programme was the use of apheresis. Only three patients included in a phase II study received apheresis. Nevertheless, the positive clinical effect detected following treatment initiation with apheresis (i.e. immediate relief of clinical symptoms) cannot be observed following treatement with mipomersen only. Due to the limited data available at present, the experts would not recommend a switch from apheresis to mipomersen treatment, especially in case of patients who are well controlled on apheresis, since their response to mipomersen could be inadequate. However, for those not tolerating this non-risk free procedure well, an add-on treatment with mipomersen might decrease the frequency of these interventions. This would require clarification of the issue of enhanced rate of elimination of mipomersen from the circulation during apheresis. Such claim would need to be supported by clinical data. The patient

representative, being a regular receiver of apheresis, expressed his view on the decreased quality of life associated with this invasive procedure, but acknowledged that he would not agree with apheresis being discontinued in favour of mipomersen.

- *Increased incidence of MACEs in the patient group treated with mipomersen*

The experts noted the increased incidence of several MACEs in the phase III clinical trials. The analysis of MACEs was conducted retrospectively, without a pre-defined protocol for categorisation of MACE or appropriate adjudication, in spite of the Scientific Advice received. Thus, the studies were not conducted in a suitable way to identify CVD events. This further increases the doubt about being able to identify a subpopulation that would benefit from mipomersen. Some experts considered that the lack of clear CVD benefits and adverse effects on CVD risk factors (inflammation, blood pressure, kidneys) observed with mipomersen could constitute a signal of direct harm to the patients.

Furthermore, the group believed that mipomersen's effects on the CVD risk profile should be better characterised. Data on systematic follow-up of cardiac events / cardiac surrogate endpoints should be presented, e.g. coronary physiology scans, use of other non-invasive imagining techniques for atherosclerosis assessment and measurements of the stability of coronary plaques. Even though mipomersen is intended to lower CVD risk, there was no real indication from the presented clinical trial data that lowering LDL-C in HoFH and HeFH patients would finally improve the overall CVD outcomes. Data supporting a favourable profile for mipomersen are needed and should be provided. There was no information on hospitalisation rates due to adverse events, although they would have been reported during the clinical trials as SAEs. The applicant should be asked to provide these.

- *The occurrence of neoplasms, proteinuria and the role of pro-inflammatory markers*

The increased incidence of neoplasms in mipomersen-treated patients observed in clinical trials remains an unresolved issue of concern. There is no clear pattern in the type of neoplasms observed and the systematic evaluation of neoplasms in the clinical trials was not conducted. With respect to the renal damage, proteinuria and potential role of a pro-inflammatory reaction, there is no sufficient data to conclude on these issues, but the experts believed that a negative clinical impact counter-acting the effect on LDL-C cannot be ruled out.

Based on the above considerations – the lack of clinical benefit of the lowered LDC-C levels, unfavourable cardiac and hepatic safety, and the occurrence of neoplasms - the experts were of the view that the available data are not considered sufficient to support a positive B/R, neither in HoFH or HeFH patients. The HoFH patients are severely affected by the disease and they are far less responsive to the currently available treatments compared to HeFH patients. In addition, apheresis is quite a complex and invasive procedure and is not available in some countries. Therefore, HoFH patients seem most vulnerable and mipomersen might indeed present a new treatment option for this condition. However, in order to restrict mipomersen's indication to patients with HoFH, further clinical data unequivocally showing safety and improved CVD profile/outcome would be essential. An extension of clinical programme only to HoFH patients is advisable, especially considering the existence of dedicated registries. The MACE endpoints should be clearly pre-defined and followed up. In terms of the timing of such studies, the experts agreed by consensus that these results are needed pre-approval.

Conclusions

There is no indication that there is a favourable B/R ratio in a specific group of patients because the safety concerns apply to all patient groups examined. Prior to its authorisation, further data including studies evaluating CVD endpoints and safety, liver toxicity, pro-inflammatory functions, and compatibility with apheresis are needed.

Given the inadequate therapeutic options, treatment could be initially considered in HoFH patients either refusing apheresis or in HoFH patients who do not have access to apheresis with a strict follow-up of individual subjects, i.e. regular liver biopsies, monitoring of liver enzymes and fatty liver. However, there is no evidence of clinical improvement in HoFH patients and mipomersen is a drug with a new mechanism of action exhibiting major safety concerns. By consensus, the experts agreed that further data in HoFH patients to confirm the benefits of mipomersen are needed prior to authorisation. Among other issues, these should examine mipomersen in patients on apheresis.

Mipomersen treatment is not warranted in patients with HeFH due to the lack of data supporting the CVD benefits of mipomersen therapy and unresolved safety aspects relating to neoplasms, CVD events, and hepatotoxicity. Additional clinical development exploring compatibility of apheresis and mipomersen combination and examination of the mechanism behind the apparent negative/none coronary and CVD events is needed, before indication in HeFH patients can be considered.

2.6.2. Conclusions on the clinical safety

The safety database presented is limited for a target population that intends to include patients with HeFH and HoFH, even if it is limited to severe cases, and raises serious safety concerns for the whole spectrum of patients. For a medicinal product that is intended to protect patients at high CV risk, the data on MACE during the phase 3 studies raise a safety concern. Mipomersen reduces LDL level in a relevant manner, but might induce other changes in CV risk factors that could counteract such effect.

Mipomersen is hepatotoxic and other mechanisms of liver damage beyond fat accumulation cannot be excluded. Importantly, steatosis is plausibly correlated with the effect on cholesterol levels, which introduces an additional doubt on the long-term use of this therapy, particularly in those patients where the beneficial effect in the lipid profile is more marked. There is no known threshold at which hepatic steatosis or liver fat fraction results in inflammation and progressive liver disease, which renders the monitoring of onset of liver related adverse events difficult. The long-term consequences of mipomersen-induced liver steatosis are of major concern and given the difficulties to monitor in clinical practice through non-invasive tests, it is considered a relevant ground for refusal of the marketing authorisation.

The numerically higher number of neoplasms and cancer raises an additional safety concern. There is no proven relationship between mipomersen treatment and the occurrence of neoplasm, mainly due to the low incidence rate, lack of systematic evaluation during the studies, and the short timing after start of mipomersen (1 year), but uncertainties remain. Mipomersen is also associated with a high incidence of IDRs, flu-like symptoms, effect on inflammatory markers and decrease on C3. Mipomersen may be immunogenic and antibodies were detected in 65% of subjects taking the

product. In addition, C3 decrease was more pronounced in patients with antibody formation. However, the consequences of these findings are unclear and have not been addressed under the current clinical development programme.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The documents that set out the detailed description of the system of pharmacovigilance (version 8, dated on July 1st, 2011) have been provided. Since April 8th, 2011, Genzyme became a wholly-owned subsidiary of Sanofi-Aventis. Because Genzyme and Sanofi-Aventis continue to exist as separate legal entities, their pharmacovigilance organisations will continue to operate separately. The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a risk management plan, which included a risk minimisation plan.

The RMP as proposed by the applicant is summarised as follows:

Summary of the EU Risk Management Plan

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Important Identified Risks		
Liver enzyme elevations	Ongoing Clinical Trials Active Surveillance – PASS Study Routine Pharmacovigilance	SmPC (Section 4.4) Package Leaflet Physician Education – Physician's guide to prescribing, monitoring, and patient management. Physician Education - Prescribing/dispensing algorithm/checklist
Increases in hepatic fat/steatosis	Ongoing Clinical Trials Active Surveillance – PASS Study Routine Pharmacovigilance	SmPC (Section 4.4) Package Leaflet Physician Education - Physician's guide to prescribing, monitoring, and patient management Physician Education - Prescribing/dispensing algorithm/checklist
Injection site reactions	Ongoing Clinical Trials Active Surveillance – PASS Study	SmPC (Section 4.4) Package Leaflet

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
	Routine Pharmacovigilance	
Flu-like symptoms	Ongoing Clinical Trials Active Surveillance – PASS Study Routine Pharmacovigilance	SmPC (Section 4.4) Package Leaflet
Immunogenicity	Ongoing Clinical Trials Routine Pharmacovigilance	Pending further data from risk evaluation activities; no specific risk minimization activities are proposed.
Important Potential Risks		
Hepatotoxicity (including hepatic fibrosis)	Ongoing Randomised Controlled Trials Active Surveillance – PASS Study Routine Pharmacovigilance	SmPC (Section 4.4) Package Leaflet
Inflammatory effects	Ongoing Clinical Trials	SmPC (Section 4.8) Pending further data from risk evaluation activities; no specific risk minimization activities are proposed.
Cardiovascular effects	Ongoing Clinical Trials Active Surveillance – PASS Study Routine Pharmacovigilance	SmPC (Section 4.4) Package Leaflet
Renal damage	Ongoing Clinical Trials Routine Pharmacovigilance	SmPC (Section 4.4)
Malignant neoplasm	Ongoing Clinical Trials Active Surveillance – PASS Study Routine Pharmacovigilance	Pending further data from risk evaluation activities; no specific risk minimization activities are proposed.
Decrease of platelet level	Ongoing Clinical Trials Active Surveillance – PASS Study Routine Pharmacovigilance	SmPC (Section 4.8)
Important Missing Information		
Exposure beyond 6 months	Ongoing Clinical Trials Active Surveillance – PASS Study Routine Pharmacovigilance	SmPC (Section 4.4)
Pre-existing hepatic disease	Active Surveillance – PASS Study Routine Pharmacovigilance	SmPC (Section 4.2) Package Leaflet
Pre-existing renal disease	Active Surveillance – PASS Study Routine Pharmacovigilance	SmPC (Section 4.2) Package Leaflet
Concomitant use of potential hepatotoxins (e.g., alcohol and paracetamol)	Active Surveillance –PASS Study Routine Pharmacovigilance	SmPC (Section 4.4) Package Leaflet
Use of mipomersen following acute cardiovascular events	Active Surveillance – PASS Study Routine Pharmacovigilance	SmPC (Section 4.4) Package Leaflet

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Use in paediatric patients ≥12 to <18 years of age	Randomised Controlled Trials Active Surveillance – PASS Study Routine Pharmacovigilance	SmPC (Section 4.2) Package Leaflet
Use in paediatric patients <12 years of age	Active Surveillance – PASS Study Routine Pharmacovigilance	SmPC (Section 4.2) Package Leaflet
Effects on pregnancy outcome	Active Surveillance – PASS Study Routine Pharmacovigilance	SmPC (Section 4.6) Package Leaflet
Use in patients with type I diabetes mellitus	Active Surveillance – PASS Study Routine Pharmacovigilance	SmPC (Section 4.2) Package Leaflet
Use in non-Caucasian populations	Ongoing Clinical Trials Active Surveillance – PASS Study Routine Pharmacovigilance	SmPC (Section 5.2) Package Leaflet
Use in lactating women	Routine Pharmacovigilance	SmPC (Section 4.6) Package Leaflet
Use in elderly patients ≥ 65 years of age	Routine Pharmacovigilance Active Surveillance – PASS Study	SmPC (Section 4.2) Package Leaflet
Antibody-mediated reactions	Ongoing Clinical Trials Active Surveillance – PASS Study Routine Pharmacovigilance	Pending further data from risk evaluation activities; no specific risk minimization activities are proposed.

SmPC, Summary of Product Characteristics

The CHMP, having considered the data submitted in the application was of the opinion that the proposed pharmacovigilance activities were not sufficiently detailed.

The CHMP questioned whether the studies proposed could adequately solve the concerns in an acceptable timeframe during post-authorisation, so that a possible harm to the patients could be avoided. The CHMP was of the opinion that the additional clinical data to answer the major relevant uncertainties should be provided prior to authorisation.

The CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to consider risk minimisation activities at this time due to the uncertainties regarding potential negative effects and feasibility to implement the proposed risk minimization measures in clinical practice.

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

However, due to the CHMP's conclusion on negative benefit-risk balance for mipomersen, the Product Information was not adopted.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Mipomersen is an antisense oligonucleotide that inhibits synthesis of apolipoprotein B by binding to a specific segment of the coding region of the mRNA. In patients with HoFH and severe HeFH, treatment with mipomersen on top of statins resulted in a marked statistically significant decline in LDL-C levels at primary efficacy timepoint (PET) at 6 months in comparison with the baseline. Approximately 70% of patients in the mipomersen groups of pivotal trials had at least a 15% decrease in LDL-C levels from baseline to PET in comparison with approximately 20% of patients in the placebo groups. The lowering of LFL-C is generally recognised as a surrogate endpoint for clinical development of lipid-lowering agents and it is expected that such effect would translate in to a cardiovascular benefit, which is in line with the valid CHMP guideline (CPMP/EWP/3020/03).

