28 January 2021
EMA/145271/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vazkepa

International non-proprietary name: icosapent ethyl

Procedure No. EMEA/H/C/005398/0000

Note

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

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Table of contents

List of abbreviations

Abbreviation	Definition
AMR101	Vazkepa, Miraxion, LAX-101
AUC_{ss}	area under the curve at steady state
AUC_{0-24}	area under the curve from zero to 24 hours
CE	cholesteryl esters
C_{max}	maximum concentration
C_{min}	trough (predose) concentration
CNS	central nervous system
DDI	drug-drug interaction
DPA	docosapentaenoic acid
EPA	eicosapentaenoic acid
ethyl-EPA	icosapent ethyl, ethyl eicosapentaenoate
GC	gas chromatography
HPLC	high-pressure liquid chromatography
IQR	interquartile range
LC/MS-MS	liquid chromatography with tandem mass spectrometry
LLOQ	lower limit of quantitation
LOD	limit of detection
LOQ	limit of quantitation
OM3	omega-3-acid ethyl esters
PD	pharmacodynamics
PK	pharmacokinetics
PL	phospholipids
SD	standard deviation

SPE	solid phase extraction
RBC	red blood cells
TAG	triacylglycerols
Vazkepa	icosapent ethyl, AMR101, ethyl-EPA

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Amarin Pharmaceuticals Ireland Limited submitted on 8 November 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Vazkepa, through the centralised procedure under Article 3 (2) (a). The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 29 May 2019.

The applicant applied for the following indication:

Vazkepa is indicated to reduce cardiovascular risk as an adjunct to statin therapy in adult patients with elevated triglyceride levels and other risk factors for cardiovascular disease.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - 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 test(s) or study(ies).

Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0217/2012 on the granting of a product-specific waiver.

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.

Applicant's request(s) for consideration

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

New active substance status

The applicant requested the active substance icosapent ethyl contained in the above medicinal product to be considered as a new active substance in comparison to the known mixture of "omega-3-acid

ethyl esters 90" previously authorised in the European Union as the applicant claimed that icosapent ethyl differs significantly in properties with regard to safety and/or efficacy from the already authorised active substance.

Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Martina Weise Co-Rapporteur: Alar Irs

The application was received by the EMA on	8 November 2019
The procedure started on	28 November 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	21 February 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	25 February 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	2 March 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	26 March 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	15 July 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	31 August 2020
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	17 September 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	06 November 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	01 December 2020
The CHMP agreed on a 2nd list of outstanding issues in writing to be sent to the applicant on	10 December 2020
The applicant submitted the responses to the 2nd CHMP List of Outstanding Issues on	30 December 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	13 January 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting	28 January 2021

a marketing authorisation to Vazkepa on	

2. Scientific discussion

2.1. Problem statement

Amarin Pharmaceuticals Ireland Limited applied for a marketing authorization in accordance with Article 8(3) of Directive No 2001/83/EC for Vazkepa, Icosapent ethyl (AMR101, ethyl-EPA) 1 g* soft capsules for the treatment of

Vascepa is indicated to reduce cardiovascular risk as an adjunct to statin therapy in adult patients with elevated triglyceride levels and other risk factors for cardiovascular disease.

The proposed daily oral dose of icosapent ethyl was 4 *g to be taken as two 1 *g capsules twice daily.

The CHMP approved Vazkepa for the following indication:

Vazkepa is indicated to reduce the risk of cardiovascular events in adult statin-treated patients at high cardiovascular risk with elevated triglycerides (≥150 mg/dL) and

- *established cardiovascular disease, or*
- *diabetes, and at least one other cardiovascular risk factor.*

For study details including cardiovascular risk factors and results with respect to effects on cardiovascular events see section 5.1.

The recommended daily oral dose is 4 capsules taken as two 998* mg capsules twice daily.

*During the review process, the strength was redefined in accordance with EU guidelines to 998 mg which represents the content of the active substance without the antioxidant. In the clinical studies the strength is stated to be 1 g as this is the declaration that was used until the redefinition during the EU review.

2.1.1. Disease or condition

Cardiovascular disease encompasses a broad group of medical problems that affect the circulatory system (the heart, blood vessels and arteries). Despite medical advances and broader use of available therapies such as statins, CVD remains the number one cause of death globally.

2.1.2. Epidemiology, Aetiology and pathogenesis

Cardiovascular disease causes more than half of all deaths across the European Region (World Health Organization [WHO] data accessed 13 May 2019). In the EU, each year CVD causes over 1.8 million deaths (around 800 000 deaths in men and 1 million deaths in women) which is 37% of all deaths (European Heart Network Report, 2017). In 2015, there were 6.1 million new cases of CVD in the EU and almost 49 million people were living with CVD in the EU. Half of these new CVD cases were due to ischaemic heart disease (1.63 million new cases in males, 1.4 million new cases in females), while

around 10% of new CVD cases were due to stroke (286 000 among males and 340 000 in females). Prevalence of severe hypertriglyceridemia (500 to 2,000 mg/dl) is rare Christian JB et al., The American Journal of Cardiology 2011; 107: 891 – 897) but elevated triglycerides at 150 mg/dL are a frequent observation. In Europe, the overall prevalence of hypertriglyceridemia (> 150 mg/dL) has been reported as 29.6% (Qiao Q, Group DS Diabetologia 2006; 49:2837–2846), while the prevalence of hypertriglyceridemia in individuals with coronary artery disease ranges between 21.1 and 44.6 % (KotsevaK et al., Eur J Cardiovasc Prev Rehabil 2009; 16:121–137).

Hypertriglyceridaemia (HTG) has been shown to be an independent risk factor for cardiovascular disease (CVD). high TG levels are often associated with low HDL-C and high levels of small dense LDL particles. The burden of HTG is high, with about one-third of adult individuals having TG levels >1.7 mmol/l (150 mg/dL) (Bergheanu SC et al. Neth Heart J 2017; 25: 231–242), Catapano AL et al., Eur Heart J. 2016;37:2999).

Lp(a) is a specialised form of LDL and consists of an LDL-like particle and the specific apolipoprotein (apo) A. Elevated Lp(a) is an additional independent risk marker and genetic data made it likely to be causal in the pathophysiology of atherosclerotic vascular disease and aortic stenosis (Kronenberg F et al., J Int Med. 2013; 273:6–30).

2.1.3. Clinical presentation, diagnosis and stage/prognosis

For a detailed review over clinical presentation and diagnostic approaches in patients with hypertriglyceridemia at increased CV risk it is referred to current clinical guidelines. Since 2003, the European Guidelines on CVD prevention in clinical practice recommend use of the SCORE system to evaluate CV risk, because it is based on large, representative European cohort datasets. Patients at higher risk of CVD include those with hyperlipidaemia (total cholesterol [TC], TG, LDL-C or combined hyperlipidaemia [both TC and TG], diabetes mellitus (DM), hypertension, smoking, and/or a family history of CVD. A more recent approach of differentiating CV risk in the context of the treatment of dyslipidemias has been proposed in the ESC/EAS Guideline for the management of dyslipidaemias, European Heart Journal (2020) 41, 111 – 188, Table 4, differentiating in more detail how CV risk categories relate to underlying conditions in this therapeutic area.

2.1.4. Management

Current Treatments for Prevention of Cardiovascular Disease in Patients with Elevated Lipids

Drugs that lower lipid levels include inhibitors of statins, PCSK9 inhibitors, selective cholesterol absorption inhibitors (e.g. ezetimibe), fibrates, niacin (nicotinic acid) and bile acid sequestrants (anion exchange resins).

In the EU, statins are currently the primary choice for lowering lipids due to their positive effect on decreasing CV morbidity and mortality (Catapano 2016). Patients with dyslipidaemia, particularly those with established CVD, diabetes mellitus (DM) or asymptomatic high risk individuals, may not always reach treatment goals, even with the highest tolerated statin dose. Therefore, combination treatment with statin may be recommended to prevent CVD in patients with persistent dyslipidaemia. Combined therapies with statin approved in the EU for prevention of CVD include PCSK9 inhibitors and selective cholesterol absorption inhibitors. The evidence of the CV benefit of fibrates (combined with statin and as monotherapy) and niacin is limited. Bile acid sequestrants are poorly tolerated and tend to increase plasma TG concentrations and are therefore not recommended by the ESC/EAS for routine use in CVD prevention2.

The use of statins in the EU for primary and/or secondary prevention of CVD is well established. Findings from 24 European countries reported the use of statins at 86% on average (Kotseva 2016). Statins, by decreasing LDL C, reduce CV morbidity and mortality as well as the need for coronary artery interventions (Colhoun 2004, Collins 2003). Statins at doses that effectively reduce LDL C by at least 50% also seem to halt progression or even contribute to regression of coronary atherosclerosis (Nissen 2006). A large meta-analysis reported a 10% proportional reduction in all cause mortality and 20% proportional reduction in coronary artery disease (CAD) death per 1 mmol/L (40 mg/dL) LDL C reduction (Baigent 2010). The risk of major coronary events was reduced by 24% and the risk of stroke was reduced by 16% per 1 mmol/L (40 mg/dL) LDL C reduction. Relative CV risk declines as LDL C is decreased, and, while theoretically a 'floor' exists, the level at which LDL C reduction does not further reduce risk has not yet been defined.

PCSK9 inhibitors and selective cholesterol absorption inhibitors are used as statin add on therapies in patients with persistent elevated LDL C. PCSK9 inhibitors can produce a rapid decrease in LDL C by up to 60%, either as monotherapy or in addition to the maximal statin dose (Piepoli 2016). A meta analysis of data from 20 trials indicated that compared with placebo, PCSK9 inhibitors (alirocumab, bococizumab and evolocumab) decreased the risk of CVD events, with a risk difference of 0.91%, but also increased the risk of adverse events, with a risk difference on 1.54%, the latter primarily due to the adverse effects of bococizumab, the development of which has been discontinued due to its immunogenicity (Schmidt 2017). Selective cholesterol absorption inhibitors (e.g. ezetimibe) are not usually used as monotherapy to decrease LDL C concentrations, unless patients are intolerant to statins. The ESC/EAS guidelines recommend selective cholesterol absorption inhibitors as combination therapy with statins in selected patients when a specific goal is not reached with the maximal tolerated dose of a statin (Catapano 2016)4. Based on the relatively limited body of evidence, clinicians may restrict the use of combination therapy with ezetimibe and statin to patients at high or very high risk of CVD.

Fibrates and niacin are used primarily to lower TG levels and increase HDL C and have the potential to be used as statin add on therapies in patients with persistent elevated TG levels. Evidence supporting the use of fibrates or niacin for CVD event reduction is limited. Furthermore, niacin is not currently approved in the EU. The 2016 ESC/ESA guidelines recommend combination treatment of statins with fenofibrate in high risk statin treated subjects with TGs >2.3 mmol/L (200 mg/dL)4. The efficacy of fibrates on CVD outcomes has not been clearly demonstrated (Jakob 2016, Cochrane review), despite reducing TG by up to 50% and increasing HDL C up to 10 15% (Catapano 2016). It has been reported that combinations of statins with fibrates may enhance the risk for myopathy (Catapano 2016)4. The joint ESC/ESA state that gemfibrozil should not be added to a statin treatment, because of the high potential for interactions (Piepoli 2016). The EMA conducted a review of nicotinic acid and related substances in 2013 (EMA/402540/2013). This resulted in the suspension of medicines containing the combination of nicotinic acid and laropiprant across the EU because new data failed to show any reduction in risk of major CV events (such as heart attack and stroke) and a higher frequency of non fatal but serious side effects.

In conclusion, current treatments for the prevention of CVD are available for statin treated patients with persistent elevated LDL C levels. However, elevated TG levels are also associated with atherosclerosis, increased risk of CVD events and all-cause mortality. In the EU there are no authorised treatments for the prevention of CVD in statin treated patients with elevated TG levels. Vazkepa is proposed for use in patients with elevated TGs who are already being treated with statins but remain at risk for major adverse coronary events (MACE).

About the product

Vazkepa contains icosapent ethyl, a derivative of EPA (eicosapentaenoic acid). EPA is part of approved medicinal products containing EPA/DHA that are licenced for the treatment of hypertriglyceridemia.

"*Vazkepa is indicated to reduce the risk of cardiovascular events in adult statin-treated patients at high cardiovascular risk with elevated triglycerides (≥150 mg/dL) and:*

• *established cardiovascular disease, or*

• *diabetes, and at least one other cardiovascular risk factor*

For study details including cardiovascular risk factors and results with respect to effects on cardiovascular events see Section 5.1. "

(revised wording)

It is intended for long-term therapy. The recommended daily oral dose is 4 capsules taken as two 998 mg capsules twice daily.

Type of Application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on the following argumentation.

"Although treatment options are available aiming at reduction of cardiovascular risk on top of statin therapy (PCSK9, ezetimibe) or at reduction of high triglyceride levels (fibrates, niacin, Omacor [containing EPA.DHA]), there is still a need to further reduce cardiovascular morbidity and mortality in patients at increased cardiovascular risk despite appropriate baseline therapy. This constitutes a major public health interest. However, it is not obvious that Vazkepa addresses this unmet medical need.

Vazkepa contains icosapent ethyl, a derivative of EPA (eicosapentaenoic acid). EPA is part of approved medicinal products containing EPA/DHA that are licenced for the treatment of hypertriglyceridemia. Previous trials investigating EPA/DHA and EPA in lower doses provided conflicting results. EPA/DHA containing drugs at lower doses lack efficacy in patients after myocardial infarction, and the results of another study with EPA at 1800 mg daily (JELIS study) are not straightforward in demonstrating a beneficial effect on CV outcome and all-cause mortality.

Different from previous trials, in the single pivotal trial supporting Vazkepa (REDUCE IT), the purified active moiety eicosapentaenoic acid was ethyl esterified and used at a higher dose (4 g daily) and DHA was not part of the product.

The association between the reduction of high TG and the CV outcomes is the matter of the discussion. The results of previous studies targeting the TG to reduce the CV risk are conflicting. In addition, the mode of action of EPA is not clear as the reduction of TG can explain only partly the beneficial effects observed in the REDUCE IT study.

The top-line results of the REDUCE-IT were seen as promising. However, a thorough review of all available data is needed as in this single pivotal trial there were some safety issues identified (e.g. increase risk of atrial fibrillation/flutter or serious bleeding events including intracranial in the active treatment arm) that require in depth analyses of benefit/risk balance in subgroups and with co-medications. Also, the choice of the comparator in the pivotal trial (mineral oil) could be questioned.

These considerations together with the numerous areas of uncertainty raise doubts that this medicinal product is of major interest from the point of view of public health, in particular from the viewpoint of

therapeutic innovation and if an accelerated time frame is appropriate given that it can be foreseen that an assessment of benefit and risk balance may not be straightforward and requires time and resources for the initial assessment and detailed discussions with the applicant within the procedure."

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as soft capsules containing 998 mg of icosapent ethyl as active substance.

Other ingredients are:

Capsule fill: all-rac-alpha-tocopherol

Capsule shell: gelatin, glycerol, maltitol liquid (E965 ii), sorbitol liquid, non-crystallising (E420 ii), purified water, and lecithin

Printing ink: titanium dioxide, propylene glycol, and hypromellose

The product is available in high density polyethylene (HDPE) bottles with a child-resistant polypropylene heat induction sealed closure and PVC/PCTFE/Al perforated unit dose blisters as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of active substance is ethyl (*5Z,8Z,11Z,14Z,17Z*)-5,8,11,14,17-icosapentaenoate corresponding to the molecular formula $C_{22}H_{34}O_2$. It has a relative molecular weight of 330.50 and the following structure:

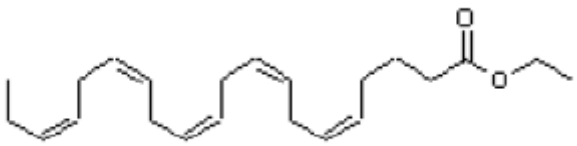


Figure 1: Active substance structure

The chemical structure of active substance was elucidated by a combination of GC-MS spectrometry, ^{13}C-NMR and ^{1}H-NMR spectroscopy, FT-IR spectroscopy, UV-visible spectrometry, and elemental analysis.

The active substance is a liquid oil at ambient room temperature with high solubility in organic solvents but no detectable solubility in water. The active substance has a low aqueous solubility and high permeability, it therefore is classified as a Class 2 compound according to the Biopharmaceutical

Classification System. The active substance is an oil that is insoluble in water and therefore not hygroscopic.

The active substance has a non-chiral molecular structure and polymorphism has not been observed.

The active substance can be readily oxidized, thus reducing the amount of eicosapentaenoic acid available for release following hydrolysis and also affecting the taste and smell of the oil. Therefore, it requires protection against oxidation. An antioxidant, all-rac-α-tocopherol, is added to the bulk active substance. Tocopherol is commonly used as an antioxidant by manufacturers of purified fish oil products. The addition of a suitable anti-oxidant (tocopherol) to the active substance is in line with the requirements of the Ph. Eur. monographs 2063 Omega-3-acid ethyl ester 60 and 1250 Omega-3-acid ethyl ester 90. In this case, none of these Ph. Eur. monographs is considered applicable in the entire form due to significantly different content of ethyl ester of eicosapentaenoic acid (EPA-EE) and docosahexaenoic acid (DHA-EE).

Manufacture, characterisation and process controls

Two active substance manufacturers were approved.

Different manufacturing processes are conducted by the individual active substance manufacturers. The applied production processes are based only on multiple purification procedures such as rectification/distillation and chromatography alone or combination of rectification/ distillation with chromatography lacking any synthetic chemical step. Depending on the individual active substance manufacturer, classification of the production process as dis-continuous or continuous or a combination of both is requested where necessary. In each case, tocopherol is added during the last manufacturing step.

Detailed information on the manufacturing of the active substance for the two approved manufacturers has been provided and it was considered satisfactory.

According to current ICH and EMA Guidelines, there is no specific guidance on the control of organic pollutants in active substances and finished products. However, principles of the ICH M7 Guideline would apply for mutagenic substances. Satisfactory information on potential impurities has been provided.

Furthermore, considering in general the requirements of the Ph. Eur. monograph 1250 Omega-3-acid ethyl ester 90, a sufficient control strategy for polychlorinated dibenzo-p-dioxines and polychlorinated dibenzofuranes, polychlorinated dibenzo-p-dioxines and polychlorinated dibenzofuranes and dioxinlike polychlorinated biphenyls, non-dioxinlike polychlorinated biphenyls and polybrominated diphenylether was required in each ASMF as Major Objection (MO). The control strategy was provided, and it was considered satisfactory.

In addition, transfer of the requirements for pesticides of Ph. Eur. monograph 2.8.13 Pesticide residues (which is primarily applicable for herbal drugs) to chemical medicinal products is considered possible, from the toxicological point of view. Sufficient control strategies for the most relevant pesticides in the API was requested where necessary as MO for both ASMFs. The control strategy was provided and considered satisfactory.An additional MO was raised regarding the limited of information provided on potential impurities for one of the manufacturers of the active substance. The information on potential impurities was provided and it was considered satisfactory.

Adequate in-process controls are applied during the syntheses. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance packaging materials comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification from the manufacturer of the finished product includes tests for description (visual), identification of icosapent ethyl (IR, GC), identification of tocopherol (HPLC), assay of icosapent ethyl (GC), tocopherol (HPCL), refractive index (Ph. Eur.), peroxide value (Ph. Eur.), anisidine value (Ph. Eur.), acid value (Ph. Eur.), cholesterol (USP), oligomers (Ph. Eur.), moisture (Ph. Eur.), sulphated ash/residue on ignition (Ph. Eur.), relative density/specific gravity (Ph. Eur.), inorganic impurities (ICP), residual solvents (GC), environmental contaminants (GC-MS), related substances (GC), other individual related substances (GC), and total related substances (GC).

The potential sources of impurities which may be present in icosapent ethyl are process impurities present in the active substance, and degradation products generated during active substance handling or storage.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis data of 52 batches of the active substance were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability studies were performed by the two manufactures of the active substances proposed, in general, the results of long-term, intermediate and accelerate stability data show that there is no significant change in any of the parameters studied. Based on the results from forced degradation and photo-stability studies, it was shown that the active substance is stable under light and high temperature but unstable with acid, base, humidity and oxygen.

More specific information on stability of the two manufacturers of the active substance is given bellow:

Active Substance Manufacturer 1

Stability data from 3 commercial scale batches of active substance from the proposed manufacturer stored simulated market containers for up to 36 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested*:* appearance, EPA EE assay, alpha-tocopherol assay, peroxide value and p-anisidine value*.* The analytical methods used were the same as for release and were stability indicating.

All parameters tested comply with the specification at accelerated stability study, and at long term stability study in the specified packaging. There are minimal changes in the tested parameters except for the oxidation indicating parameters, i.e. anisidine value and peroxide value. The results comply with the specification at all time points up to 36 months with exception of the assay results discussed

above which were due to possible degradation during testing of the samples. All other stability indicating parameters were within specification.

Photostability testing following the ICH guideline Q1B was performed on one batch. In the photostability study, the peroxide value slightly increased which can be attributed to the formation of peroxides caused by photo-oxidation. The only other slight change is the odour of the sample which has been reported as a slight fishy odour. This could be consistent with the production of low concentrations of volatile components as a by-product of photo-oxidation, which are commonly attributed as the cause of fishy odour of omega-3 products. There was no change in the other test parameters.

Results on stress conditions (high temperature and oxidative) were also provide on one batch There are no significant changes in EPA EE or α-tocopherol assay, which confirms that elevated storage temperatures do affect the oxidative stability of the active substance, but not to the degree that the assay decreases, or the antioxidant is consumed.

The overall stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months when stored in original containers blanketed with nitrogen in the proposed container.

Active Substance Manufacturer 2

Stability data from 12 commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 36 months under long term conditions (25 ºC / 60% RH), for up 12 months under intermediate conditions (30 ºC / 65% RH), and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The parameters tested are the same as for release.

All batches remain within specifications under long term, intermediate and accelerated stability conditions.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months without restrictions in storage conditions in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is supplied as soft gelatin capsules for oral administration containing 998 mg of the active substance. The soft gelatin capsule is oblong measuring 25 x 10 mm and printed with "IPE" in white ink, with a light yellow to amber shell containing a colourless to pale yellow liquid.

Soft gelatine capsules containing fish oil are standard dosage form that has been available for many years. Based on historical experience, a standard soft gelatine capsule formulation, including suitable plasticizer excipients, was selected for the finished product.