The effect on LDL-C was consistent, regardless of the pivotal study or geographic region. In general, sensitivity analyses conducted were robust and supported the results of the primary analysis on change in LDL-C. The beneficial effects in terms of reductions in LDL-C appeared to be sustained over time in patients who tolerated the drug up to 2 years. Consistent positive effects were also observed for other lipid parameters, like apo B, TC, and non HDL-C.

Uncertainty in the knowledge about the beneficial effects

Benefits at the population level

The lipid lowering strategies in general, and in HoFH and severe HeFH in particular, are intended for life-long therapy, since transient reductions of lipid levels are of no benefit. Tolerability to mipomersen is poor and, as shown by the submitted data, as many as 60-70% of patients had withdrawn from mipomersen treatment at 2 years in the extension study CS6. This was mainly due to mipomersen treatment intolerance. Thus, the benefits of mipomersen at the population level are significantly affected by the poor tolerability, markedly decreasing the rate of patients that may benefit from the lipid-lowering effect of the drug in the long-term. Even in case of the potentially more motivated HoFH patients, the retention rate was only 8% at 3 years (3 of 38 patients), with 63% (24 of 38 patients) withdrawing due to adverse events and 29% (11 of 38) who did only consented for one or two years of additional treatment.

Long-term benefits at the individual level

High LDL-C levels are well-known predictors of cardiovascular risk. In principle, in the EU, the effect of lipid lowering agents on LDL-C is accepted as a surrogate of clinical outcome for regulatory purposes, unless there is a suspicion from clinical data that the drug is associated with an increased CV risk through mechanisms other than its effect on lipids. The expected protective effect of mipomersen with respect to the CV risk in patients with HoFH and severe HeFH cannot be confirmed given the inconsistencies in the numbers of MACE between phase 3 pivotal studies and overall phase 3 studies in mipomersen treated patients. This casts the doubts on whether the drug is actually exerting its supposed protective effect. It is remarkable that in this target population, the analysis of MACE has been only undertaken on a retrospective basis, with no

pre-definition of MACE according to accepted standards, and no blind adjudication of events. The applicant did not sufficiently discuss these findings and considered this imbalance as a matter of chance in a population where MACE can be regarded as naturally occurring. Further analyses of CV risk markers suggested no differences between mipomersen-treated and placebo-treated patients in the pivotal studies (CS5 and MIPO35) with regards to blood pressure, chronic hsCRP levels, or renal function parameters. However, the results are inconclusive due to low numbers, unequal baseline values, and inconsistencies between studies or between datasets considered.

Place of mipomersen in the treatment of HoFH and HeFH patients

Comparative or additive studies of mipomersen and apheresis are lacking. Although most patients included in pivotal trials with mipomersen had LDL-C levels that would have qualified them for LDL apheresis, LDL apheresis was not permitted. It is acknowledged, that LDL apheresis is not widely available across Europe, guidance for its use vary from country to country and thus, it cannot be considered as a standard of care in HoFH or severe HeFH patients. Limited data suggest that the exposure and the effect of mipomersen might be dramatically reduced in patients undergoing apheresis. It is anticipated that in a large number of patients, particularly those with HoFH, mipomersen might be insufficient to reach the target of blood lipid parameters making it necessary to maintain apheresis. Further investigation is needed on the concomitant use of these treatments, i.e. whether mipomersen is able to reduce the requirements for apheresis, whether both treatments can coexist in a given patient and under which conditions. Until such data become available, the switch from LDL-apheresis to Kynamro and the concomitant use cannot be recommended.

Efficacy of mipomersen in special populations

Efficacy and pharmacokinetic data in subgroups are limited. Some important populations were excluded during mipomersen clinical development: patients with significant hepatic or renal disease, recent major cardiovascular event, congestive heart failure, recent LDL apheresis, elevated TG. The effect of mipomersen on LDL-C in elderly and pediatric patients seems to be in line with those in the overall population, but the number of patients (less than 10 subjects in each age group) is too small to draw definitive conclusions on mipomersen efficacy and safety in these special populations.

Risks

Unfavourable effects

Adverse events

Mipomersen therapy was associated with a clearly higher frequency of adverse events compared to patients who were on background lipid lowering therapy only. Nausea (13.8%), headache (11.9%), pain in extremity (6.5%), dizziness (5.0%), and cough (5.4%) were the most frequently reported nonspecific adverse events that occurred more frequently in mipomersen than placebo-treated patients.

In general, adverse events tended to reverse after treatment cessation, but definitely indicate that mipomersen is poorly tolerated and up to 30% of patients discontinued therapy during phase 3 studies and up to 50-70% in the 2-year open-label studies. ISRs, hepatotoxicity and

flu-like symptoms were the adverse reactions most commonly resulting in treatment discontinuation.

Hepatotoxicity

Hepatotoxicity is a major limiting factor of mipomersen safety. Fat (triglycerides) accumulation in the liver associated to the decrease in ApoB occurs as a direct consequence of the pharmacological effect of this drug and is correlated with its effect on blood lipid levels. 62% of patients in the mipomersen treatment group showed an increase in liver fat fraction ≥5% from baseline compared to 8% in the placebo group. Mean percent increase of liver fat content from baseline was above 12% in mipomersen-treated patients and less than 0.5% in placebo at 26 weeks.

Increases in liver enzymes were also more frequently observed in mipomersen. Results showed a trend correlating change in liver fat fraction and elevations in ALT values. 43/261 (16%) of mipomersen treated patients presented an increase in ALT above 3 ULN, 12 of them above 5 ULN. In 8% of cases there were 2 or more consecutive determinations of elevated ALT. In the placebo group only 1 patient showed an elevation of ALT above 3 ULN. Regarding AST, 9% of patients showed at least once values above 3 ULN vs. 1% in placebo. In the long-term study 16% of patients experienced increases in ALT and AST that met protocol-defined monitoring/safety rules for liver chemistry. In 8 (5.7%) of these patients, dosing with mipomersen was stopped.

Laboratory examinations

Proteinuria was more frequently observed with mipomersen than in placebo. The mechanism underlying this finding remains unclear. Mild elevations of hsCRP can be observed in patients receiving mipomersen, peaking during the first 2 days after dosing and then returning to baseline. No significant differences were observed during the double blind studies, however it is noted that baseline values differed between treatment group and hsCRP were done at through levels, just before next dosing.

Immunogenicity

Around 65% of patients develop antibodies to mipomersen while on therapy. According to the data provided, efficacy does not appear to be affected. The long-term safety consequences remain unknown. Antibody formation might induce complement consumption, although not to a significant extent, and formation of immunocomplexes can be detected in up to 30% of patients with antibodies. There seems to be an association between antibody detection and the presentation FLS. No clear relationship is observed with ISR, since this reaction is more likely mediated locally by cells.

Uncertainty in the knowledge about the unfavourable effects

The number of patients treated with mipomersen for at least 6 and 12 months is limited.

Cardiovascular safety

The major and unexpected limitation of the dossier is that the assessment of cardiovascular events was not prospectively defined and standardised during the clinical development of this medicinal product. A numerical imbalance in CV events versus placebo is apparent in controlled

phase 3 trials, mainly driven by MACE in pivotal trials and by hypertension in the pooled phase III trial population. There is also an imbalance in CV hospitalisations in comparison with placebo. Causality relationship between mipomersen and CV events is difficult to establish because the enrolled population is at high risk of CV events.

Based on detailed analyses of the comparative effects of mipomersen and placebo on key CV risk factors during phase 3 studies, an increased rate of proteinuria is apparent. The analysis of the effects on BP and CRP due to marked differences in baseline values and inconsistent results between trials is difficult to interpret. With respect to the renal damage, proteinuria and potential role of a pro-inflammatory reaction, there is no sufficient data to conclude on these issues, but a negative clinical impact counter-acting the effect on LDL-C cannot be ruled out. In addition, the mipomersen-induced fat accumulation in the liver might in the long-term be seen as a factor influencing the CV risk.

Hepatic safety

The long-term hepatic safety is not known. Fat liver accumulation increases over time and may naturally end up in liver fibrosis. It is not clinically confirmed whether these effects are reversible in the long-term use and for all patients. Even so, considering that liver fat accumulation correlates with effects on LDL, this hepatic effect is likely to appear in virtually all patients in whom the drug is exerting the therapeutic effect. Expert advice was requested on this specific concern. It was noted that there were limited data available on the exact effect of mipomersen on the liver. The doubts of hepatotoxicity, fat accumulation, and possible development of cirrhosis remain and the treated patients would need to be strictly monitored for their liver enzyme levels and detection of fatty liver using imaging techniques. Also, many patients develop fibrosis without enzyme level increases. Therefore, patients would also have to undergo regular liver biopsies. In general, conduct of biopsies was suggested every 2 years and after ALT levels increase significantly (e.g. 1 ½ over normal level), or when the fat liver content increases.

Neoplasms

An increased number of newly diagnosed neoplasms was observed: 22 in mipomersen (9 malignant) and 2 in placebo group (1 malignant). Neoplasms were not systematically evaluated throughout the studies and no particular pattern in type of neoplasia was observed. Definite conclusions are difficult to make as baseline examinations were not consistently made. This adds to the uncertainty of a potential association since the short-term duration between exposure and a newly found neoplasm renders an association in most cases unlikely, although a tumour unmasking effect cannot be ruled out. The increased incidence of neoplasms in mipomersen-treated patients observed in clinical trials remains an unresolved issue of concern.

Immunologically mediated reactions

Some of the more relevant reactions leading to treatment discontinuation are most likely immunologically mediated (ISR, FLS). Up to 60% of mipomersen treated patients develops antibodies. Circulating immune-complexes and C3 complement fraction consumption may be present. Thus, it is not known whether these findings may have long-term organ specific consequences.

Importance of favourable and unfavourable effects

Mipomersen demonstrated significant reductions in LDL-C levels in both, HoFH and severe HeFH patients, as well as in less severe HeFH and hypercholesterolemic patients with CAD. In particular, the HoFH patients have poorly controlled LDL-C levels and adequate therapy is lacking, so there is a clear medical need in this population. Although the long-term effect of lipid reduction of mipomersen on cardiovascular events has currently not been established, reduction in LDL-cholesterol is considered as an important surrogate endpoint with potential benefits in terms of cardiovascular outcome. The favourable effect on LDL-C of mipomersen in the long-term is, however, restricted to a small proportion of patients with HoFH or severe HeFH who tolerate the drug. Nevertheless, its clinical benefits in this setting remain undetermined. Mipomersen might be an alternative to LDL apheresis, but comparative or additive studies are lacking and at present its concomitant use or the switch from apheresis to mipomersen cannot be agreed.

The scarce clinical data with this new agent preclude a final conclusion on the absence of a detrimental effect on cardiovascular morbidity. A numerical imbalance in MACE events versus placebo is observed in pivotal studies but this was not apparent in the overall phase 3 studies. However, an increase in CV hospitalisations is apparent in the overall phase 3 studies. Any positive or negative effect in this regard should focus on ischemic CV risk. For these events, a similar rate of 3.85 vs 3.3/100 patient years (total 10 events) and a similar rate of hospitalisation due to ischemic events, in the phase 3 population was observed. A quantitative and detailed analysis of the effect of mipomersen on biological markers of CV risk (mean blood pressure, proteinuria, elevated hsCRP) neither confirms nor rules out this association due to low numbers, unequal baseline values, inconsistencies between studies or between datasets considered. Liver steatosis has been associated with insulin resistance and increased cardiovascular risk. No glucose alterations have been detected in the pivotal studies comparing mipomersen with placebo, but study duration is limited up to 26 weeks. In conclusion, although the LDL-C lowering effect of mipomersen is unquestionable and supposed to result in the long term in CV risk reduction, it is at this point in time unclear whether this could be counteracted through parallel unfavourable effects on other CV biomarkers.