The active substance is the ethyl ester of eicosapentaenoic acid (EPA-EE). It is hydrolyzed by esterases to liberate the free fatty acid EPA. Extensive stability studies have demonstrated compatibility and stability of the active substance with the capsule shell excipients.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards except opacode which is tested according to in-house specifications. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The primary packaging material is high density polyethylene (HDPE) bottles with a child-resistant polypropylene heat induction sealed closure and PVC/PCTFE/Al perforated unit dose blisters. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The bulk product is manufactured by three manufacturing sites.

The manufacturing process consists of 5 main steps: fill material preparation process, gelatine shell preparation process, encapsulation and drying process, capsule printing process, and bulk packaging process. The process is considered to be a standard manufacturing process.

The finished product dossier information provided, indicated that the three finished product manufacturing sites proposed, seemed to produce different medicinal products. The approval three different medicinal products within one marketing authorization was not considered acceptable. Consequently, the CHMP requested as Major Objection (MO) that the following issues should be solved: the composition of the finished product should be the same for all manufacturing sites, to provide the common manufacturing description with unified IPCs and separately identify as well as justify technical adaptions applied to the different manufacturing sites hence a single section containing information on the manufacturing process has to be provided. In addition, the stability data provided indicated that the different manufacturing sites produce finished products of different quality, therefore a discussion and justification of the impact of observed differences in regard to the product quality and stability should be provided. As response, the applicant combined the information from the three finished product sections, and slight differences between the manufacturing process were identified and justified. Description and composition of the finished product were combined for all manufacturing sites and the composition of finished product was presented across manufacturers. A common manufacturing description of the manufacturing process has been presented to provide an overall description of the manufacturing process that applies across all manufacturers, including a description of the process for primary packaging. The stability data for the finished product is extensive in number of batches, with data generated for finished product manufactured by all three proposed manufacturers. Results are generally within specifications at long term conditions and no significant trends are observed. It is, however, recognized that some variability is seen, which in most cases is related to analytical variability; this was considered satisfactory.

Critical steps were identified, and the proposed in-process controls are adequate for this type of manufacturing process. Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. Taking into account the applicant's long-time experience in producing soft capsules and validation data available no additional validation data are considered necessary within this marketing authorization procedure. Confirmation has been provided that validation activities conducted to support the scale up of the commercial batch size. However, it could not be concluded that the process to manufacture of the finished product is fully validated for each proposed batch size with the data provided. Therefore, the CHMP recommended that per manufacturing site, the first three consecutive commercial batches of the largest scale batches should be fully validated. Process validation batches will be prepared and executed according to the validation

scheme as provided in Module 3.2.R. The process validation at the maximum capsule batch size should take into consideration all previous process validation data for smaller batch sizes and demonstrate that the manufacturing process is independent of batch size within the range of all previous process validation batches. With this successful demonstration of scale independence all batch sizes within this range will be.

Product specification

The finished product release and shelf life specifications include appropriate tests for this kind of dosage form: description (visual), identification of icosapent ethyl (GC, IR); identification of tocopherol (HPLC), uniformity of dosage form (Ph. Eur.), assay of icosapent ethyl (GC), assay of tocopherol (HPLC), disintegration, minutes (Ph. Eur.), peroxide value (Ph. Eur.), anisidine Value (Ph. Eur.) and microbiological examination (Ph. Eur.)

The specification parameters and limits are considered acceptable.

Each of the finished product manufacturers have performed risk assessments to evaluate the potential presence of elemental impurities in the finished product in accordance with the ICH Q3D Guideline for Elemental Impurities. The assessment of elemental impurities contributed from potential sources including active substance, excipients, manufacturing process, and container closure systems was provided. The overall risk assessment supports that the current manufacturing process and in-process controls in place provide adequate control for elemental impurities. No additional controls have been recommended by the manufacturers and no changes have been made to them due to the risk assessment.

The applicant has conducted a risk assessment for the presence of nitrosamine impurities in the finished product in response to the CHMP request and in accordance with Guidance EMA/189634/2019. This risk assessment included a review of the entire product supply chain including excipient / active pharmaceutical ingredient manufacturing, bulk finished product manufacturing, and packaging components. The risk assessments and supplier statements for each component resulted in no risk identified for nitrosamine contamination.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used testing has been presented.

Batch analysis results were provided for several batches from the three manufacturers confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability studies have been performed in the finished product manufactured by the three manufacturers.

Stability data from numerous batches of the finished product from each one of the three manufacturers and the physician sample presentation were provided. The batches were stored for up to 60 months from the date of manufacture (of bulk capsules) under long term conditions (25ºC / 60% RH), and for up to 6 months from the date of manufacture (of bulk capsules) under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed within two proposed for marketing container-closures.

Stability data in bulk container from one commercial scale batch of the finished product from each the proposed manufacturer stored for up to 24 months under long term conditions (25ºC / 60% RH).

Samples were tested for description (capsules), description (package), disintegration, hardness, peroxide value, anisidine value, assay icosapent ethyl, assay of tocopherol, related substances, each other individual impurities, total related impurities, and microbiological enumeration. The analytical procedures used are stability indicating.

There are no trends observed with finished product at long term and accelerated stability conditions for the finished product in the two containers proposed for marketing manufactured by the 3 manufacturers. The data remain well within the shelf-life specification.

No stability studies have been initiated on the capsules packed in PVC/PCTFE/Al blisters manufactured by one manufacturing site. The applicant justified that all packaging activities for both bottle and blister presentations occur at the same packaging manufacturers regardless of the source of the bulk finished product. The applicant stated that the stability data for blister packages is fully representative of the quality and performance of the finished product for all bulk finished product manufacturers and the reason why stability studies for blister packages made using this bulk finished product had not been initiated due to the less frequent manufacturing schedule compared to bottles. The CHMP recommended that, although the product has shown good stability based on the data provided, the first three commercial scale batches manufactured at each manufacturing site (largest scale validation batches) should be placed on long term as well as accelerated stability program to get representative data confirming stability of the finished product at each manufacturing site.

One batch of three packaging configurations (bottle, blister and bulk) were studied in a photostability program in accordance with ICH Q1B, Photostability Testing of New Drug Substances and Products, Option 2. All samples met the acceptance criteria specified in the protocol, and there are no apparent data trends. The data demonstrate that the finished product packaged in the proposed primary packaging is stable to light conditionsThe primary and supportive stability data demonstrate that the finished product is stable in bulk for up to 24 months at 25°C/60%RH. There was an observed trend of increasing Peroxide Value, but the data remain well within the shelf-life specification. No other significant changes in test results are observed for test intervals up to 24 months in capsules stored at the long-term condition.

Based on available stability data, the proposed shelf-life of 4 years from the date of manufacture (of bulk capsules) and store below 30°C as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

This product is a soft capsule containing 998 mg of icosapent ethyl. It is manufactured from fish oil and is further highly purified through multiple purification procedures. The active moiety of icosapent ethyl (EPA-EE) is eicosapentaenoic acid (EPA).

The major objections relating to absence of organic pollutants in the active substance control and for polychlorinated dibenzo-p-dioxines and polychlorinated dibenzofuranes, polychlorinated dibenzo-p-dioxines and polychlorinated dibenzofuranes and dioxinlike polychlorinated biphenyls, non-dioxinlike

polychlorinated biphenyls and polybrominated diphenylether control have has been resolved by implementing a control strategy. Regarding the major objection on the limited information on potential impurities of the active substance by one of the ASMFH, this information has been provided and considered satisfactory. Moreover, an additional major objection on the finished product in relation to the demonstration of comparability of finished product from different manufacturing sites was raised. The applicant has provided information which demonstrates that the finished product manufactured at different manufacturing sites produce finished product of the same quality. However, some variability is seen, which in most cases is related to analytical variability and this was considered satisfactory.

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 clinical use.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- Per manufacturing site the first three consecutive commercial batches of the largest scale batches should be fully validated. Process validation batches will be prepared and executed according to the validation scheme as provided in Module 3.2.R. The process validation at the maximum capsule batch size should take into consideration all previous process validation data for smaller batch sizes and demonstrate that the manufacturing process is independent of batch size within the range of all previous process validation batches. With this successful demonstration of scale independence all batch sizes within this range will be considered validated.

- First three commercial scale batches manufactured at each manufacturing site (largest scale validation batches) should be placed on long term as well as accelerated stability program to get representative data confirming stability of the finished product at each manufacturing site.

2.3. Non-clinical aspects

2.3.1. Introduction

The applicant has not performed its own studies on the pre-clinical pharmacology of EPA, but instead the applicant discussed the results of some published pharmacology studies performed with EPA.

The nonclinical testing strategy for AMR101 was based on extensive information on the toxicology profile, and the clinical safety of Ethyl-EPA in the public domain.

Amarin has evaluated the extensive published literature available on the safety of Ethyl-EPA, and accordingly commissioned a relevant, Good Laboratory Practice (GLP)-compliant, animal sparing, toxicology program in mice, rats and dogs according to ICH M3(R2).

These studies include: a 28-day study in wild-type rasH2 mice, two 28-day studies in rats (Wistar, Sprague Dawley), a 14-day dose-range finding study in beagle dogs, a 39-week study in beagle dogs, a developmental toxicity study in rats (Wistar), standard battery of genotoxicity studies, a 104-week carcinogenicity study in rats (Wistar), and a 26-week carcinogenicity study in 001178-T (hemizygous) mice. Amarin's investigation of the literature identified toxicology studies conducted by Mochida and these are provided in lieu of study reports.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The primary mechanism of action of EPA is due to enhanced beta-oxidation of fatty acids resulting in less substrate for very low-density lipoprotein (VLDL) synthesis, enhancement of lipoprotein lipase (LPL) activity, inhibition of apolipoprotein C3 (apoC3), activation of peroxisome proliferator-activated receptors (PPARs), hepatic lipase (HL) and cholesteryl ester transfer protein (CETP); reduction of proprotein convertase subtilisin/kexin type 9 (PCSK9) may also be affected by Ω-3FA intake. EPA has an inhibitory effect on intestinal cholesterol absorption and hepatic cholesterol biosynthesis, and an enhancing effect on hepatic biliary secretion. Ethyl-EPA treatment increases the clearance of serum lipoproteins from the serum. Administration of EPA leads to an increase in the EPA content of all the fractions of phospholipids, cholesteryl esters and TG. Ethyl-EPA reduced the incorporation of oleate into TG in hepatic microsomes and also reduced the rate of hepatic TG secretion. Ethyl-EPA exerts an inhibitory effect on hepatic TG synthesis/secretion and a stimulatory effect on TG degradation, resulting in a reduction in particle size and an increase in the ratio of apoE/apoC. Ethyl-EPA causes a modification of LDL such that Ethyl-EPA has an enhancing effect on the hepatic uptake of LDL. EPA-E attenuates progression of hepatic fibrosis in developed steatohepatitis via an inhibition of ROS production.

Secondary pharmacodynamic studies

EPA suppresses the platelet aggregation induced by collagen, arachidonic acid (AA) and ADP, and EPA-E can reduce platelet aggregability by the change of the EPA level in the platelet phospholipids. Ω-3FAs result in reduced levels of fibrinogen, factor V and thrombin.

Ω-3FA-induced atheroprotection include their role as anti-oxidant and anti-inflammatory agents; EPA attenuates nitric oxide synthesis, lipid peroxidation and generation of reactive oxygen species in human-derived embryonic endothelial cells and reduces LDL oxidation and glucose-induced lipid peroxidation and inflammatory markers associated with atherosclerosis. EPA-E has a suppressive effect on thrombosis and reduces atherosclerotic lesions through its anti-inflammatory effects. EPA attenuates arterial medial calcification through an inhibition of macrophage infiltration and improves the in-vivo distensibility of arteriosclerotic arteries. EPA administration also promotes neovascularization in ischemic models and improves endothelium-derived vasodilatation.

Ω-3 PUFAs prevent cardiac arrhythmias based on their actions to inhibit the voltage-dependent Na^+ current and the L-type Ca^{2+} currents and prevent triggered arrhythmic after-potential discharges caused by excessive cytosolic Ca^{2+} fluctuations. PUFAs have a negative inotropic effect due to

reduction of $I_{Ca,L}$ and intracellular Ca^{2+} concentration in cardiac myocytes. EPA attenuated atrial fibrillation promotion and atrial remodelling.

EPA has anti-inflammatory properties inhibiting arachidonic acid metabolism and COX-2 activity. Mediators from major Ω-3 fatty acids EPA and DHA termed resolvins (resolution-phase interaction products) and protectins possess pro-resolving, anti-inflammatory (reducing neutrophil traffic, pro-inflammatory cytokines and excessive proinflammatory gene expression) and antifibrotic as well as host-directed antimicrobial actions. Ω-3FA intake reduces leukotrienes, prostaglandins and other markers of leukocyte activation (e.g. TNF-α, IL-1 and hsCRP). Ω-3FAs have multiple hemodynamic effects: reductions in resting heart rate and blood pressure, in addition to increased vasodilatation and arterial compliance.

Obesity and insulin resistance have been associated with high levels of free fatty acids from the breakdown of dysregulated TG (lipolysis) in adipose tissue, and TNF-α is a proinflammatory cytokine that is increased in obesity and implicated in the development of insulin resistance. EPA inhibits pro-inflammatory cytokine-induced lipolysis in adipocytes, and this effect might contribute to the insulin-sensitizing properties of EPA.

Administration of Ω-3 fatty acid improves neurological disorders such as Alzheimer's disease, Huntington's disease (HD) and schizophrenia. EPA protects against neurodegeneration by modulating synaptic plasticity, preventing oxidative stress-triggered apoptotic cell death, reversing age-related changes in interleukin-1ß-induced apoptotic cell death, and by its capacity to increase brain docosahexaenoic acid, leading to sustained long-term potentiation.

Safety pharmacology programme

No safety pharmacology studies have been conducted.

At micromolar concentrations EPA inhibits cardiac $I_{Ca,L}$, I_{Na} and several cardiac K^+ channels (I_{to}, I_K and I_{Kur}). These effects on cardiac ion channels might be responsible for the increased incidence of atrial fibrillation observed after the administration of EPA in humans. To date no study evaluating the effect of EPA on hERG channels has been performed or is available in the public literature. Because EPA inhibits I_K (which is composed of I_{Kr} and I_{Ks}), but has no effect on I_{Ks}, it is tempting to speculate that EPA has inhibitory effects on I_{Kr}/hERG channels, and this hypothesis is reinforced by the observation that the structurally similar arachidonic acid and docosahexaenoic acid both inhibit hERG channels. According to the requirement laid down in ICH S7B and in order to characterize the electrophysiology of EPA, hERG channel inhibition by unbound EPA will be studied by the applicant via whole-cell patch-clamp recordings in cells stably transfected with hERG cDNA, and the final report will be available by the end of February 2021.

Pharmacodynamic drug interactions

The Applicant mentions a study of Yanagisawa (1992) where no synergistic effects on bleeding time or ADP-induced platelet aggregation were observed in rabbits when EPA and ticlopidine were administered concomitantly.

Conclusion

The primary pharmacologic effects of Ethyl-EPA are on lipid and lipoprotein levels (reduction of serum lipids and lipoproteins).

The secondary pharmacology effects of Ethyl-EPA that have been discussed in the literature are:

- beneficial effect on thrombosis and artherosclerosis (inhibition of platelet aggregation and thrombus formation),
- anti-inflammatory properties (formation of anti-inflammatory eicosanoids such as resolvins, down-regulation of pro-inflammatory cytokines, down-regulation of arachidonic acid metabolism),
- cardioprotective effects (maintenance of arterial elasticity and effect on blood flow),
- neuroprotective effects (neuro-anti-inflammatory effects, effects on central nervous system (CNS) disorders and psychiatric disorders),
- and improvement of the metabolic profile in animal models of diabetes

2.3.3. Pharmacokinetics

Fatty acids are absorbed from the small intestine without being absorbed by the stomach; whereas short to medium-chain fatty acids are transferred into the physiological environment via the portal vein, long-chain fatty acids are transferred via the lymph; the formation of a mixed micelle with bile acids is necessary for absorption of lipids.

The absorption speed and degree of absorption of 14C-EPA-E was promoted by bile, since fatty acids form a mixed micelle immediately before absorption, and the presence of bile acids is important for the formation of this mixed micelle. EPA has a very high extent of plasma protein binding (nearly 100 % in dogs, 98.8 – 99.8 % in humans and 97.3 – 99.9 % in rats).

In rats unchanged Ethyl-EPA was not absorbed from the gastrointestinal tract, and all lipid radioactivity in lymph was attributed to de-esterified Ethyl-EPA (i.e. EPA). Dogs orally administered ^{14}C-EPA-E showed a distribution pattern considerably different from rats, since most of the radioactivity was in LDL and HDL, but little in VLDL and chylomicron. Such a difference could partly be attributable to the lower rate of gastrointestinal absorption of EPA-E in dogs and an interspecies difference of the rate of conversion of chylomicron or VLDL to LDL could also exist: in humans 75 - 90 % of VLDL is converted to LDL, whereas only 10 % of VLDL is metabolized to LDL in rats.

In rats after oral administration of Ethyl-EPA, the results of whole-body autoradiography demonstrated that the tissue concentrations showed maxima after 9 - 24 hours and then slowly declined. Repeated administrations result in the increase in the concentrations of radioactivity in the heart, liver, brain and adipose tissues, and maximum values in brain, fat and skin are reached 1 week after administration, and elimination from the brain was particularly slow (half-life of 8 - 40 days). Tissue concentration after daily administrations of ^{14}C-EPA-E over 4 to 12 days was higher than that after a single administration with the concentration after 12 administrations rising to 3.5 - 40-fold that after a single administration. The elimination half-life of radioactivity from tissues was 7.6 – 8.4 days, and, thus, similar to that from plasma and from adipose tissue, suggesting that the elimination of Ethyl-EPA and its metabolites follows the metabolic cycle of fat.

After absorption, long-chain fatty acids are incorporated in the triglycerides in the epithelial cells of the small intestine, then are bound to apo-proteins, secreted by chylomicrons or VLDL to lymph, before being transferred into the blood and then into the tissues.

When ^{14}C-Ethyl-EPA (30 mg/kg) was administered orally to pregnant rats on the 12th and 19th days of gestation, radioactivity was transferred to the foetus. In lactating rats, radiolabelled EPA reached C_{max} in milk 6 – 14-times higher than the ^{14}C-EPA concentrations in maternal blood.

The supplementation of EPA promoted the omega-3 metabolic pathway thus displacing omega-6 and 9 series fatty acids from the lipid fractions.

The following metabolic pathway can be proposed for EPA-E: EPA-E is first de-esterified in small intestine and incorporated into TG and PL mainly as a compositional fatty acid, then distributed to various tissues through lymph and plasma, and finally ß-oxidized by mitochondria and peroxisomes, mainly in the liver and also in each tissue. A certain portion of EPA is metabolized to DPA and DHA by elongation and desaturation reactions in microsomes and/or peroxisomes. DPA and DHA also undergo ß-oxidation in the mitochondrial fraction containing peroxisomes. DHA is a polyunsaturated fatty acid present in various tissues, especially in nerve tissues and synaptic membranes. A retroconversion enzyme that converts DHA to EPA has been found in rat liver. DPA and DHA may, either after conversion to EPA or directly, be also metabolized through the ß-oxidation process and tricarboxylic acid (TCA) cycle to CO_2 and water.

EPA is an efficient substrate of CYP2C enzymes. EPA is metabolized to several classes of oxygenated metabolites by the same CYP isoforms as those that metabolize arachidonic acid (AA). The CYP-mediated metabolites of EPA elicit biological effects different from the CYP-mediated metabolites of AA, and dosing with Ethyl-EPA shifts the CYP-dependent generation of physiologically active eicosanoids from AA-derived metabolites to those derived from EPA and this shift may be partially responsible for some of the beneficial effects of EPA.

After administration of ^{14}C-Ethyl-EPA to Wistar rats, the radioactivity is mainly excreted in expired breath, and the excretion rates over 7 days in urine, faeces and expired air were 2.7 - 3.3 %, 16.7 – 18.3 % and 44.4 – 51.4 %, respectively. In dogs, the excretion was 1.0 % in urine and 19.2 % in faeces.

The inhibitory effect of EPA and other polyunsaturated fatty acids on human CYPs obtained from a recombinant expression system consisting of baculovirus-transfected insect cells were studied, and furthermore, EPA was evaluated as an inhibitor of human Cytochrome P450 (CYP) enzymes using an in vitro model based on biotransformation rates of index substrates by human liver microsomes. EPS was found to inhibit CYP 1A2, 2C9, 2C19, 2D6, 2E1 and 3A with Ki values of 4.4 – 127 µM, and the most sensitive were CYP isoforms of the 2C family. After dosing with 2 and 4 g/day AMR101 for 28 days in healthy volunteers (Study AMR-01-01-0018), the mean C_{max} values of unesterified EPA in plasma were 2.55 µM and 5.04 µM, respectively. Therefore, an inhibition of the following CYP isoforms by EPA indicated a possible DDI (in decreasing order of potential): 2C19, 2C9, 2C8 and 2B6. Based on the results from the in vitro evaluation of the inhibition potential of EPA on CYP isoenzymes, the Applicant has performed clinical drug-drug interaction studies (see Clinical AR).

EPA was not an inducer of human CYP enzymes CYP3A, CYP2C9 and CYP1A2 using an in-vitro model based on cultured human hepatocytes.

EPA at a concentration of 1 µM did not inhibit P-gp, BCRP, OCT2, OAT1, OATP1B1 or OATP1B3 mediated transport of probe substrate, but slightly inhibited the transport of probe substrate of OAT3.

Ethyl-EPA, given to Male Wistar rats as single doses or as repeated doses for 14 days at 30 mg/kg, has little effect on the microsomal drug metabolizing system.

2.3.4. Toxicology

Single dose toxicity

No single dose toxicity testing of AMR101 was conducted in rodents. Instead, two study reports from acute toxicity testing of Epadel® (Ethyl-EPA) and its main metabolites and impurities found in public databases were submitted. Epadel® was licenced in Japan since 1991 for the treatment of similar indications like arteriosclerosis obliterans. The study reports submitted were all part of the registration process for Epadel® in Japan. Comparison of these study reports to the current OECD guidelines for GLP indicated compliance (determination of the scientific validity of using published studies according Klimisch et al, 1997) to GLP requirements with several exceptions (i.e. absence of a statement of compliance with GLP, lack of individual data).