The weekly subcutaneous administration in itself is not considered to be a major limitation. However, important unfavourable effects have also been observed leading to approximately 50-70% of the patients discontinuing treatment within 2 years. This is about 60% for the HoFH patient population with 80% of discontinuations due to AEs. Flu-like symptoms, injection site reactions and liver toxicity had a major impact on the tolerability of mipomersen. A major drawback of mipomersen treatment is the clear relation with hepatic adverse reactions that are linked to its mechanism of action. Progressive hepatic toxicity in the long term due to the occurrence of hepatic steatohepatitis cannot be ruled out and given of lack of adequate non-invasive monitoring methods for the detection of hepatic adverse events at an early stage to prevent liver damage, this has been considered a major drawback and a reason for the refusal of authorisation.

Unexpectedly, the numbers of neoplasms was increased. Definite conclusions are difficult to make as baseline examinations were not conducted consistently and the true association between mipomersen and any tumour promotion remains uncertain.

In summary, the relative importance of the favourable effects of mipomersen on lipid parameters (without a reduction in CV events) is limited by its poor tolerability and does not outweigh the

clinical importance of the unfavourable effects and the number of relevant uncertainties in relation to some unfavourable effects. This greatly limits its use in daily practice and questions it long term safety, in particular hepatic safety.

Benefit-risk balance

The B/R balance of mipomersen in the targeted population and indication is considered negative.

Discussion on the benefit-risk balance

Mipomersen significantly decreases LDL-C levels versus placebo at 6 months in patients with HoFH and severe HeFH on top of statins. However, only a limited portion of patient may benefit from this favourable effect in the long term given the poor tolerability of the treatment, which led to a high rate of treatment discontinuation in the clinical trials. In fact, a withdrawal rate of between 50% to 70% after 2 years (study CS6) may even be an underestimation of what could happen in a less selected population in standard practice, thus seriously diminishing the number of patients who may be benefit from the lipid lowering effect of mipomersen in the long-term. Unfortunately, it is currently not possible to identify a population with the highest benefit at the lowest risk for adverse reactions and subsequent withdrawal. Even in the restricted indication to the HoFH population, retention rate after 3 years of therapy may be as low as 8%.

A reliable safety profile of mipomersen is not demonstrated for a drug that is intended for life-long administration. The effect on lipid parameters has not been accompanied by a detectable effect (or even a trend) towards the reduction in MACE and/or CV mortality. On the contrary, a numerical higher rate of CV AEs (including MACE and CV hospitalisations) for mipomersen compared to placebo was observed. This imbalance cannot be considered in itself as a demonstration of any detrimental effect on CV outcome, but at least a trend favouring mipomersen or a neutral reporting rate would have been expected. As discussed above, uncertainties remain regarding potential negative effects on other cardiovascular risk factors that may counteract any beneficial effect due to reduction in LDL-C.

In addition, mipomersen induces liver toxicity with a clear relationship between mipomersen exposure and LDL-C decrease, as well as between mipomersen exposure, liver steatosis and treatment intolerability. Therefore, those patients in whom mipomersen is more effective are also the patients who are more likely to develop liver steatosis with higher withdrawal rates due to intolerability. The question remains how to identify patients at risk and whether persistent hepatotoxicity can evolve for some of inappropriately treated patients whose transaminases and liver fat fraction do not return to baseline after discontinuation and who are at risk to develop progressive disease. While in the limited number of patients treated during a short-medium period of time with mipomersen under close observation no irreversible damage has been observed, the long-term consequences of maintaining a pharmacologically induced non-alcoholic fatty liver disease, and in the long-term a potential non-alcoholic steatohepatitis remain unknown.

Therefore, the CHMP is of the opinion that the benefit/risk ratio for mipomersen is not favourable.

4. Recommendations

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that mipomersen (sodium) is qualified as a new active substance.

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Kynamro, an apolipoprotein B (apo B) synthesis inhibitor indicated as an adjunct to maximally tolerated lipid-lowering medicines and diet to reduce low density lipoprotein-cholesterol (LDL-C) in adult patients with homozygous familial hypercholesterolaemia, the CHMP considers by majority that:

the safety and efficacy of the above mentioned medicinal product is not sufficiently demonstrated, and, therefore recommends by majority the refusal of the granting of the Marketing Authorisation for the above mentioned medicinal product.

The CHMP considers that the following three grounds for the refusal of the MA:

The long-term benefit/risk of mipomersen remains undetermined, even if the indication is restricted to patients with HoFH.

- The long-term consequences of mipomersen-induced liver steatosis are of major concern and difficult to monitor in clinical practice through non-invasive tests.
- Uncertainties remain regarding effects of mipomersen on long-term cardiovascular outcome. In particular, the numerical imbalance in overall CV events, MACE and CV hospitalisations is of concern. Potential negative effects, in particular inflammatory effects, immunological reactivity, increase in blood pressure and renal toxicity (as shown by proteinuria) on other cardiovascular risk factors may counteract the potential beneficial effect on CV outcome due to reduction in LDL-C.
- The high overall withdrawal rate with mipomersen after 2-3 years, even in the restricted HoFH population, remains a major concern, thus severely limiting the number of patients that may obtain a potential benefit from its lipid-lowering effect. Given that withdrawals are mainly due to intolerance, it is unlikely that retention rates may be improved in a less selected population in standard practice.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, pharmacovigilance system, risk management plan and follow-up measures to address other concerns cannot be agreed at this stage.

Re-examination of the CHMP opinion of 13 December 2012

Following the CHMP conclusion that Kynamro was not approvable for the following indication:

Kynamro is an apolipoprotein B (apo B) synthesis inhibitor indicated as an adjunct to maximally tolerated lipid-lowering medicines and diet to reduce low density lipoprotein-cholesterol (LDL-C) in adult patients with homozygous familial hypercholesterolaemia (HoFH),

the applicant submitted detailed grounds for the re-examination of the above mentioned CHMP grounds for refusal, on 31 January 2013.

Following a request from the applicant at the time of the re-examination, the CHMP convened an Ad Hoc Expert Group inviting the experts, including patient representative, to provide their views on the questions posed by the CHMP, taking into account the applicant's response to the grounds for refusal. The applicant provided with the grounds for re-examination revised Summary of Product Characteristics (SmPC) and Risk Management Plan (RMP) proposals. The CHMP requested the advice of the Pharmacovigilance Risk Assessment Committee (PRAC) on specific questions related to the proposed RMP proposals. The PRAC's recommendation on specific CHMP questions was issued on 7 March 2013.

The applicant presented their detailed grounds for re-examination in writing on 31 January 2013 and at an oral explanation on 18 March 2013.

Detailed grounds for re-examination submitted by the applicant

Summary of applicant's detailed grounds for re-examination

The applicant requested a re-examination of the CHMP's opinion for mipomersen, to re-assess the benefit/risk in the very rare Homozygous Familial Hypercholesterolaemia (HoFH) population (estimated size in the European Union, 500 patients) with a high unmet medical need. The applicant addressed the CHMP's concerns of liver and cardiovascular safety, tolerability and patient retention, as well as post-approval management plans, in light of the benefit/risk in the HoFH population, which the applicant believes is positive.

The indication originally proposed in the mipomersen MAA included both HoFH and severe HeFH. Following discussions at the Scientific Advisory Group (SAG) meeting in September 2012, the applicant restricted the indication to HoFH patients only, in which the lifetime exposure to extremely high low density lipoprotein cholesterol (LDL-C) levels is responsible for CVS morbidity and early age mortality. The benefits of mipomersen-induced reductions in LDL-C in this population, which is at great risk of premature death, are anticipated to be large (potentially greater than 50% risk reduction of CHD, based on meta-analysis of multiple clinical trials), in contrast to the known and hypothetical risks of treatment with mipomersen.

The following issues were addressed by the applicant;

- A statistically significant mean reduction in LDL-C of approximately 25% (absolute change -2.92mmol/L) in patients with HoFH already receiving maximally tolerated lipid-lowering therapy is highly relevant for this small group of patients with a high unmet medical need;

- Effects of mipomersen on the liver (including increases in hepatic transaminases and hepatic fat) decrease or stabilize with continued treatment in most patients and return towards baseline when patients discontinue mipomersen treatment. The applicant presents a comprehensive approach to risk management for liver effects, including hepatic transaminase monitoring, liver imaging to assess hepatic fat, and observations of clinical signs/symptoms of possible liver damage.

- Within the context of the small number of patients tested, the 6-month treatment time of placebo-controlled studies, and the 6-month follow-up time, final conclusions regarding CVS adverse effects as demonstrated in the clinical studies cannot be reached at this time; however, the results of analyses performed to date do not provide support for a difference in the rate of MACE between treatment groups. Additional data will be collected in on-going and proposed studies.

- The rates of discontinuation from mipomersen treatment (taking into account the patient's consented length of treatment) are similar to those observed with statins and other lipid-lowering therapies and with other approved SC injectable therapies studied in similar long-term studies, although, due to a lack of placebo control in the long-term extension study, the true adherence rate in this study is not possible to assess. The applicant has proposed a Patient Support Programme (a broad adherence support programme) to help address this concern. While some patients might discontinue, patients remaining long-term are anticipated to receive benefit from substantial reductions in LDL-C.

The applicant presented an updated proposed SmPC and RMP, and the post-authorisation safety study (PASS) and believes that mipomersen would serve as an important therapeutic option to help address the significant unmet medical need of patients with HoFH.

The applicant addresses specifically the CHMP's initial grounds for refusal:

The long-term benefit/risk of mipomersen remains undetermined, even if the indication is restricted to patients with HoFH.

GROUND 1: *The long-term consequences of mipomersen-induced liver steatosis are of major concern and difficult to monitor in clinical practice through non-invasive tests.*

Applicant's position

Mipomersen results in increased hepatic transaminases and liver fat in some patients, which decreases or stabilises with continued treatment in most patients and return towards baseline when patients discontinue mipomersen treatment. However, the occurrence pattern of steatosis resembles that of benign nature. Although on the basis of the current data it cannot be ruled out that an individual patient might still develop long-term complications, close patient monitoring, thorough follow-up, and other proposed risk minimisation measures are considered sufficient.

The applicant agrees that it is vital to ensure that hepatic risks are minimised and closely monitored, and to collect further data regarding the hepatic effects of mipomersen. An approach to risk management for liver effects that supports the appropriate use of mipomersen in practice and ensures a positive benefit/risk for patients was proposed. Monitoring of liver effects in the proposed SmPC has been amended to include liver imaging to assess hepatic fat, both prior to

and during therapy, in addition to liver transaminase monitoring. This approach takes into account the possibility that significant hepatic fat could accumulate even in the absence of transaminase elevations. Increases in liver transaminases, hepatic fat, or clinical signs/symptoms of possible liver damage will lead to referral to a specialist (hepatologist) for further assessment and follow-up, which may include liver biopsy, if indicated. With this approach to monitoring, the patients who experience liver effects will be identified and followed such that appropriate action can be taken. Proposed post-approval plans to assess the hepatic effects of mipomersen thus include liver imaging, hepatic transaminases. Biopsy data will continue to be collected in ongoing and future studies, including ISIS 301012-CS6, MIPO38, and the PASS. The applicant believes that the framework of potential approval under exceptional circumstances, which prescribes a yearly re-assessment of the risk-benefit profile of mipomersen, constitutes a robust tool for the continuous monitoring of the drug profile while more data are becoming available.

Liver effects: During the course of the clinical programme, increases in hepatic transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) and hepatic fat were observed in a number of patients receiving mipomersen. The applicant describes that these effects decrease or stabilise in most patients with continued treatment and revert towards baseline levels upon discontinuation of mipomersen administration. In the pooled phase 3 studies, 16.5% of mipomersen-treated patients had at least 1 ALT result that was ≥ 3 x upper limit of normal (ULN) during the treatment period. One placebo-treated patient (0.8%) met this criterion. In the pooled phase 3 studies (n=261), 22 (8.4%) mipomersen-treated patients experienced treatment emergent ALT levels ≥ 3 x ULN on at least 2 consecutive occasions at least 7 days apart. Of the 22 patients with ALT levels ≥ 3 x ULN, 19 experienced decreases in ALT levels below 3 x ULN during continued treatment. Of the three patients whose ALT increase had not returned to < 3 x ULN within the treatment period, 1 withdrew from the study and further data are unavailable; ALT levels for another returned to < 3 x ULN before the end of the 24-week safety follow-up period and ALT for the third patient trended downward after the end of treatment but had not reached < 3 x ULN by the end of the follow-up period. No patients exhibited consecutive ALT elevations ≥ 3 x ULN in the placebo group.

In the pooled phase 3 analysis, there were no clinically significant changes in total bilirubin, alkaline phosphatase, albumin or prothrombin time (PT), including those patients with ALT elevations during the treatment period. No patients experienced ALT increases ≥ 3 x ULN with concomitant elevations in total bilirubin ≥ 2 x ULN during the treatment period. There were 4 patients across the phase 3 population with elevations in total bilirubin ≥ 2 x ULN during the treatment period but not in association with changes in either ALT or AST. Due to the mechanism of action of mipomersen, hepatic fat was assessed with MRI. In the two phase studies ISIS 301012-CS7 and ISIS 301012-CS12, where hepatic fat fraction was assessed with MRI at baseline and week 28, a median increase in hepatic fat fraction of 9.6% in mipomersen-treated patients *vs* 0.02% in placebo-treated patients was observed. Additionally, 61.8% of patients with paired MRI studies experienced a ≥5% increase from baseline in hepatic fat. In the pooled phase 3 studies, there was an association between higher increases in hepatic fat content and greater percent reductions in apo B consistent with the mipomersen mechanism of action. Study CS5 was initiated before it was fully appreciated that an increase in hepatic fat was likely to occur, and therefore hepatic fat was not routinely measured post-baseline in this study. There were 11 HoFH patients from CS5 with liver fat content assessments at baseline and at 12 months or longer on

mipomersen treatment. Changes in the liver fat content for these 11 HoFH patients were small; 2 of the 11 patients had a change of 5% or greater (+21.8% and +6.6%). The other 9 patients had slight negative change or less than a 5% increase.

The elevations in both hepatic transaminases and hepatic fat often decreased or stabilised with continued treatment and returned toward baseline, over a time period consistent with the 1- to 2-month half-life of mipomersen, upon cessation of mipomersen therapy. In patients on longer-term treatment in CS6, many patients did not have a documented increase in liver fat >5%. In some of the patients who had an increase in liver fat and continued mipomersen treatment, extended treatment with mipomersen was associated with liver fat stabilisation or decrease while on treatment. Liver biopsies were not initially included as part of the study protocols, but referral to a hepatologist for consideration of biopsy was added to the OLE CS6 protocol. In the course of the phase 2/3 clinical programme, 5 patients had liver biopsies. None of these patients had baseline biopsies. All patients with biopsies had increases in hepatic fat on MRS or MRI, and 4 of 5 patients had elevations in ALT ≥ 3 x ULN. Results of liver biopsy in these 5 patients with elevated fat fraction confirmed the presence of hepatic fat but showed minimal signs of inflammation with minimal to no liver fibrosis. Liver histology in biopsies to date has been consistent with the benign form of non-alcoholic fatty liver disease (NAFLD).

GROUND 2: *Uncertainties remain regarding effects of mipomersen on long-term cardiovascular outcome. In particular, the numerical imbalance in overall CVS events, MACE and CV hospitalisations is of concern. Potential negative effects, in particular inflammatory effects, immunological reactivity, increase in blood pressure and renal toxicity (as shown by proteinuria) on other cardiovascular risk factors may counteract the potential beneficial effect on CV outcome due to reduction in LDL-C.*

Applicant's position

The applicant believes that the post-hoc analysis of MACE that was the foundation of the CHMP's concern is based on a definition of MACE that as far as the applicant can ascertain has not been used previously. The applicant believes that this definition might be expected to yield misleading conclusions. Four post-hoc analyses have been performed to understand the available data from mipomersen-treated patients, including analyses by the applicant and by blinded independent reviewers. These include an analysis of prospectively defined events adjudicated by an independent agency, as requested by the CHMP, and a risk analysis performed by the US FDA. The mipomersen studies were not powered to compare CVS outcomes between treatment groups, and included only 6 months of placebo-controlled treatment and 6 months of follow-up.

Of the four analyses presented, only the cardiovascular morbidity analysis requested by the CHMP showed an identifiable difference in CVS events between the treatment arms. This analysis was based on an uncommon definition of CVS morbidity, since endpoints like hypertension AEs and venous thrombosis were requested to be included in this analysis, but have not been utilised in large randomised controlled clinical trials as a component of MACE analyses. Additionally, the EMA's draft guideline for assessing medicinal products in the treatment of lipid disorders does not include hypertension in its definition of MACE. The result presented from this analysis underpinning the CHMP's concern about CVS outcomes was driven by an imbalance in the reporting of an AE of hypertension, in the absence of an increase in mean blood pressure, changes in anti-hypertensive treatment, or shifts in blood pressure categories. No evidence of

changes in mean systolic or diastolic blood pressure in mipomersen treated patients has been shown. The CHMP discussion focuses on an analysis of events from CS5 plus MIPO35 studies, while noting that this imbalance is less apparent in the full phase 3 population. In fact, in the largest safety database analysed (pooled phase 2 and 3 patients), there was no significant difference in the occurrence of MACE events. The expected CVS impact of potential secondary effects, changes in other inflammatory biomarkers, or increases in hepatic fat in a subset of patients is likely to be minimal, as none of these factors are known to be causal. No evidence of changes in mean blood pressure has been shown. The effects of sustained LDL-C reductions of the size observed with mipomersen treatment are expected based on meta-analyses of data from multiple studies to result in a potential reduction in coronary heart disease risk greater than 50%. Because of the above considerations, the applicant agrees with the conclusions from the divergent positions document regarding the analyses that were reviewed.

Additional information on post-approval plans to further assess the CVS effects of mipomersen includes prospective adjudication of MACE implemented in placebo-controlled study MIPO38, and proposed for inclusion in the PASS study. Additionally, measurements of hsCRP, renal function parameters, and other items to further address the above concerns will be collected in MIPO38. The applicant believes that the framework of potential approval under exceptional circumstances, which prescribes a yearly reassessment of the risk-benefit profile of mipomersen, constitutes a robust tool for the continuous monitoring of the drug profile while more data are becoming available.

In CS5, statistically significant percent reductions in LDL-C were observed with mipomersen compared to placebo in HoFH patients receiving maximally tolerated lipid lowering medications (see table below). The mean percent change from baseline was -24.7% in mipomersen treated patients and -3.3% in placebo patients, resulting in a mean effect size of -21.4% (95% confidence interval [CI]: -32.7, -10.0). The mean absolute change in LDL-C in the mipomersen group was -2.92 mmol/L. For the placebo group, the mean absolute change in LDL-C was -0.31 mmol/L.

Table 1: Percent Change in LDL-C from Baseline to Primary Efficacy Time Point in Pivotal Study ISIS 301012-CS5

Statistic	Treatment Arm		p-value
	Mipomersen (N=34)	Placebo (N=17)	
Mean (SD) LDL-C at Baseline, mmol/L	11.37 (3.588)	10.37 (3.666)	
Mean (SD) LDL-C at PET, mmol/L	8.45 (3.142)	10.06 (3.899)	
Mean (SD) % Change from Baseline to PET	-24.7 (19.86)	-3.3 (17.06)	< 0.001
95% CI for % Change from Baseline to PET	(-31.6, -17.7)	(-12.1, 5.5)	--

The mean percent change in LDL-C over time in HoFH patients (CS5) is presented in the below figure. Results from patients who elected to participate in the on-going OLE study, CS6, demonstrated that long-term mipomersen treatment produces sustained reductions in LDL-C over at least 2 years of therapy. This was true for the overall population as well as the HoFH subgroup enrolled in ISIS 301012-CS6 (Figure below: HoFH and full population presented on the same panel for comparison purposes). The mean percent changes in lipid parameters during this

OLE study were consistent with those observed during the 26-week, double-blind treatment periods of the index studies.

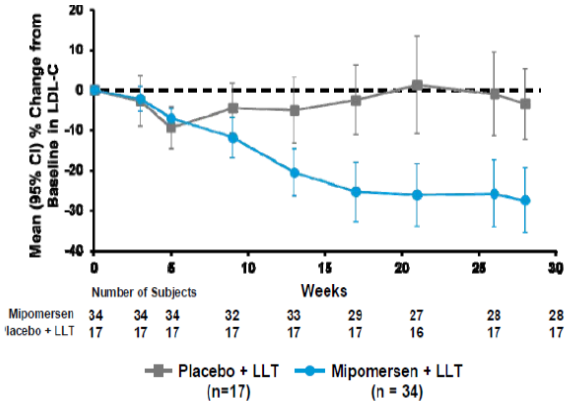
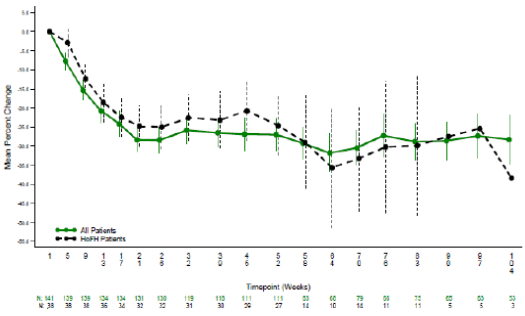


Figure 1: Mean Percent Change in LDL-C in ISIS 301012-CS5

Source: ISIS 301012-CS5 Figure 11-1

Figure 2: Mean Percent Change in LDL-C in ISIS 301012-CS6-- HoFH Patients and Full Patient Population



Source: POSTOE-FE-MEAN-LDL-OT-CS5-ALL-CS6.RTF

Note: Error bars indicate the 95% confidence intervals. In order to ensure a reasonable range for the y-axis, the 95% confidence interval is not shown when the number of patients (N) is less than 10.

Data are through 30 November 2011

CVS Benefit Based on LDL-C Levels

The causal role of LDL (as measured by LDL-C) in atherogenesis is well established and the LDL-C reductions provide outcome benefit across a wide range of LDL-C levels including the extremes of HoFH (Raal, 2011, Circulation) and are not specific to statins (Reiner, 2011, Eur Heart J). The LDL-C levels observed in HoFH patients confer excessive risk of morbidity and mortality on these patients. In one 5-year study, patients with LDL-C above 207 mg/dL (5.3 mmol/L) had an approximate 6% annual rate of non-fatal MI and cardiac death (Scandinavian Simvastatin Survival Study Group, 1995, Lancet). Another study showed that patients with FH with LDL-C levels above 260 mg/dL had an 8.29 fold increased risk of CAD incidence as compared to those with LDL-C levels below 206 mg/dL (Sugisawa, 2012, J Athero Thromb). The observed reductions in LDL-C with mipomersen would be expected to result in clinical benefit beyond that conferred by the patients' baseline lipid lowering regimen (including maximally tolerated statin), with a potential reduction in 5-year CHD risk greater than 50% based on extrapolation from a 2010 extensive review of lipid-lowering therapy effect on risk/events (Baigent, 2010, Lancet). Therefore, the observed decreases in LDL-C would be considered clinically important in the context of the high CHD risk associated with HoFH. Consistent with the mechanism of action, mipomersen produced the same or greater effect on apo B than LDL-C, with a mean decline of 26.8% in patients with HoFH. A significant reduction in Lp(a) of 31.1% was also observed in the pivotal Phase 3 study in patients with HoFH treated with mipomersen. These findings were confirmed in all three supportive mipomersen Phase 3 clinical studies. The reduction in Lp(a) is noteworthy since this lipoprotein, which is frequently elevated in FH patients (Mbewu, 1991, Arterioscler Thromb) and has been suggested to play a causal role in coronary disease (Clarke, 2009, N Engl J Med), is largely unaffected by other lipid-lowering therapies with the exception of niacin which lowers it minimally. Mipomersen treatment in patients with HoFH results in sustained efficacy with clinically significant mean percent reductions in LDL-C over two years of

therapy as demonstrated by data from a long-term extension study (CS6). In the proposed SmPC, it is advised that physicians continue monitoring the efficacy of the drug during longer periods of mipomersen therapy, and this proposal is considered to be feasible and appropriate in the context of the close clinical management of these particularly vulnerable patients, which is routine in specialized lipid treatment centres. Patients with HoFH are expected to derive clinically significant CV risk reductions with mipomersen therapy as a result of further reductions in LDL-C beyond what is achieved from current maximally-tolerated lipid lowering therapies. Therefore, mipomersen can be an important new potential therapeutic option for this population.