To show comparability between both Ethyl-EPA products the applicant submitted a pivotal 28-day repeat-dose study in rats treated with equal amounts of AMR101- and Epadel® demonstrating qualitative and quantitative consistency between both products.

No systemic toxicity or special target organs were detected for the mother substance, major metabolites or impurities up to the highest dose tested (2000 mg/kg) in mice and rats. The toxicological profiles were consistent with the observations from all other studies submitted for rodents.

After oral administration LD_{50} values in rodents (mouse, rat) were approximately 20000 mg/kg and above, the highest dose tested. This corresponds to Ethyl-EPA safety margins of 28 x in mice and 56 x in rat based on the HED (human equivalent dose) concept with a maximal clinical dose of 4000 mg.

Repeat dose toxicity

Toxikokinetics

Safety margins in repeat-dose toxicity studies have been calculated based on total plasma concentrations for EPA. As EPA is highly protein bound to a similar extend across species, this is acceptable. Ethyl-EPA was hardly detectable in plasma of animals. Therefore, the applicant has also performed safety margin calculations based on body surface area (HED concept) for Ethyl-EPA, which are mostly in line with AUC-based safety margins for EPA (see respective repeat-dose toxicity studies).

Studies in rats

In the rat chronic administration testing (3 month and 12 month) of Ethyl-EPA were adapted from two study reports from public databases with the Ethyl-EPA product Epadel® licenced in Japan. No toxikokinetic (TK) data were determined in these studies. Additional two pivotal GLP 28-day rat repeat-dose toxicity studies with AMR101 were conducted to show qualitative and quantitative consistency between both Ethyl-EPA products at equal dosages. TK data of (unesterified) EPA were determined in both studies.

In the 3-month and 12-month rat toxicity studies by Shibutani and both pivotal 28-day GLP rat studies consistent toxicology profiles of Ethyl-EPA at equal dosages were obtained. Except expected pharmacodynamic effects no serious toxic systemic effects in any organ were detected. Major findings were transient decreases in body weight and irritation of the skin caused by leakage of the test substance from the anus and restricted to the highest dosages of Ethyl-EPA. All other findings were

small in magnitude, reversible and without histopathologic correlate. The toxicological profiles were consistent with the observations from all other studies submitted for rodents.

In the 28-day rat comparative pivotal toxicity study according GLP, no significant differences between AMR101 and Epadel® as well as compared to control were detected regarding to PD, PK/TK and toxicology of (Ethyl)-EPA.

Toxicity findings were restricted to expected pharmacodynamic-related decreases in cholesterol and triglycerides and therefore not considered of concern. Other observations were consistent with the toxicology profile observed in other toxicology studies conducted in rodents.

Small variations in haematology and clinical chemistry parameters were without correlated haematological abnormality and were therefore considered to be normal biological variation.

Histopathologic observations were without microscopic correlates or with a similar incidence in control and regarded as incidental findings normal for the age and strain of rats. Except expected pharmacodynamic effects no serious toxic systemic effects in any organ were detected.

No significant differences with respect to pharmacodynamic and TK parameters between AMR101 and Epadel® were observed.

Safety margins based on TK at NOAEL (2000 mg/kg/d, $C_{max\ unesterified}$ EPA (d 28) 16400 (♂)/17300 (♀) ng/ml, $AUC_{unesterified\ EPA}$ (d 28) 196000 (♂)/140200 (♀) ng h/ml) and clinical exposures (4000 mg/d, $C_{max\ unesterified}$ EPA (d 28) 1520 ng/ml, $AUC_{unesterified\ EPA}$ (d 28) 20300 ng h/ml) were approximately 11 x for C_{max}, respectively 8 x for AUC.

In the pivotal GLP 28-day rat study, no significant differences with respect to the toxicology profile were observed compared to the other toxicology studies conducted in rodents. Variations in haematology parameters were small in magnitude and without histopathologic abnormality. TK data were concomitantly obtained in this study. Exposures (C_{max}, AUC) increased sub-proportional with increasing doses suggesting a saturation of absorption. No clear or consistent sex related differences were determined.

In conclusion, no significant differences with respect to quality and quantity characteristics were detected between AMR-101 from different suppliers and Epadel®. The NOAEL corresponded to the highest dose consistently in every rodent study and showed appropriate exposure margins towards human therapeutic exposures. Together with the long-time clinical experience with Epadel® and with respect to safety, the assessor agrees that AMR101 is sufficiently tested in rodents.

Studies in dogs

In a 39-weeks repeat-dose toxicity studies in dogs observed toxicities were mostly related to the pharmacological action of EPA (changes in plasma concentrations of lipids) and local irritation due to increased excretion. Findings in animals at 1000 mg/kg/day were considered not to be adverse and there was evidence that they were reversible or were of a type that would be reversible. Thus, the NOAEL in this study was set at 1000 mg/kg/day, which is endorsed. This corresponds ~9 x the maximum recommended human dose of 4000 mg/d based on body surface area comparison for Ethyl-EPA and 8 x relative to the AUC of EPA at the dose of 4000 mg/d obtained from the healthy volunteer study AMR-01-01-0018. TK investigations showed low systemic exposure to Ethyl-EPA when compared with the metabolite EPA and that systemic exposure to EPA was extensive. EPA systemic exposure increased in a supra-proportional manner with increasing dose following administration of AMR101 on Day 1. Exposure ($C_{max(obs)}$ and AUC0-t) to EPA was higher during Week 13 than on Day 1 in both males and females, which is an indication of accumulation, as expected from a drug with a long half-life.

Genotoxicity

A complete GLP-conform genotoxicty test battery has been performed with AMR101 (Ethyl-EPA + 0.2% DLαTocopherol) including an Ames test, in vitro chromosome aberration assay and a in vivo micronucleus test in albino mice. In addition, GLP-conform Ames tests and in vitro chromosome aberration assays have been performed with AMR101 from suppliers. One further in vitro chromosome aberration assay has been performed with EPA and oleic- and linoleic acid as reference compounds. All Ethyl-EPA preparations were negative in Ames assays up to 5000 µg/plate indicating that they are not mutagenic. A positive response was seen for all preparations in in vitro chromosome aberration assays including DEA, and linoleic and oleic acid. This implicates that clastogenicity is a class effect of fatty acids under these test conditions. To follow up these positive results Amarin has performed an in vivo micronucleus test albino mice treated with a single ip dose of 4550 mg/kg AMR101. No increase in micronucleated erythrocytes was observed after 24 and 48 hours post dose. Mice showed no clinical signs, exposure was not determined. According to ICH S2(R1) a positive outcome in an in vitro test would trigger the need for a second endpoint in the in vivo genotoxicity assay. However, because Ethyl-EPA is a naturally occurring fatty acid and was negative in carcinogenicity studies performed in mice and rats, no further studies are warranted.

Carcinogenicity

Carcinogenicity studies with Ethyl-EPA have been performed in rats (2-year carcinogenicity study) and Tg-RasH2 mice for 6 months. Ethyl-EPA was negative in the 2-year rat carcinogenicity study at doses up to 910 mg/kg/d. Haemangioma and haemangiosarcoma were observed in mesenteric lymph nodes in all male groups, including control, and females at ≥270 mg/kg/d. However, overall incidence of haemangiomas and haemangiosarcomas in all vascular tissues did not increase with treatment and findings in mesenteric lymph nodes were not considered of human relevance. Exposure was not determined in this study, however, EPA TK data could be bridged from 28-day rat repeat-dose toxicity study at 1000 mg/kg/d indicating sufficiently high exposure of rats which is approx. 7-fold human exposure at 4000 mg/daily dose. Ethyl-EPA was also negative in the 6-month Tg-RasH2 mice carcinogenicity study at doses up to 4600 mg/kg/d. Ethyl-EPA-related incidences of benign squamous cell papilloma in the skin and subcutis of the proximal tail were observed at 4600 mg/kg/day in male mice only. Papillomas were considered to develop secondary to chronic irritation of the proximal tail associated with faecal excretion of oil and therefore not clinically relevant. EPA exposure at the high dose was approximately 4 x human exposure at 4000 mg/daily dose. Based on the results of the carcinogenicity studies with Ethyl-EPA no carcinogenic risk is expected for humans.

Reproduction Toxicity

Except for a pivotal GLP-conform embryo-foetal development study in rats no further reproductive and developmental toxicity testing of AMR101 was conducted. For an appropriate reproductive and developmental toxicity testing the applicant referred to the reference product Epadel® licensed since 1991 in Japan and the respective studies published in the literature.

These studies represented a full reproductive and developmental toxicity program according to the ICH M3 guideline. The study reports had several limitations concerning the OECD guideline for GLP (1997), among other things, a statement of compliance with GLP is missing and individual data are lacking. With respect to the long-time clinical experience and the extensive toxicological and clinical safety data together with the results of the two 4-week comparative rat toxicology studies with AMR101 alone and AMR101 and Epadel® this seems acceptable.

No TK data were measured in any reproductive toxicology studies conducted in pregnant rats or rabbits. According to the Japanese authority, Ministry of Health and Welfare, there was no requirement to collect TK data at that time. However, TK analysis was performed in two 4-week comparative rat toxicology studies with AMR101 alone and AMR101 and Epadel® with no significant qualitative and quantitative differences observed between the two Ethyl-EPA products.

Ethyl-EPA indicated no influence on fertility in rats of both genders up to the highest doses tested.

Ethyl-EPA indicated no reproductive toxicity in rats. In rabbits a not significant tendency of an increased number of resorbed or dead foetuses accompanied by marked but reversible maternal toxicity (body weight loss) was observed in the high dose group.

Toxicology studies indicate that Ethyl-EPA crossed the placenta, found in foetal plasma and was excreted in breast-milk.

Safety margins to clinical exposures were not calculated (C_{max}, AUC) and only HED based calculations at NO(A)EL dose levels were presented.

An estimation of a safety margin based on rat and human exposures (C_{max}, AUC) were calculated on the basis of TK results obtained from the 28-day pivotal toxicity study conducted in rats and human study AMR-01-01-0018. Safety margins based on TK at NOAEL (2000 mg/kg/d, $C_{max\ unesterified\ EPA}$ (d 28) 16400 (♂)/17300 (♀) ng/ml, $AUC_{unesterified\ EPA}$ (d 28) 196000 (♂)/140200 (♀) ng h/ml) and clinical exposures (4000 mg/d, $C_{max\ unesterified}$ EPA (d 28) 1520 ng/ml, $AUC_{unesterified\ EPA}$ (d 28) 20300 ng h/ml) were approximately 11 x for C_{max}, respectively 8 x for AUC.

No TK data was submitted for the rabbit. Ethyl-EPA safety margins based on the HED at rabbit NOEL (1000 mg/kg/d) for reproduction and embryo-foetal development and the clinical dose (4000 mg/kg/d) were approximately 5.8 x.

Under the conditions of the studies Ethyl-EPA had no influence on fertility in rats and was not teratogenic in rats and rabbits under the conditions of the study.

Juvenile animal studies

No juvenile toxicity studies were provided by the applicant which is acceptable, since AMR101 is not intended for juvenile patients.