Mipomersen safety

This summary provides data related to concerns noted by the CHMP (i.e. potential liver and CVS effects). The safety summary focuses on the pooled safety data from the four Phase 3 placebo controlled clinical studies (CS5, MIPO35, ISIS 301012-CS7, and ISIS 301012-CS12) and the single-arm OLE study, CS6. While overall safety results in HoFH patients were generally similar to the pooled population, in the focused safety concerns addressed below, the effects observed in the HoFH population are compared to the full population analysis, particularly where meaningful differences were observed. Pooling of the Phase 3 studies for analysis was performed because the safety profile is best informed by the full set of available 6-month controlled data. This pooling was facilitated by the many common design elements (randomized, double-blind, placebo controlled studies of once weekly 189 mg mipomersen SC with 6-month treatment durations) to allow assessment of a larger data set from patients across a spectrum of CHD risk. The OLE study, CS6, provides the primary source of long-term safety data and demonstrates that the safety profile of mipomersen is consistent over time with no new or unexpected findings with longer-term treatment.

MACE and CVS Events

In the initial statistical analysis plan for the MAA, no assessment of MACE benefit was planned. Based on the small population size and 6-month controlled treatment followed by 6-month follow-up in the phase 3 studies, a cardiovascular event analysis would not be anticipated to provide meaningful data in the phase 3 study population nor in the even smaller indicated population. Additionally, MACE were neither prospectively defined nor independently adjudicated in the initial MAA. Despite these caveats, four post-hoc analyses have been performed to address this concern, both by the applicant and by independent reviewers:

1. A post-hoc analysis of MACE events (including acute coronary syndrome, acute myocardial infarction, angina unstable, cardiac failure, cardiogenic shock, cerebrovascular accident, infarction, and myocardial infarction [MI]) in the pooled phase 3 population, with the narratives for each of these events included. The results of this analysis showed that in the pooled phase 3 population during placebo-controlled studies, the MACE incidence was similar in the mipomersen-treated group (3.4%) and the placebo group (3.1%).

2. A post-hoc analysis using events requested by the CHMP (including Acute MI, Stroke or cerebrovascular accident (CVA), Unstable angina, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), Pulmonary embolism, Deep vein thrombosis, Transient ischemic attack, Hypertension, all of these events combined [termed "Cardiovascular morbidity"], and MACE events [defined as acute myocardial infarction, stroke or CVA, unstable angina, PCI, and CABG]) were presented both as number and

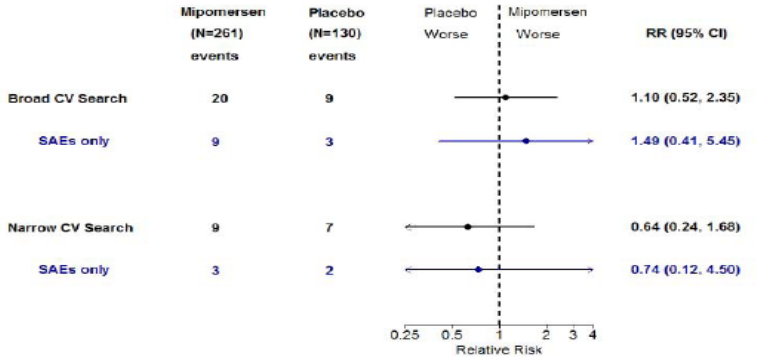
percent of patients with the events in each population, as well as the numbers of new events per 100 patient-years. While more cardiovascular morbidity events were noted in mipomersen-treated patients (18.8 events/100 patient-years) compared to placebo treated patients (10.1 events/100 patient-years) in the pooled phase 3 population, the imbalance was mainly due to an imbalance in the reported number of AEs of hypertension (12.0 events/100 patient-years in mipomersen-treated patients vs 4.4 events/100 patient-years in placebo-treated patients), which is not normally included in MACE analyses. In the largest safety database analysed (pooled phase 2 and 3 patients), there was no significant difference in the occurrence of MACE events per 100 patient-years between mipomersen treated patients (5.6 events/100 patient-years) and placebo-treated patients (5.3 events/100 patient-years). Only a single MACE event occurred in CS5, so no conclusions can be drawn regarding the HoFH population. Further analysis determined that there is no evidence of increases in either diastolic or systolic blood pressure over time in mipomersen-treated patients. It is possible that the increased number of reports of AEs of hypertension may be due to the advanced age of the patients, existing hypertension at baseline, and/or reporting bias. The occurrence of other individual events was not informative due to the small numbers of events, and no notable findings were observed.

3. An analysis using blinded retrospective adjudication performed by an independent consultant (SOCAR Research) requested by the Applicant in response to a request from the CHMP, presented in the response to JAR Question 1.3. As described in SOCAR's charter, the Applicant supplied SOCAR with all SAEs, all AEs and all procedures from these studies as recorded in the clinical database. No information pertaining to treatment assignment or treatment duration was supplied to SOCAR. SOCAR provided the prospectively defined list of events, and adjudicated the following: all fatal events; non-fatal MI; non-fatal stroke; hospitalization for unstable angina / acute coronary syndrome requiring an emergency coronary intervention (PCI/CABG); hospitalization for worsening heart failure; planned coronary revascularization procedures associated with angina or an angina equivalent; and peripheral revascularization procedures associated with (worsening) claudication. This independent analysis showed no difference in the incidence of MACE events per 100 patient-years in mipomersen treated patients (5.4 events/100 patient-years) versus placebo-treated patients (5.4 events/100 patient-years) in the pooled phase 3 population. Moreover, in general, patients reporting MACE in the mipomersen-treated group in the Pooled Phase 3 population had normal lab parameters with regard to inflammatory, immunogenic, blood pressure, and renal parameters, although in the patients with MACE events, hsCRP was higher prior to treatment (at baseline) than in the full Pooled Phase 3 population, but did not increase with mipomersen treatment. Only a single qualifying event occurred in CS5, so no conclusions can be drawn regarding the HoFH population.

4. An independent analysis performed by the FDA during the course of their review of the mipomersen dossier was also presented. This exploratory analysis was performed by searching CVS AEs included in pre-specified Broad and Narrow Standardised MedDRA Queries (SMQs) in the four Phase 3 clinical trials for mipomersen. Adverse events with Preferred Terms listed in the following MedDRA v14.1 SMQs were included in the “Broad” CVS search: Haemorrhagic cerebrovascular conditions SMQ; Ischaemic cerebrovascular conditions SMQ; and Ischaemic heart disease SMQ. Adverse events with Preferred Terms

listed in the following MedDRA v14.1 SMQs were included in the more specific "Narrow" CV search: Ischaemic cerebrovascular conditions SMQ and Myocardial infarction SMQ. The Relative Risk was estimated comparing mipomersen to placebo based on the results of these Broad and Narrow CV searches. This analysis included only the 26-week, placebo controlled treatment period. Results of this analysis are shown in the figure below. Twenty individuals on mipomersen (7.7%, N=261) and 9 individuals on placebo (6.9%, N=130) had a reported AE in the "Broad" SMQ search category. Nine individuals on mipomersen (3.5%) and 7 individuals on placebo (5.4%) had a reported AE in the "Narrow" SMQ search category. The estimated relative risk and 95% CI for the "Broad" CVS search were 1.10 (0.52, 2.35). The estimated relative risk and 95% CI for the "Narrow" CVS 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.

Figure 3: Relative Risk of Broad and Narrow Cardiovascular SMQs



Source:http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM323927.pdf.

GROUND 3: *The high overall withdrawal rate with mipomersen after 2-3 years, even in the restricted HoFH population, remains a major concern, thus severely limiting the number of patients that may obtain a potential benefit from its lipid-lowering effect. Given that withdrawals are mainly due to intolerance, it is unlikely that retention rates may be improved in a less selected population in standard practice.*

Applicant's position

Patients with HoFH frequently have extremely high LDL-C levels despite optimized existing therapies. While the applicant recognises that not every patient will remain on mipomersen treatment long-term, given the risks of early CV morbidity and death associated with HoFH, those who do remain on treatment are anticipated to benefit greatly, based on the long-term efficacy data from mipomersen studies. During the clinical trials, in those patients who did not benefit from mipomersen treatment or who withdrew due to tolerability issues, it is important to

note that no long-term adverse sequelae have been observed as a result of this limited exposure. Observed effects on liver enzymes and liver fat, when present, returned toward baseline levels after treatment discontinuation. Injection site reactions (ISRs) and flu-like symptoms (FLS) are self-limiting in nature. The overall benefit-risk assessment is therefore not adversely impacted by shorter-term treatment that does not provide long-term benefit to the patient. Patients with HoFH have an unmet medical need for additional therapeutic options. Failure to provide new options leaves these patients with few options to delay or prevent premature CV death. In the pivotal study in HoFH patients (CS5), 82.4% of mipomersen-treated patients completed the 6-month treatment period. The open-label extension study (OLE) CS6 was not designed to and cannot properly assess long-term adherence to mipomersen. The absence of a placebo group in this long-term study makes assessment of drug tolerability impossible. It is reasonable to expect that long-term motivation for remaining on an extension study with frequent clinical visits may fade, and that AEs that would not cause discontinuation of treatment in a post-approval "real world" setting may be used as reasons for leaving the extension study. It should also be noted that the CHMP AR cites retention rates that do not take into account the amount of time patients consented to treatment (for example, patients who consented to and completed 1 year of treatment were counted as discontinuations for the 3-year retention rate). Patients with HoFH are quite rare and are often entered into other clinical trials as soon as they complete the previous trial, so it is essential to take the consented length of study into consideration. Only a minority of patients were either eligible or were available at the times when the extension study was amended to two or more years; thus, most HoFH patients only consented to the 1-year extension. In the analysis of HoFH patients enrolled in the open-label extension study ISIS 301012-CS6 (which includes the time treated with mipomersen in CS5), 60.5% (23/38) of patients discontinued prior to their consented length of treatment (1 or 2 years) within the first 2 years, 47.4% (18/38) of these due to AEs. This rate is similar to that observed with statins and other lipid-lowering therapies and with other approved SC injectable therapies studied in similar long-term studies.

In clinical practice, prescribers and physicians will have access to the patients' on treatment LDL-C levels, and thus will be able to make an individualized benefit-risk assessment for each patient. While some patients might discontinue, patients remaining long-term are expected to receive benefit from substantial reductions in LDL-C. Additionally, all patients will receive the package leaflet and have access to the Kynamro Patient Support programme. Where allowed by local laws and guidelines, this broad adherence programme will include support phone lines, disease/therapy education, injection training (when possible from home-visiting nurses), information on expectations regarding ISRs and FLS, and a follow-up programme. The applicant is committed to fully and adequately resourcing this programme. Provider and patient education materials are intended to optimize patient benefit while minimizing risk and can encourage patients to continue mipomersen use when experiencing benefit while faced with transient tolerability issues.

Additional expert consultation - Report from the expert group meeting

Following a request from the applicant at the time of the re-examination, the CHMP convened an ad hoc expert group meeting inviting the experts, including patient representative, to provide their views on the questions posed by the CHMP, taking into account the applicant’s response to

the grounds for refusal.

1. **Do the experts consider that restriction of the indication to HoFH identifies the most appropriate patient population for treatment with Kynamro? If so, could the experts comment on the degree of unmet medical need and what diagnostic criteria should be used for homozygous hypercholesterolemia before Kynamro is recommended?**

The experts debated the definition of the HoFH and the diagnostic criteria needed for identification of patient population for treatment with mipomersen.

It was acknowledged, that some HoFH patients do not have high LDL-C levels. There is also a large variability in the genetic profile of HoFH patients. Consequently, not all HoFH patients would automatically become candidates for mipomersen treatment (based on individual assessment of risk/benefit). Therefore, the experts strongly recommended that all genetically confirmed HoFH patients be further phenotyped, and only patients with LDL-C levels above certain threshold at the baseline could be treated with mipomersen. The patient representative confirmed these requirements based on personal experience.