Other toxicity studies

Comparative studies

To demonstrate qualitative and quantitative comparability between AMR101 from different suppliers the applicant conducted three 28-day rat repeat-dose studies according GLP. A study duration of 1 month will maximize the exposure to any new impurities. Due to the limited TK sampling, except exposure data (C_{max}), TK parameters were not calculated. No significant differences between AMR101 (Ethyl-EPA) from different suppliers concerning toxicological endpoints and TK (Cmax) were observed in comparative 1-month toxicity studies conducted in rats.

Impurities

The related substance specifications for unknown, identified and qualified impurities have been set in compliance with ICH Q3A(R2). As all of these compounds are structurally related to Ethyl-EPA no safety concern arises from higher amounts than the specification limit in the drug substance. In conclusion, all related impurities can be considered as qualified from a toxicological point of view and no new toxicity studies are warranted.

2.3.5. Ecotoxicity/environmental risk assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, eicosapentaenoic acid is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

No major non-clinical safety findings have been identified which may be of significant clinical relevance.

The primary pharmacologic effects of Ethyl-EPA are on lipid and lipoprotein levels (reduction of serum lipids and lipoproteins). Among the secondary pharmacology effects of Ethyl-EPA that have been discussed in the literature are beneficial effect on thrombosis and atherosclerosis (inhibition of platelet aggregation and thrombus formation), anti-inflammatory properties (formation of anti-inflammatory eicosanoids such as resolvins, down-regulation of pro-inflammatory cytokines, down-regulation of arachidonic acid metabolism), cardioprotective effects (maintenance of arterial elasticity and effect on blood flow), neuroprotective effects (neuro-anti-inflammatory effects, effects on central nervous system (CNS) disorders and psychiatric disorders) and improvement of the metabolic profile in animal models of diabetes.

No safety pharmacology studies have been conducted. According to the ICH S7B Guideline and in order to characterize the electrophysiology of EPA, hERG channel inhibition by unbound EPA will be studied by the Applicant via whole-cell patch-clamp recordings in cells stably transfected with hERG cDNA, and the final report will be available by the end of February 2021.

2.3.7. Conclusion on the non-clinical aspects

No non-clinical safety findings have been identified which may be of significant clinical relevance and the safety specification of the RMP. A hERG study with unbound EPA will be performed by the Applicant and the final report will be available by the end of February 2021 (REC). The application was considered approvable from nonclinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

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

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dose Regimen; (Route of Administration)	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Healthy Subjects								
PK/Safety	LA01.01.0009	Safety, PlasmaPK and EPA into RBC membranes	Open-label, Randomized, Parallel-Group; No control group	AMR101 2g single dose oral + 2 g/day (oral)	24	Healthy male volunteers	30 days	Complete; Full
PK/Safety	AMR-01-01-0018	Safety, Plasma PK and EPA into RBC membranes	Randomized, Open-Label, Parallel-Group, Comparative	AMR101 2 g or 4 g/day (oral)	48	Healthy volunteers	28 days	Complete; Full
DDI	AMR-01-01-0020	Effect of AMR101 on the PK characteristics of omeprazole and rosiglitazone	A Phase 1, Open-Label, Crossover	AMR101 4 g/day (oral)	30	Healthy volunteers	30 days	Complete; Full
DDI	AMR-01-01-0021	Effect of AMR101 on the PK and anticoagulation PD of warfarin	A Phase 1, Open-label, Crossover	AMR101 4 g/day (oral)	26	Healthy volunteers	36 days	Complete; Full
DDI	AMR-01-01-0023	Effects of AMR101 on the PK of atorvastatin	A Phase 1, Open-Label, Crossover	AMR101 4 g/day (oral)	30	Healthy volunteers	36 days	Complete; Full
Target Indications								

Efficacy	AMR-01-01-0017 (ANCHOR)	Efficacy and safety; Changes in TG	Double-Blind, Randomized, Placebo-Controlled	AMR101 2 g or 4 g/day (oral)	702	Patients with High Triglycerides	12 weeks	Complete; Full
Efficacy	AMR-01-01-0016 (MARINE)	Efficacy and safety; Changes in TG	Double-Blind, Randomized, Placebo-Controlled, with Open-Label Extension	AMR101 2 g or 4 g/day (oral)	229	Patients with Very High Triglycerides	12 weeks – double-blind treatment period[c]	Complete; Full
Safety and efficacy	AMR-01-01-0016 (MARINE OLE)	Safety	Open-Label Extension	AMR101 4 g/day (oral)	210	Patients with Very High Triglycerides	40-week open label extension	Complete; Full
Efficacy	AMR-01-01-0019 (REDUCE-IT)	Efficacy and safety; Cardiovascular Risk Reduction	Double-Blind, Randomized, Parallel-Group, Placebo Controlled	AMR101 4 g/day (oral)	8179	Patients with High Triglycerides and at risk for CVD	4.9-year median follow-up duration	Complete; Full
Other Indications								
Efficacy	LA01.01.0005	Efficacy and safety; EPA into RBC membranes	Double-Blind, Randomized, Parallel-Group, Placebo-Controlled	AMR101 2 g/day (oral)	135	Patients with Huntington's Disease	12 months + 12 months open-label extension [a]	Complete; Full
Efficacy	AN01.01.0011	Efficacy and safety; Changes in RBC EFA	Double-Blind, Randomized, Parallel-Group, Placebo-Controlled	AMR101 2 g/day (oral)	316	Patients with Huntington's Disease	6 months + 6 months open-label extension [a]	Complete; Full

Efficacy	AN01.01.0012	Efficacy and safety; Changes in RBC EFA	Double-Blind, Randomized, Parallel-Group, Placebo-Controlled	AMR101 2 g/day (oral)	290	Patients with Huntington's Disease	6 months + 6 months open-label extension [a]	Complete; Full
Efficacy	LA01.01.0001	Efficacy and safety; EPA into RBC membranes	Double-Blind, Randomized, Placebo-Controlled	AMR101 1, 2 or 4 g/day (oral)	122	Patients with Schizophrenia	12 weeks	Complete; Full
Efficacy	LA01.01.0002	Efficacy and safety	Double-Blind, Randomized, Placebo-Controlled	AMR101 1, 2 or 4 g/day (oral)	70	Patients with Depression	12 weeks	Complete; Full
Efficacy	LA01.01.0006	Efficacy and safety; EPA into plasma and RBC membranes	Double-Blind, Randomized, Placebo-Controlled	AMR101 1 g/day (oral)	115	Patients with Depression	12 weeks + 12 months open-label extension [b]	Complete; Full
Efficacy	LA01.01.0008A	Efficacy and safety; EPA into plasma and RBC membranes	Double-Blind, Randomized, Placebo-Controlled	AMR101 0.5, 1 or 2 g/day (oral)	77	Patients with Depression	6 weeks	Complete; Full
Efficacy	AN01.01.0014	Efficacy and safety; EPA into plasma and RBC membranes	Double-Blind, Randomized, Placebo-Controlled	AMR101 1, 2 or 4 g/day (oral)	94	Patients with Age-Associated Memory Impairment	6 weeks	Complete; Full

RBC = Red Blood Cells; EFA = Essential Fatty Acids; PK= pharmacokinetics; DDI= drug-drug interaction; EPA= eicosapentaenoic acid; TG= triglyceride

a. All patients rolled over into open-label extension received AMR101 capsules 2 g/day

a. All patients rolled over into open-label extension received AMR101 capsules 1 g/day

b. All patients rolled over into open-label extension received AMR101 capsules 4 g/day

2.4.2. Pharmacokinetics

Absorption

Vazkepa (icosapent ethyl or ethyl-EPA) is the ethyl ester of the omega-3 fatty acid eicosapentaenoic acid (EPA). After dosing humans with clinical doses of Vazkepa, only very low levels of ethyl-EPA are sporadically detected in plasma. Therefore, the major chemical moiety in the systemic circulation after Vazkepa administration is the active metabolite EPA, and appropriate assays were developed to measure EPA in plasma for the evaluation of pharmacokinetics (PK).

After oral administration of ethyl-EPA (icosapent ethyl), the parent drug is completely or nearly completely de-esterified during the absorption process and the active metabolite EPA is absorbed into the systemic circulation via the thoracic duct lymphatic system.

EPA is incorporated into circulating phospholipids (PL), triacylglycerols (TAG) or triglycerides and cholesteryl esters (CE). Only a small fraction of the total circulating EPA concentration is unesterified, i.e., free or protein bound, and not incorporated in these lipids. Therefore, the major assay for PK evaluations measured total EPA: the total EPA concentration in plasma includes unesterified EPA and EPA incorporated in PL, TAG, and CE.

EPA is also incorporated in the phospholipids of cell membranes wherein EPA provides structural properties to the membrane (for example fluidity in red blood cell membranes), but more importantly, is a source for intracellular activities related to its triglyceride-lowering and anti-inflammatory effects. Because of the ease of sample collection, omega-3 fatty acids are often measured in red blood cells (RBC) as a marker for tissue exposure. Therefore, the appropriate assays were also developed to measure EPA in RBC after Vazkepa administration. In RBC, almost all EPA is incorporated in phospholipids of the cell membrane.

Analytical methods

A Gas Chromatography Plus Flame Ionization Detector assay was used to quantify 28 fatty acids (the fatty acid profile), including EPA, in RBC and plasma samples. For each fatty acid, the total concentrations are measured, which include unesterified fatty acids and fatty acids incorporated (esterified) in TAG, PL and CE.

Liquid Chromatography-Tandem Mass Spectrometry (LC/MS-MS) assay method was used for measuring total EPA in human plasma and RBC.

Liquid Chromatography-Tandem Mass Spectrometry (LC/MS-MS) assay method was used for measuring total EPA in human serum.

Liquid Chromatography-Tandem Mass Spectrometry (LC/MS-MS) assay method was used for measuring unesterified EPA in human plasma. This assay was also used in Amarin-sponsored nonclinical toxicology studies in mouse, rat, and dog.

Liquid Chromatography-Tandem Mass Spectrometry (LC/MS-MS) assay method for measuring ethyl-EPA in human plasma.

Baseline total EPA plasma concentrations

Baseline total EPA plasma concentrations were variable between the subjects, with study-wide mean (± SD) of 15.3 ± 15.2 µg/mL.

Unesterified EPA

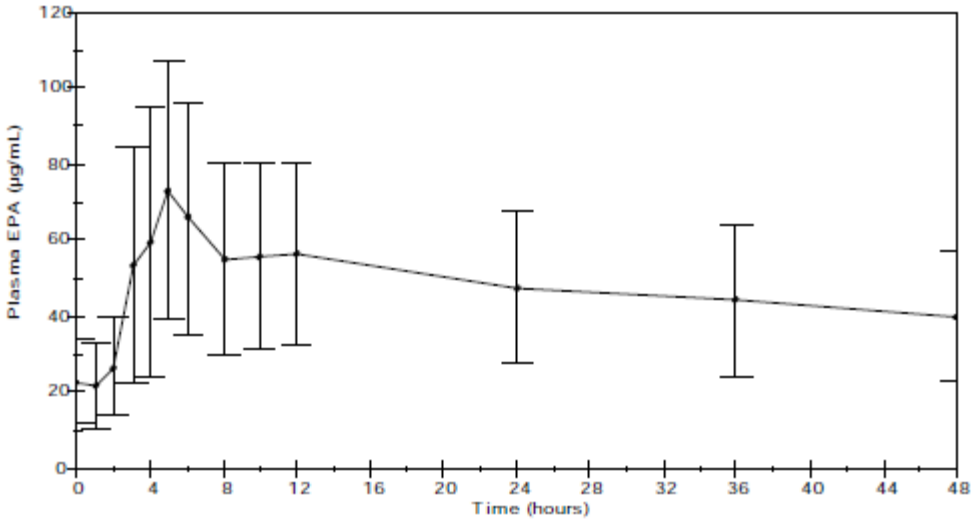
Only a small fraction of total EPA exposure is unesterified EPA. The study-wide mean ± SD baseline unesterified EPA plasma concentration was 0.099 ± 0.095 µg/mL, which is less than 1% of the total EPA plasma concentration. Based on plasma AUC and C_{max} after dosing Vazkepa, 0.3 to 0.5 % of the total EPA was unesterified. Unesterified EPA concentrations in both plasma and RBC accumulated in a similar fashion as for total EPA.

Ethyl-EPA

Because of the expected low exposure of the parent drug, ethyl-EPA, plasma concentrations of ethyl-EPA were not routinely measured in the Amarin-sponsored clinical studies. However, as a post-hoc analysis, a limited number of plasma samples were analyzed for ethyl-EPA. Ethyl-EPA was not quantifiable (<50 ng/mL) in most samples.

Single dose PK

Mean curve of plasma EPA (Unadjusted) following a single dose of 2 g Vazkepa in male volunteers



Pharmacokinetic Parameters Based on Total EPA Concentrations in Plasma Following a Single Dose of 2 g Vazkepa in Male Volunteers

Baseline Adjusted	**λ_z (hr^{-1})**	**$T_{1/2}$ (hr)**	**T_{max} (hr)**	**C_{max} (µg/g)**	**AUC_{0-48hr} (µg*hr/g)**	**$AUC_{0-\infty}$ (µg*hr/g)**	**V_z/F (L)**	**CL/F (mL/hr)**
No	0.010 (0.004)	86.6 (65.4)	4.64 (0.92)	78.3 (33.7)	2299 (972)	7615 (5251)	37.0 (13.2)	381 (202)
Yes	0.021 (0.009)	42.2 (30.9)	4.64 (0.92)	55.5 (28.2)	1206 (617)	2375 (1615)	58.8 (23.9)	1270 (830)

Values expressed as mean (SD) of N=11 subjects.

A single oral dose of 2 g Vazkepa resulted in a slow rise in plasma EPA concentrations. Maximum values were observed 5 hours after dosing, with EPA concentrations remaining above baseline 48 hours after administration.

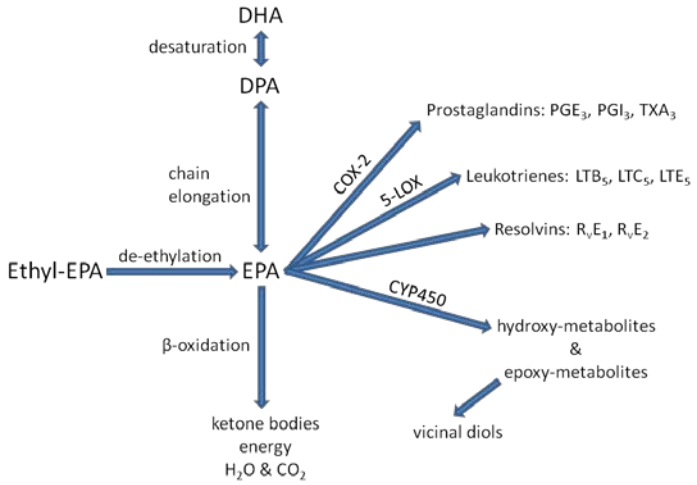
Distribution, Metabolism, Elimination

EPA is naturally present in plasma and RBC. After absorption, EPA is distributed and (re)incorporated into circulating PL, TAG and CE, and into the phospholipid components of cell membranes. In RBC, almost all EPA is incorporated into PL of the cell membrane. Only a small fraction of the total circulating EPA concentration is unesterified, i.e., not incorporated in TAG, PL, CE, and RBC.

The steady-state volume of distribution of EPA after 28 days administration of Vazkepa, was large (~80 L).

Metabolism is according to standard lipid turnover of the body.

Pathways of Hydrolysis of Ethyl-EPA and Metabolism/Bio-activation of EPA



COX = cyclooxygenase; LOX = lipoxygenase; LT = leukotriene; PG = prostaglandin; R_v = resolving; TX = thromboxane

Elimination of EPA and its metabolites is similar to that of fatty acids from dietary and endogenous lipids, with the end products (CO_2 and water) principally excreted in expired breath.

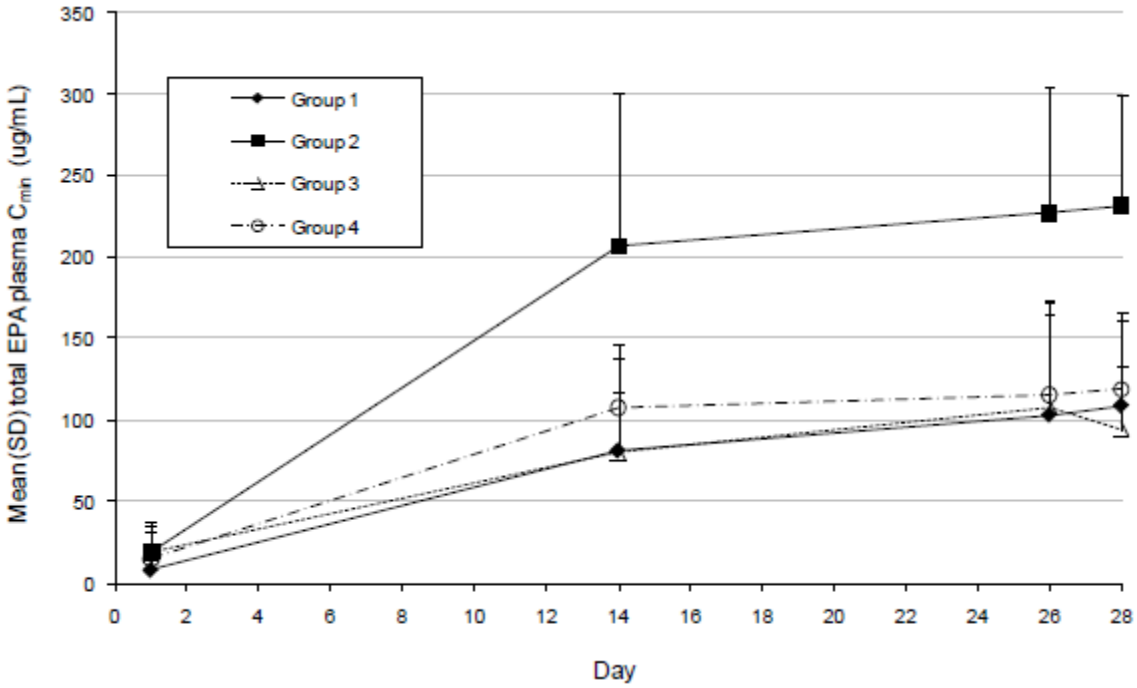
After oral 14C-ethyl-EPA administration to rats, the radioactivity was principally excreted in expired breath (~50 %), minimally in urine (~3 %), and ~17 % in faeces. A similar experiment in dogs showed 1 % in urine and 19 % in faeces (expired air was not analysed).

Thus, EPA is metabolized and excreted through a high-capacity process that is almost unaffected by variables such as kidney and liver function.

Elimination kinetic after 28 days of dosing was examined in study AMR-01-01-0018. In-group 2 (2 g BID) T1/2 (mean (SD)) after the last dose was 152 (53.3) hrs.

Dose proportionality and time dependencies

Mean (SD) baseline-unadjusted total EPA plasma trough concentration (group 2 with 2 g Vazkepa BID)



Though not significant, it appears that EPA plasma trough concentrations still increase from day 14 to day 26 / day 28. This is underpinned by RBC EPA trough concentrations.

Geometric Means			Ratio of Geo. Means (95% CI)		p values	
Day 14	Day 26	Day 28	Day 14:28	Day 26:28	Day 14:28	Day 26:28
33.51	42.83	62.06	0.54 (42.29, 68.95)	0.69 (54.87, 86.81)	0.0007	0.0135

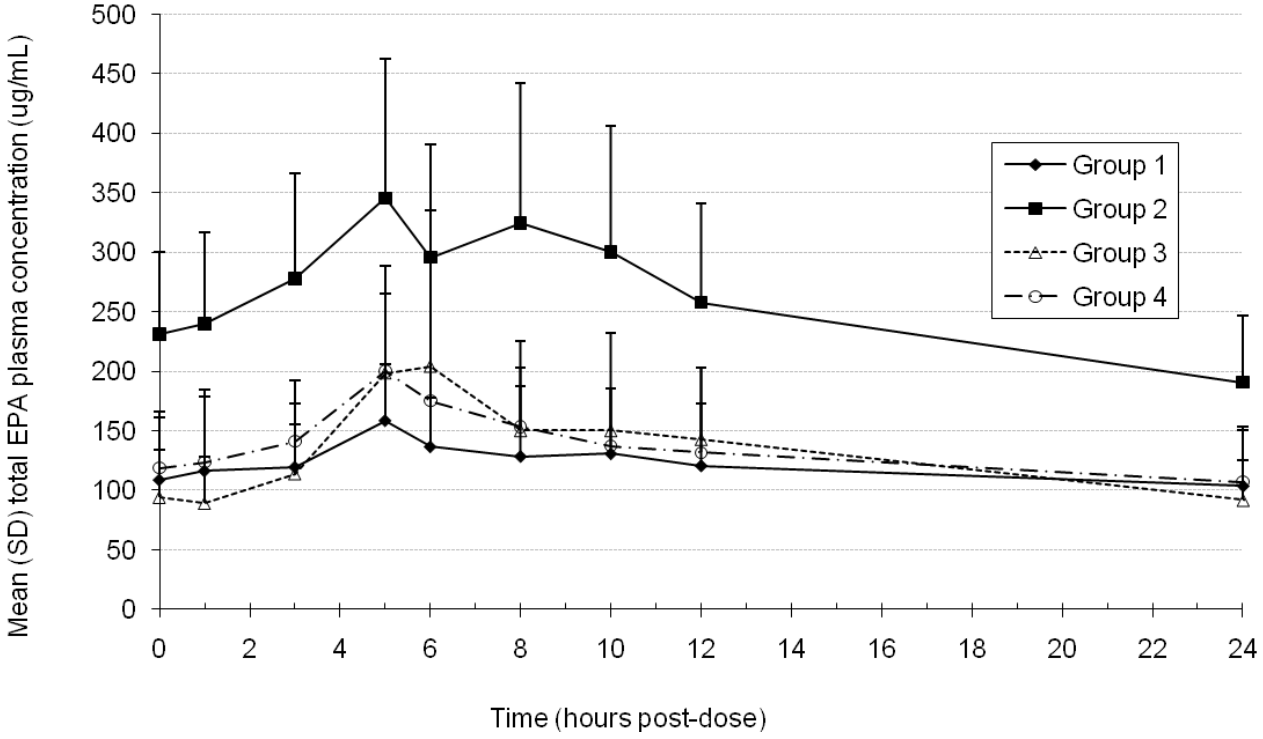
Therefore, it is assumed, that total EPA concentration in the body increases over at least a period of 28 days with Vazkepa 4 g / day.