Conclusion: The experts concluded that the population with high unmet medical need would be constituted of phenotype compatible with high risk familiar hypercholesterolemia whose baseline LDL-C levels are >8mmol/L while being treated with optimal therapy AND genotype-confirmed HoFH patients and compound HeFH patients. In terms of response, at least a 25% decline in LDL-C level has to be obtained to consider the B/R favourable. The diagnostic criteria for these patients should be adhered to.

2. **Do the experts believe the effect on LDL-C in the homozygous population is clinically meaningful and expected to result in a significantly reduced CV risk? In addition, could the experts comment on the applicant´s assertion that LDL-C reductions of such magnitude would be "expected to translate into a potential reduction in 5-year CHD risk greater than 50%"?**

In general, the observed reduction in LDL-C levels appears to be meaningful; however, the proposed potential reduction in 5-year CHD risk remains to the confirmed in clinical practise, especially since the safety may be compromised (please refer to response to question 3).

Based on patient representative's feedback and hepatologists' experience, the patients undergoing apheresis experienced an immediate relief, i.e. sudden drop on LDL-C level, which is not present upon the mipomersen treatment initiation.

Several experts also pointed out that even if mipomersen lowers LDL-C levels, and even if this would diminish the risks for CHD, the real clinical meaning and prediction of CVS outcome is not possible to conclude on.

The experts concluded that although the effect on lowering the LDC-C level is relevant and a potentially important surrogate endpoint, there are no date supporting the assumed clinical cardiovascular benefit. Therefore, the experts did not support the assumption that the effect would translate to a >50% reduction in the 5-year CHD risk. This extrapolation was considered only hypothetical.

3. One of the concerns was the suggested numerically higher CV, renal events (proteinuria) and pro-inflammatory effects with Kynamro than with the comparator treatments, in the overall population. The experts are asked to comment on this apparent imbalance, and, in particular, if the difference/imbalance is of such concern that it would render the use of Kynamro in the HoFH population unsafe considering the magnitude of LDL-C reduction.

All experts considered the large number of negative signals and their various degrees of significance, since these could be suggestive of either the lack of efficacy or the unfavourable safety profile of mipomersen. These observed imbalances show a negative trend and of special concern is the lack of adjudication and pre-defined monitoring of the CVS events in the clinical studies. Overall, the CVS events are believed to be of major concern, especially when considering their lack in the placebo group with HoFH patients. Hospitalisation occurrence and rates are part of a composite event and should have been thoroughly followed by the applicant. Some experts noted that the applicant used several approaches to interpret the same data on CVS events, but each time concluding differently.

The cardiovascular benefit of mipomersen is not known due to the lack of data, and the expected benefit is hampered by the adverse events. Although the quality of safety data set is low, the experts concluded by consensus that a possible harmful effect cannot be excluded.

In terms of the observed renal and inflammatory events, the mechanism of action is unknown at this point in time and thus, these events need to be evaluated carefully. The applicant used a dipstick to access proteinuria and the results obtained from the small number of patients are questionable. It is believed that mipomersen accumulates in kidney and liver. In addition, given that mipomersen is an antisense protein, development of antibodies is not unexpected and occurred in a large percentage of patients. These can circulate in the body for a substantial length of time and influence kidney function.

The majority of experts concluded that in case the reduction in LDL-C is accepted as clinically meaningful (at least a 25% reduction), there is a main concern that the CVS, renal and inflammatory adverse events may counteract the assumed clinical benefit of mipomersen. One expert did not consider this of concern.

In conclusion, in the absence of a solid clinical outcome, lack of adjudication of CVS events and inconsistent pot-hoc analyses, the panel of experts wear not reassured that mipomersen is not conclusively linked to renal and CVS harm.

Due to the nature of the following two questions, these were addressed together.

4. The experts are asked to discuss whether:
- **the pattern of hepatic steatosis observed in mipomersen treated patients is likely to cause long term liver damage; and if**
- **there is a clear epidemiological or other evidence of progression of steatosis into inflammatory liver disease.**

Additionally, the experts are asked to comment on the relevance of increased transaminases in the setting of steatosis and if this increase is indicative of subclinical inflammatory process.

5. The applicant argues that steatosis is reversible and monitoring can detect steatosis or other hepatic damage. The experts are asked to comment what type of monitoring should be mandated in the label to ensure patient safety, the timing of such monitoring, and in which patients.

The experts debated the likelihood of liver steatosis progressing to steatohepatitis or fibrosis while patients are treated with mipomersen. It was noted that cirrhosis can occur even in children with steatohepatitis. If treatment with mipomersen leads only to the development of steatosis, the experts suggested that this risk could be manageable. However, based on clinical experience, 5 – 15% of patients with steatosis progress to the development of steatohepatitis within 3-4 years. With regards to the use of mipomersen, there are no data to contradict this clinical observation and thus, the risk of liver toxicity remains.

The applicant suggested measuring of ALT and AST levels as well as the employment of the MRI or other imaging techniques. However, the hepatologists advised that these methods are not reflective of the progress of significant liver damage. Measurements of the levels of transaminases, the use of imagining techniques or elastometry are insufficient and the only reliable method is liver biopsy.

At a baseline, i.e. initiation of mipomersen treatment, biopsy would not be needed, but becomes mandatory within the first year of treatment and must be repeated 2-3 years later, and this should be stated in the Product Information. If a cohort of 30-40 patients show that there is no progression to steatohepatitis or fibrosis, these monitoring requirements can be re-evaluate. Nevertheless, it was also acknowledged that patients cannot be forced to undergo biopsy.

In conclusion, the experts could not agree that there is not a definite epidemiological evidence of progression from steatosis to fibrosis. Mipomersen might not cause long term liver damage but there is no evidence to prove this. Neither is there a reassurance that the observed adverse effect will not progress to inflammatory liver disease.

Liver biopsy after 1 year if mipomersen treatment is mandatory for all patients with elevated transaminases or fatty liver (at Echo or MRI). If the first biopsy shows inflammatory liver disease, the benefit/risk and CVS benefit of mipomersen should be re-assessed by a specialist hepatologist and treatment can be stopped. If simple steatosis is shown, patients can remain on the treatment, but biopsy should be repeated at 2-3 years later.

6. The experts are asked to consider whether the observed hepatic effects are of sufficient concern to preclude the use of Kynamro in the HoFH population, also considering a third line option as an adjunct to maximally tolerated lipid-lowering medications and diet in HoFH patients who do not have other treatment options.

In light of the above discussion on the significance of the hepatic adverse events, the experts concluded that the current data do not allow for firm conclusions but under agreed follow up, the observed liver toxicity would not be expected to preclude the intended use of Kynamro in the identified population. Nevertheless, a reliable and thorough post-marketing monitoring should be mandated (liver biopsy) in this limited number of patients.

7. The experts are asked to comment on the overall tolerability of mipomersen, and whether there are steps that can be taken to improve adherence in the long term use.

The experts concluded by consensus that the overall tolerability of mipomersen is poor. The

observed 60% discontinuation after 2 years of treatment is of major concern considering that mipomersen is intended as a life-time therapy. Furthermore, in the open label study, a large number of patients decided to discontinue the treatment due to adverse event such as injection site reactions, flu like symptoms, etc., which represent adverse effects with high impact on patient's quality of life. Some experts also expressed concern if such events could and would be followed up diligently, since the treating physicians might be unlikely to address them. The experts felt that potentially, a restricted prescription programme in dedicated centres capable of providing support on individual patient basis might be helpful.

8. Given the limitation of the overall data set, are there post marketing studies or risk minimisation steps that could be utilised to provide answers to the concerns noted or reduce the risks of treatment? In addition, an indication of the duration of any such studies would be helpful.

The experts were of the opinion that the clinical programme presented for mipomersen was not adequate. There was a small sample size of HoFH patients. In addition, the lack of active comparator does not allow for adequate evaluation of the drug's benefit. In case of mipomersen's future authorisation, it was questioned whether a postmarketing study, with the inclusion of heterogeneous population and a lack of comparator, would resolve the current unfavourable safety profile of mipomersen or confirm its efficacy.

The question of a registry with mipomersen treated patients was also debated; however, this would not resolve the need for a comparator but would be mandatory to monitor the risk of the treatment.

Based on patient's representative's feedback, he would not discontinue apheresis and switch to mipomersen.

Therefore, the experts concluded that the only option in order to confirm the potential clinical efficacy of mipomersen and to assess its safety would be a prospective, comparator-controlled clinical trial in a wider patient population (HoFU and HeFH) and with a long duration of follow up.

PRAC Advice

Based on the PRAC review of the Risk Management Plan for Kynamro (version dated 14 January 2013), the PRAC considered by consensus that the risk management system for mipomersen is not acceptable.

PRAC advice on the specific CHMP questions:

Does the RMP adequately identify the risks involved i.e. hepatic, CV and renal risks?

Although the relevant risks (other than off label use) are identified within the proposed RMP, the PRAC considers that the proposed RMP is deficient in a number of important areas:

i) it fails to focus on the risks and missing information in the proposed indication – HoHF and does not present specific results and data relevant to HoFH patients. For example, no comparisons are made with results in other study populations and there is no information on the time to onset, extent and duration of increase of the AE, whether the AE resulted in a discontinuation of therapy and whether there was any association with efficacy. This

information is essential in order to inform risk minimisation measures.

ii) it does not adequately address the influence of concomitant medications e.g. statin therapy on AEs (particularly liver effects).

iii) The safety specification does not contain information on the variability of response in the indicated population and neither does it discuss any factors that could explain the very poor response in some patients. Furthermore, it lacks any proposals for further studies to better define patients likely to benefit from treatment with mipomersen.

Further specific and detailed points related to the safety specification are provided in the proposed RMP.

Hepatic steatosis: Is there adequate reassurance that the proposed monitoring will identify those affected by steatosis, and has provisions for identification of those at risk of long term hepatotoxicity?

The PRAC noted that the proposed RMP adequately describes the recommended monitoring for hepatic steatosis as defined in the product information. Assessments for liver steatosis by liver imaging (ultrasound, MRI, MRS) are planned to be performed every 6 months for the first 18 months and if stable, yearly thereafter. In patients who develop, or have an increase in steatosis (defined as either a qualitative change by ultrasound or a clinically significant increase of hepatic fat by MRI/MRS from baseline) a referral to a specialist is recommended. Additional risk minimisation is required to ensure that patients with risk factors for steatosis (central obesity, type 2 diabetes mellitus, hypertriglyceridemia or metabolic syndrome should be assessed by liver imaging to allow estimation of liver fat prior to baseline. Caution is advised in patients with risk factors for liver disease.

Nevertheless, phase 3 studies would suggest that increases in liver fat are not associated with baseline fat levels and are not always correlated with increase in hepatic enzymes. The PRAC considers that it is therefore critical that liver fat is assessed independently from elevations in liver enzymes. In almost all patients who developed increases in liver fat, increases were apparent within 6 months of initiation of treatment and hence, the proposed monitoring should capture all patients in whom liver fat increases.

However, the PRAC is of the opinion that the current risk minimisation measures are still inadequate in this respect, as they fail to provide clear recommendations on the need for, and the stage at which liver fat accumulation should lead to referral for specialist treatment.

Furthermore, the educational materials are deficient as they do not fully reflect the information on the recommendations for monitoring of liver enzymes and liver fat.

Is the potential for off label use in heterozygous hypercholesterolaemic patients adequately mitigated against (assuming the indication is restricted to the homozygous population)?

The PRAC is of the opinion that the risk of off label use is not addressed within the proposed RMP and the applicant has not provided any clear proposals for activities that would help to mitigate this risk and ensure that use is restricted to the HoFH population.

The proposed RMP fails to consider the potential for off label use in patients with heterozygous familial hypercholesterolaemia and severe hypercholesterolaemia or in paediatric patients (all

age subgroups below the age of 18 years).

Furthermore, off-label use in these populations is not included as a potential risk in the proposed RMP, and the proposed RMP does not include proposals for pharmacovigilance activities including studies to monitor off label use in the post-authorisation setting. It is unclear what further studies would be able to capture additional information on the potential for off-label use; a Drug Utilisation Study is unlikely to be able to capture this information in a systematic way and it is not clear whether the proposed PASS will adequately capture data in this respect.

Given the limitation of the overall data set, are there post marketing studies or risk minimisation steps that could be utilised to provide answers to the concerns noted or reduce the risks of treatment? In addition, an indication of the duration of any such studies would be helpful

The PRAC noted that the current proposed RMP describes three post marketing studies which the applicant considers can be utilised to extend safety information with Kynamro, MIPO3801011, ISIS 301012-CS6 and a PASS study.

The proposed RMP describes a randomised placebo controlled trial (MIPO3801011) in patients with severe heterozygous FH (HeFH) and inadequately controlled low density lipoprotein cholesterol. The study currently is proposed to examine two different dosing protocols, subcutaneous mipomersen 200mg once weekly and SC mipomersen 70mg thrice weekly (160 patients in each arm) versus placebo (160 patients) over a 60 week blinded treatment phase.

However, the applicant has stated that they are considering restricting this study to patients with more severe HeFH and therefore it is unclear how many HoFH patients will be included within this study and thus, how the study will extend information about important identified and potential risks in the indicated population or contribute to missing information. The proposed study is of 60 week duration, thus it is unlikely to provide information on long term benefit or risk.

The on-going OLE study (ISIS 301012-CS6) currently only includes 3 HoFH patients and in total only 39 patients are continuing treatment in this study. The details of this study and its applicability of this study to the indicated population is not adequately described within the proposed RMP and it unlikely to add to safety knowledge in the indicated population.

Post Authorisation Safety Study

The PASS protocol is provided in the proposed RMP and states that the study will be an open label, multi centre, and prospective post authorisation study and will enrol patients who provide signed informed consent and receive mipomersen during the 8 year PASS participation period (following a 3 year enrolment period). Patients who receive Kynamro will be treated and followed at the discretion of the treating physician and as guided by the provisions of the prevailing approved product label. Throughout the PASS Participation Period, data obtained from monitoring tests (ALT and AST levels, liver imaging to assess hepatic fat/steatosis, and lipid levels) will be collected.

The protocol states that safety will be assessed in terms of the occurrence of all treatment-emergent ADRs, SAEs, prospectively defined MEOIs, and changes in specified clinical laboratory results and other diagnostic assessments/evaluations. In addition, all deaths that occur during the study will be evaluated, including the cause of death. The study forms will

specify data elements of interest to be reported by the physician during the PASS participation period. Patients will also be asked to complete a patient diary to record information about dosing and study sites will maintain a treatment log to track Kynamro use. An independent CEC will be established to apply uniform criteria for the evaluation of cardiovascular events and to adjudicate these events in a consistent and unbiased manner. A DMC will also be established to provide independent review of safety data and to assure that risk to patients is minimized. All patients who are prescribed Kynamro will be strongly encouraged to enrol in this study for an 8-year PASS participation Period in order to facilitate collection of safety data for Kynamro when used in routine medical practice. The inclusion of each patient will be based on the decision by the physician to treat the patient with Kynamro. Events associated with efficacy will also be assessed e.g. insufficient efficacy.

The PRAC considers that the critical deficiencies of this PASS are its observational nature and the lack of a comparator group. Whilst the difficulties of designing a study with an appropriate comparison group are acknowledged, it is considered that such data is necessary in order to better characterise the known risks, explore the potential risks including cardiovascular effects and gather meaningful information on the longer term benefits and risks of mipomersen. The PRAC also expressed their concerns about the difficulties in ensuring adequate enrolment in such a PASS, given its voluntary nature. No clear proposals have been provided by the applicant about the plans to ensure adequate enrolment and to provide regular updates on recruitment and progress with respect to this PASS.

Furthermore, the PRAC considered that here is no discussion in the current RMP with regard to the option of other possible PhV methods for gaining further longer term data on the benefits and risks of mipomersen, e.g. a disease registry.

Risk Minimisation Measures

The proposed RMP provides details of a number of risk minimisation measures to reduce the risks of treatment which include:

- The restriction of the indication to homozygous familial hypercholesterolaemia;
- The exclusion of patient populations thought to be at particular risk of AEs including those with clinically significant liver disease and severe renal insufficiency, the statement that use of mipomersen is not recommended in patients within 3 months of a major acute CV event, with uncontrolled hypertension or with congestive heart failure (NYHA Class II or IV) and with clinically significant proteinuria;
- Monitoring recommendations for liver enzymes and hepatic fat accumulation;
- Referral criteria for hepatic adverse events;
- Education material for healthcare professionals and patients will highlight key safety messages.

The risk minimisation measures are considered by the PRAC to be inadequate in a number of areas; in particular there are no clear referral guidelines for increases in liver fat or criteria for stopping treatment in the event that a patient fails to have an acceptable response to treatment within a specified time. In addition, no proposals have been provided with regards to recommendations for minimising and monitoring off label use.

The CHMP endorsed the PRAC advice without changes.

Additional information provided by the applicant

During the Oral Explanation on 18 March 2013, the applicant proposed to further restrict the proposed population to be treated with mipomersen and the following revised indication was presented:

Kynamro is an apolipoprotein B (apo B) synthesis inhibitor indicated as an adjunct to maximally tolerated lipid-lowering medicines and diet to reduce low density lipoprotein-cholesterol (LDL-C) in adult patients with a phenotype consistent with high risk familial hypercholesterolaemia whose baseline treated LDL-C levels are ⩾8 mmol/L and genotypically confirmed homozygous or compound heterozygous familial hypercholesterolaemia.

Furthermore, the applicant proposed to the CHMP an amended wording in section 4.4 of the originally submitted SmPC. This relates to:

- lipid level monitoring: *After initiation of mipomersen, lipid levels should be monitored at least every 3 months for the first year. In patients whose LDL-C reduction over a 20 week period from start of therapy is less than 1.5 mmol/L, discontinuation of mipomersen therapy should be considered.*
- conduct of liver biopsies: *In addition, patients who have persistent elevated transaminases or an increase in steatosis (as defined above) after 1 year of therapy should have a liver biopsy. If the first biopsy shows inflammatory liver disease, the benefit/risk of mipomersen should be re-assessed by a specialist and treatment can be stopped. If simple steatosis is shown, patients can remain on the treatment, but biopsy should be repeated 3 years later.*

Overall conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant and considered the views of the PRAC (PRAC meeting 4-7 February 2013) and the advisory expert group held on 12 March 2013.

CHMP position on ground 1

In the clinical development programme increases in hepatic transaminases (ALT, AST) and liver fat were observed frequently in patients who received mipomersen therapy.

Liver enzyme increase

With regard to ALT and AST elevations, results from the pooled phase 3 studies (mipomersen n=261, placebo n=129, including patients with HoFH and HeFH) are summarized. In the pooled phase 3 studies, thirty six (13.8%) mipomersen-treated patients experienced increases in ALT and AST that met protocol-defined monitoring/safety rules for liver chemistry. For 14 (5.4%) of these patients, dosing with mipomersen was stopped (stopping rules were ⩾8 x ULN for AST/ALT on one occasion, ⩾5 x ULN for AST/ALT over 7 days, or ⩾3 x ULN for AST/ALT and elevated bilirubin). Of the 22 patients in the mipomersen-group with ALT levels ⩾ 3 x ULN, 19 experienced decreases in ALT levels below 3 x ULN during continued treatment. In the Open-Label Extension study, patients showed ALT increases (18%), AST increases (16%), hepatic enzyme increases (3%), abnormal liver function tests (2%), and transaminases increases (0.7%). Twenty two (15.6%) patients experienced increases in ALT and AST that met protocol-defined monitoring/safety rules for liver chemistry; for 8 (5.7%) of these patients, dosing with mipomersen was stopped.

The applicant claims that in the majority of patients ALT and AST levels stabilize or decrease even with continued treatment or they return to (near) baseline following discontinuation of mipomersen treatment. This may not be the case for all patients and for patients with sustained increase of ALT or AST level the risk in terms of hepatic damage still remains unclear. From the available data, it is also not clear whether patients´ ALT or AST levels reached a maximal effect (plateau). In all phase 3 studies, patients were excluded for “significant hepatic disease”. In case of the pivotal study in HoFH patients (ISIS 301012-CS5) patients with a documented history of hepatic disease, liver cirrhosis, or liver steatosis were also excluded. Exclusion criteria were also in place to ensure adequate hepatic function based on laboratory values (ALT, ALT > 1.5 x ULN).

Steatosis

The CHMP noted that in two phase 3 studies (ISIS 301012-CS7 and ISIS 301012-CS12) hepatic fat fraction was assessed with magnetic resonance imaging (MRI) at baseline and Week 28 (or early termination):

- a median increase in hepatic fat fraction of 9.6% in mipomersen treated patients versus 0.02% in placebo-treated patients was observed,
- 61.8% (63/102) of mipomersen treated patients with paired MRI studies experienced a ⩾5% increase from baseline in hepatic fat.

In the OLE study, the number of patients with available data at baseline and week 26, week 52 and week 72 is too small to draw firm conclusions regarding long-term effects on liver fat accumulation

with mipomersen treatment. In the pivotal study in HoFH patients (ISIS 301012-CS5), hepatic fat was not routinely measured post –baseline, however, according to the applicant, there were 11 patients from CS5 with liver fat content assessment at baseline and at 12 months or longer on mipomersen treatment.

There was an association between the higher increases in hepatic fat content and greater percent reductions in apo B consistent with the mipomersen mechanism of action, suggesting a direct relationship between the degree of mipomersen lipid-lowering effect and the degree of steatosis, which the CHMP considers to be a concern still not adequately addressed.

According to literature (e.g. as summarised in the AWMF guideline on the histopathology of non-alcoholic and alcoholic fatty liver disease; German Society of Pathology, 2009), the natural course of hepatic steatosis/non-alcoholic fatty liver disease (NAFLD) in individual patients is not predictable; it is indicated that steatosis may progress to steatohepatitis/NASH in about 10-20% of cases, and of these less than 5% ultimately develop cirrhosis. As liver biopsy was not performed on a regular basis in the mipomersen study programme, it is not clear whether a small or a significant proportion of patients with mipomersen-induced steatosis also had inflammatory changes and fibrosis, i.e. might develop steatohepatitis, which may not be reversible after stopping the treatment.

Thus, the CHMP concluded that with respect to mipomersen´s hepatotoxicity, no aspects other than the ones already assessed in the initial procedure, which could lead to different conclusions, were presented by the applicant. Mipomersen treatment can cause liver enzyme elevations and hepatic steatosis and this may induce steatohepatitis. There is a concern that this could progress to hepatic fibrosis and ultimately cirrhosis, over the course of several years still remained. Considering that liver fat accumulation correlates with its effects on LDL, this hepatic effect is likely to appear in virtually all patients in whom the drug is exerting a significant effect.

The crucial question is how to identify patients at particular risk of long term liver damage and whether persistent hepatotoxicity can evolve for some patients whose transaminases and increased liver fat fraction do not return to baseline after discontinuation of mipomersen treatment and who are thus at risk to develop progressive liver disease. Though such liver disease could develop after long-term treatment, and thus patients could have experienced CVS benefit, hepatotoxicity could also develop as sequel to liver enzyme elevations following only short term treatment, even if patients are discontinued early. These patients would not have experienced any CVS benefit. Mipomersen is a drug that is intended for life-long administration; therefore further long-term data on hepatic safety in HoFH patients are essential before marketing authorisation could be granted. The CHMP concluded that such data has not been presented by the applicant at this time point.

CHMP position on ground 2:

Retrospectively analysed CVS risk

The pivotal studies with mipomersen have neither been prospectively planned nor adjudicated for CVS safety outcome and thus, only limited conclusions can be drawn from the presented data. This is regarded by the CHMP as a major deficiency, and was also criticized by the expert advisory group.

The adopted Guideline on Clinical Investigation of Medicinal Products in the Treatment of Lipid

Disorders (CPMP/EWP/3020/03/2004), states on the matter that the safety database should be large enough to reasonably rule out any suspicion of a detrimental effect of the new drug on mortality and that this requirement acquires special relevance in case of drugs belonging to a new therapeutic class. Furthermore, the guideline also states that "a new lipid-modifying agent is only acceptable for authorisation if there is no suggestion of a detrimental effect on morbidity and mortality. Otherwise, additional studies to clarify the drug effect on these parameters are mandatory." The issue of prospective planning for CVS safety outcome is even more specifically addressed in the recent Draft Guideline on Clinical Investigation of Medicinal Products in the Treatment of Lipid Disorders (EMA/CHMP/718840/2012).

The CHMP acknowledged that in a small population like that of HoFH patients, the collection of a large database is not likely; nevertheless the importance of monitoring the CVS safety data as stressed in this guidance still applies. Therefore, the lack of predefined adjudication of CVS events is clearly a deficiency and, if a marked difference in CVS events is observed, this may raise a concern despite a small database.

Numerical imbalance in CVS events

Despite the fact that CVS events analyses were performed *post hoc*, the imbalance observed in the pivotal trials is worrisome. On the other hand, given the absence of events in the placebo arms of the combined pivotal phase 3 studies in patients at very high cardiovascular risk, the relatively small sample size and short study duration, this finding might also be attributed to a chance. This is based on the consideration that in a high risk population a larger proportion of events could be expected also in the placebo group. Indeed, an annual event rate of 6% has been described for a composite endpoint of non-fatal MI and cardiac death in a comparable population (Scandinavian-Simvastatin Survival Study Group, 1995, Lancet). A similar or even higher event rate might be expected for MACE (including acute myocardial infarction, stroke or CVA, unstable angina, PCI, and CABG) in a patient population such as the one enrolled in the pivotal phase 3 studies (HoFH and severe HeFH patients). Furthermore, in the placebo arm of the pooled phase 2 and 3 trial population including patients at somewhat lower CVS risk (as compared with the very high CV risk in HoFH patients), a higher number of MACE was noted, again potentially indicating that the absence of MACE in the placebo arms of the pivotal studies of overall small size might be a chance finding. Nevertheless, the relevance of the direct comparison to mipomersen within the two trials must not be disregarded.

Potential effect of LDL reduction

The applicant argues that the degree of LDL reduction observed with mipomersen treatment is expected to result in a potential reduction in coronary heart disease risk greater than 50%, which is based on meta-analyses of data from multiple studies (Baigent, 2010, the Lancet). The CHMP felt that this assumption would imply that the benefits of mipomersen treatment in HoFH patients would outweigh an unknown detrimental effect of this new substance. However, while it is agreed that the LDL reduction is predictive of a long-term CVS risk reduction, the implied magnitude of reduction of CHD risk of 50% is speculative. It cannot be taken for granted that the proposed extrapolations apply, i.e. whether the observed LDL reduction in HoFH patients, starting from LDL levels at the upper end of the scale, will translate into equally large CVS risk reductions as claimed for statin treated broad hyperlipidaemic populations of different states of health. This view was also supported by the experts who considered the extrapolation as only hypothetical.

In addition, it must also be considered that the estimates result from a small HoFH patient set, and though a treatment effect on LDL reduction is shown, the magnitude of this estimate is still prone to some variability. Finally, LDL reduction is only one mechanism affecting cardiovascular risk and as discussed above, no detrimental effect should be present that might counteract such improvements.

To conclude on ground 2, the discussion provided by the applicant for the re-examination of Kynamro does not provide a new insight to the former CHMP assessment on mipomersen treatment and CVS risk. Clinical studies have not been prospectively planned nor adjudicated for CVS safety outcomes so that only limited conclusions can be drawn from the presented data. Though considerable uncertainty remains, overall the analyses suggest an unfavourable effect of mipomersen treatment on several CVS risk factors. The CHMP also noted that the experts were not reassured that mipomersen is not conclusively linked to renal and CVS harm, and concluded that a >50% reduction in 5-year CHD risk as envisaged by the applicant for mipomersen treatment is purely hypothetical. Furthermore, although the relevant risks (apart from the off label use) are identified within the RMP, the PRAC considers the RMP insufficient to adequately identify CVS risk. A detrimental effect of mipomersen on CVS risk has not been shown but cannot be excluded since data are too limited.

CHMP position on ground 3

Focusing on the targeted HoFH population, the CHMP noted that the withdrawal rate for HoFH patients who had been enrolled in the pivotal 6 months DB study CS5 and consented to further participate in the OL extension study CS6 (for one or two years, including the time in CS5), was approximately 60% (23/38) within the first two years. Withdrawal rate was similar in HoFH patients and in the full population of OLE CS6 (56%). Within (maximal) 2 years of treatment almost 50% (18/38) of these HoFH patients withdrew from treatment due to AEs, mainly due to injection site reactions (ISRs), flu-like symptoms (FLS) and liver enzyme elevations.

The withdrawal rate - even if “similar to that observed with statins and other lipid-lowering therapies and with other approved SC injectable therapies studied in similar long-term studies” as claimed by the applicant - must be seen in the context of the identified safety concerns and the limited population studied.

With respect to the Kynamro Patient Support programme, the CHMP considered that its usefulness, suitability and applicability in different EU countries are difficult to foresee.

With regard to ground 3, the CHMP concluded that the high withdrawal rate is not per se regarded as a sufficient reason to withhold approval of an effective treatment option in a population of very high CVS risk, but, on a population level, the low tolerability resulting in low treatment adherence will have a negative impact on the utility of a treatment intended for long-term/life-long use. For the individual patient, the worst case scenario could be that they might not obtain the potential benefit of mipomersen in terms of reduced CVS morbidity/mortality because they cannot tolerate long-term treatment, but might be harmed by progressive liver disease resulting from mipomersen-induced steatohepatitis. Furthermore, the CHMP considered the input from the expert group meeting and noted that there was an agreement amongst the experts that the tolerability of mipomersen treatment was poor. The experts felt, however, that potentially a restricted prescription programme in dedicated centres capable of providing support on individual patient basis might be helpful.

As part of their discussions, the CHMP discussed whether a Marketing Authorisation under exceptional circumstances for Kynamro in the restricted claimed indication as presented by the applicant during the oral explanation could be considered. The CHMP concluded that such type of Marketing Authorisation could not be recommended in the present case as it does not fulfil the requirements of Article 14(8) of Regulation (EC) No 726/2004, in particular, as the applicant would be able to provide comprehensive data on the efficacy and safety under normal condition of use of Kynamro.

The CHMP also discussed whether a conditional Marketing Authorisation for the claimed restricted indication could be considered. This was not considered applicable either, even if possible within the scope of Article 2 of Commission Regulation (EC) No. 507/2006, as the requirements as defined in Article 4 of the said Regulation were not met, in particular the demonstration by the applicant of a positive risk-benefit balance of the medicinal product and the likelihood to provide comprehensive clinical data by way of specific obligations. Such conditional Marketing Authorisation could therefore not be recommended.

Overall, based on the assessment of the detailed grounds for re-examination submitted by the applicant, including the revised risk management proposals for monitoring of liver lipids and liver toxicity, and the revised restricted indication, as applied for by the applicant, the CHMP concluded that the benefit/risk of Kynamro remains unfavourable.

Recommendations following re-examination

Based on the arguments put forward by the applicant and all the supporting data on quality, safety and efficacy for Kynamro proposed for the treatment of

Kynamro is an apolipoprotein B (apo B) synthesis inhibitor indicated as an adjunct to maximally tolerated lipid-lowering medicines and diet to reduce low density lipoprotein-cholesterol (LDL-C) in adult patients with a phenotype consistent with high risk familial hypercholesterolaemia whose baseline treated LDL-C levels are ⩾8 mmol/L and genotypically confirmed homozygous or compound heterozygous familial hypercholesterolaemia.

the CHMP re-examined its initial opinion and in its final opinion concluded by majority that relative importance of the favourable effects of mipomersen on lipid parameters is limited by its adverse safety profile and poor tolerability, and does not outweigh the clinical importance of the unfavourable effects, and therefore, recommends the refusal of the granting of Marketing Authorisation for the above mentioned medicinal product. The CHMP considers that:

Whereas

the long-term benefit/risk of mipomersen remains undetermined, even if the indication is restricted to patients with HoFH. Although most of the relevant risks are identified within the risk management plan, the risk management system is considered inadequate and the proposed risk minimization measures are deficient in a number of important areas. The studies proposed are poorly defined and it is questioned that these can solve the concerns of particular interest like CVS events/hepatic toxicity.

- Uncertainties remain regarding effects of mipomersen on long-term cardiovascular

outcome. In particular, the numerical imbalance in overall CVS events, MACE and CVS hospitalizations is of concern. Potential negative effects, in particular inflammatory effects, immunological and renal toxicity (as shown by proteinuria) on other cardiovascular risk factors may counteract the potential beneficial effect on CVS outcome due to reduction in LDL-C.

- No conclusive evidence was provided to support the assumption that mipomersen-induced liver steatosis, which is associated with its mechanism of action, has a benign course. Concern remains about the potential progression of fatty liver disease to steatohepatitis and fibrosis, for which monitoring of patients at risk of developing inflammatory and fibrotic changes includes repeated liver biopsy. Furthermore, there is a potential risk of irreversibility of liver disease even if mipomersen-treatment is stopped.
- The high overall withdrawal rate with mipomersen after 2-3 years, even in the restricted HoFH population, remains a concern, thus severely limiting the number of patients that may obtain a potential benefit from its lipid-lowering effect. Given that withdrawals are mainly due to intolerance, it is unlikely that retention rates may be improved in clinical practice.

The CHMP is of the opinion that the safety and efficacy of the above mentioned medicinal product is not properly or sufficiently demonstrated.

Therefore, pursuant to Article 12 of Regulation (EC) No 726/2004, the CHMP has recommended the refusal of the granting of the marketing authorisation for Kynamro.

Divergent positions to the majority recommendation are appended below.

5. Appendix

Divergent Positions

The following members of CHMP did not agree with the CHMP's opinion recommending the refusal of the granting of a Marketing Authorisation for Kynamro.

The reasons for divergent opinion were as follows:

It has been shown that treatment with mipomersen leads to a significant reduction in LDL-cholesterol with a mean change of approximately 25% in patients with HoFH. This effect is considered to be a highly relevant for the HoFH population, which represents a small group of patients with a high unmet medical need for new LDL-cholesterol lowering drugs, in order to reduce their high cardiovascular risk and the risk of dying from ischemic heart disease at a young age. Existing therapies, such as statins and non-medical treatment (LDL-apheresis, if available and tolerated), do not show adequate efficacy. LDL-cholesterol is an accepted surrogate endpoint for cardiovascular disease, in particular in this patient group, and it may be assumed that reduction of LDL-cholesterol level with mipomersen will lead to an improved cardiovascular outcome.

Within the context of the small number of patients tested, final conclusions regarding cardiovascular adverse effects as demonstrated in the clinical studies cannot be reached at this point in time. The numerical difference in the reported incidence of MACE is driven by the increased occurrence of hypertensive events in the mipomersen group as compared to placebo. There is no mechanistic explanation to these observations, which could be seen as a chance finding since a negative effect based on the adverse event profile of mipomersen is considered unlikely. No significant effect on blood pressure has been observed in the clinical studies. Furthermore, no significant differences in the occurrence of ischemic heart disease were observed. Post-approval observational data could further characterise cardiovascular safety.

Effects of mipomersen on the liver, including increase in liver enzymes and in particular the incidence of steatosis, are related to the mechanism of action of mipomersen and generally show reversible characteristics after discontinuation. The occurrence pattern of steatosis resembles that of benign nature. Although on the basis of the current data it cannot be ruled out that an individual patient might still develop long term complications, close patient monitoring, thorough follow up, and other proposed risk minimisation measures are considered sufficient.

Tolerability due to adverse events, including injection site reactions and flu-like symptoms, remains an issue of concern, but retention rates seems to vary, not only between studies, but also between study sites, inside and outside of the EU. Physician communication and additional measurements to alleviate certain AEs may be important factors that determine patient's adherence to the treatment. With the proposed PASS-like study and the implementation of various risk-minimisation measures, further data would be derived from clinical practice in order to better characterise the safety profile of mipomersen.

In summary, it is considered that the potential benefits of mipomersen treatment in terms of the reduction of LDL-C levels in HoFH patients outweigh the potential uncertainties in safety in this very selective patient group with a high unmet medical need. Therefore, the benefit/risk in HoFH

patient is deemed positive and an approval under exceptional circumstances should be considered taking into account the proposed programme for careful follow-up in order to obtain more information on the benefit/risk balance.

London, 21 March 2013

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