In ANCHOR and MARINE studies, of the total molar fatty acid concentration in plasma, EPA did constitute 1.9 mol % after 12 weeks of 2 g/day Vazkepa, and 3.4-3.6 mol % after 4 g/day Vazkepa, versus 0.4-0.5% at baseline (which did not change in the placebo group). Similar results were seen in RBC.

Single dose PK at steady state

Data from study AMR-01-01-0018 indicate comparable PK at steady state, though the increase in EPA concentration (C_{max} – C_{min}) is apparently higher (~ 135 µg/mL, c.f. a value of ~55.5 (µg/g) seen with the first 2 g Vazkepa dose).

Mean (SD) baseline-unadjusted total EPA plasma concentration versus time from study AMR-01-01-0018 on Day 28 from time 0 to 24 h postdose (group 2: 2 mg Vazkepa)

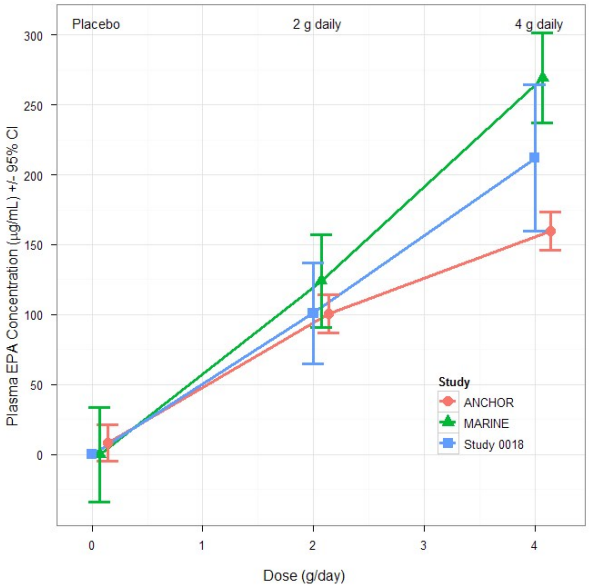


Dose proportionality

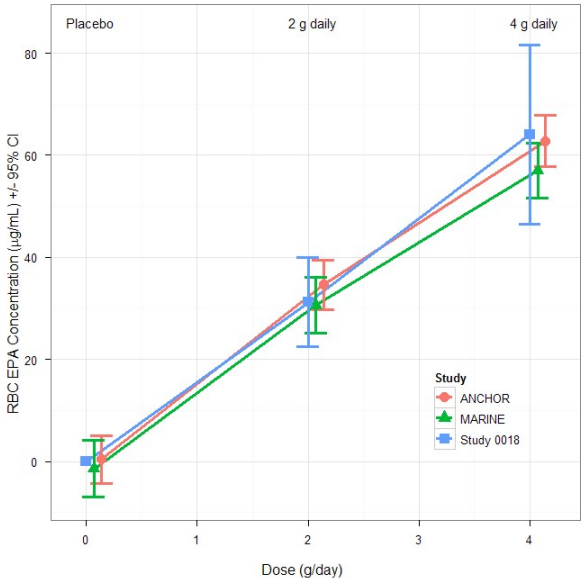
Dose dependency of mean trough EPA concentrations was evaluated in healthy volunteers (Study AMR-01-01-0018) and in patients with hypertriglyceridemia (MARINE and ANCHOR studies).

Mean Trough EPA Concentrations (95% CI)

Plasma



RBC



Based on C_{max} and AUC of total and unesterified EPA in plasma and EPA in RBCs, the mean exposure to EPA appears dose-proportional between 2 and 4 g/day AMR101, and this is supported by the statistical comparisons ($p>0.05$) of dose-normalized PK values.

Pharmacokinetics in target population

Pharmacokinetics appear to be very similar in healthy subjects, patients with hypertriglyceridemia (MARINE and ANCHOR studies) and in patients with cardiovascular risk factors (REDUCE-IT study).

Special populations

Impaired hepatic or renal function

Studies investigating the effect of renal insufficiency or hepatic insufficiency on the PK of Vazkepa were not performed. EPA pathway in the body are manifold and include neither the kidney nor the liver in an emphasized position. Available clinical data suggest neutral to positive effects of omega-3-acid ethyl esters (OM3) in patients with renal or hepatic impairment.

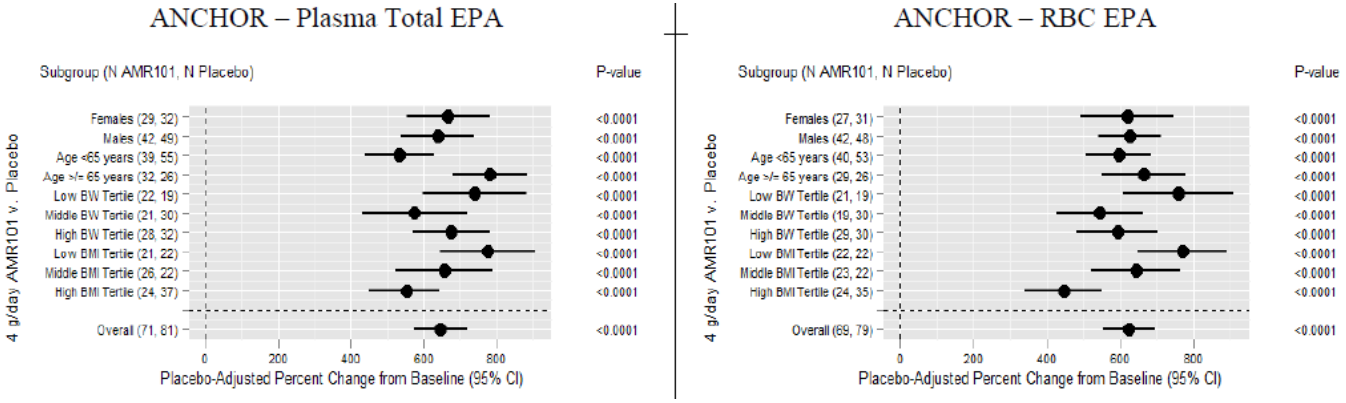
Severe renal dysfunction may be associated with a decrease in protein binding due to a decrease in protein concentrations or binding itself. However, only ~35% of albumin carries even a single fatty acid, on average and molar percentage of EPA, relative to pooled total fatty acids, increased with EPA treatment from 0.5% to 5.8%, with no increase in the total fatty acid pool. Safety data derived from key Phase 3 study based on renal function sub-populations reveal no meaningful imbalances in the frequencies of AEs between Vazkepa and placebo groups that would indicate a safety concern for patients with more advanced renal impairment.

Race

Steady-state serum concentrations from the REDUCE-IT study were evaluated with respect to race. Though partly significant differences are observed at Year 1 these differences are relatively modest and serum EPA levels after Year 1 show no statistically significant differences between subgroups of race. Based on PK considerations clinically relevant differences related to race in efficacy or safety are not expected.

Gender

In studies AMR-01-01-0018, MARINE and in ANCHOR only minor differences for EPA PK in respect of gender were observed.



Weight and BMI

In both MARINE and ANCHOR, body weight appeared to have a small and inconsistent effect on the EPA concentration in plasma or RBC. However, in the different subgroups defined by BMI tertiles in ANCHOR after 4 g/day Vazkepa differences are visible. In RBC EPA increase (mean (SE)) in the first tertile (BMI < 30 kg/m2) was 83.6 (3.90) µg/mL (n = 22) but just 39.3 (3.86) in the third tertile (>35 kg/m2; n = 24). In plasma similar data were found (187.7 (12.95) vs. 121.4 (9.21)). However, the serum levels of EPA reached on-treatment with Vazkepa at all time-points were substantial for all subgroups, with no obvious differences observed in efficacy and safety across the various BMI subgroups.

Elderly

A clinical study in age-associated memory impaired patients aged 50 to 70 years shows agreement with the PK data from healthy volunteers and from patients with other CNS disorders, demonstrating that, in general, the PK of EPA after Vazkepa administration was similar in older subjects (50-70 years) as compared to younger subjects.

Controlled Clinical Trials	**Age 65-74 (Older subjects number /total number)**			**Age 75-84 (Older subjects number /total number)**			**Age 85+ (Older subjects number /total number)**		
	Pooled n/N (%)	**2 g/day n/N (%)**	**4 g/day n/N (%)**	**Pooled n/N (%)**	**2 g/day n/N (%)**	**4 g/day n/N (%)**	**Pooled n/N (%)**	**2 g/day n/N (%)**	**4 g/day n/N (%)**
ANCHOR	145/469 (30.9)	76/236 (32.2)	69/233 (29.6)	40/469 (8.5)	19/236 (8.1)	21/233 (9.0)	1/469 (0.2)	0/236	1/233 (0.4)
MARINE	17/153 (11.1)	8/76 (10.5)	9/77 (11.7)	1/153 (0.7)	1/76 (1.3)	0/77	0/153	0/76	0/77
REDUCE-IT	1455/4089 (35.6)	-	1455/4089 (35.6)	391/4089 (9.6)	-	391/4089 (9.6)	11/4089 (0.3)	-	11/4089 (0.3)

With Vazkepa 4 g / day a higher concentration of plasma total EPA in patients with an age of 65 or older was observed (Plasma EPA Concentration, REDUCE-IT, Change from Baseline to year 1 (µg/mL Median (IQR)) <65 years 111.3 (108.4); 65-<75 years 124.5 (113.8); ⩾75 years 127.6 (125.5)). The finding was not considered clinically relevant with respect to efficacy. Concerning safety it is noted that a higher rate of bleedings and hemorrhagic strokes was observed in the ⩾75 year age group for Vazkepa vs. Placebo but not in patients < 65 years. Whether the about 15% higher mean exposure in patients ⩾75 year age contributed to this finding may not be clarified based on the data available.

Serum EPA levels appear generally similar across the age subgroups, with any mean or median differences between subgroups being modest, particularly in comparison to observed IQRs.

The serum levels of EPA reached on-treatment with Vazkepa at all time-points were substantial for all subgroups. Available EPA PK data do not provide evidence to infer a substantial difference in efficacy or safety across subgroups of age.

Children

A product-specific waiver was granted.

Pharmacokinetic interaction studies

The general interaction potential of an essential fatty acid of the omega-3 series is considered small. Due to the diversity of metabolic pathways and widely distributed storage in the body, relevant effects of other drugs on EPA-PK are unlikely.

In vitro studies show that EPA is a weak inhibitor of CYP2C19, CYP2C9, CYP2C8, and to a lesser extent of CYP2B6 and CYP3A. This was addressed by interaction studies with omeprazole (to address CYP2C19), rosiglitazone (to address CYP2C8), warfarin (to address CYP2C9) and atorvastatin (to address CYP3A4). Other CYP-enzymes are involved in metabolism of the drugs as well e.g. CYP2C9 (rosiglitazone), CYP1A2, CYP2C19 or CYP3A4 (warfarin).

Though not all results exclude any interaction, the observed deviations are small and e.g. for omeprazole and rosiglitazone not in accordance with the assumption of an increased exposure due to CYP inhibition.

In subgroup analyses from MARINE and ANCHOR studies, no consistent effect of antihypertensive drugs, antiplatelet drugs and statins (atorvastatin, rosuvastatin and simvastatin) on EPA-concentrations was detected.

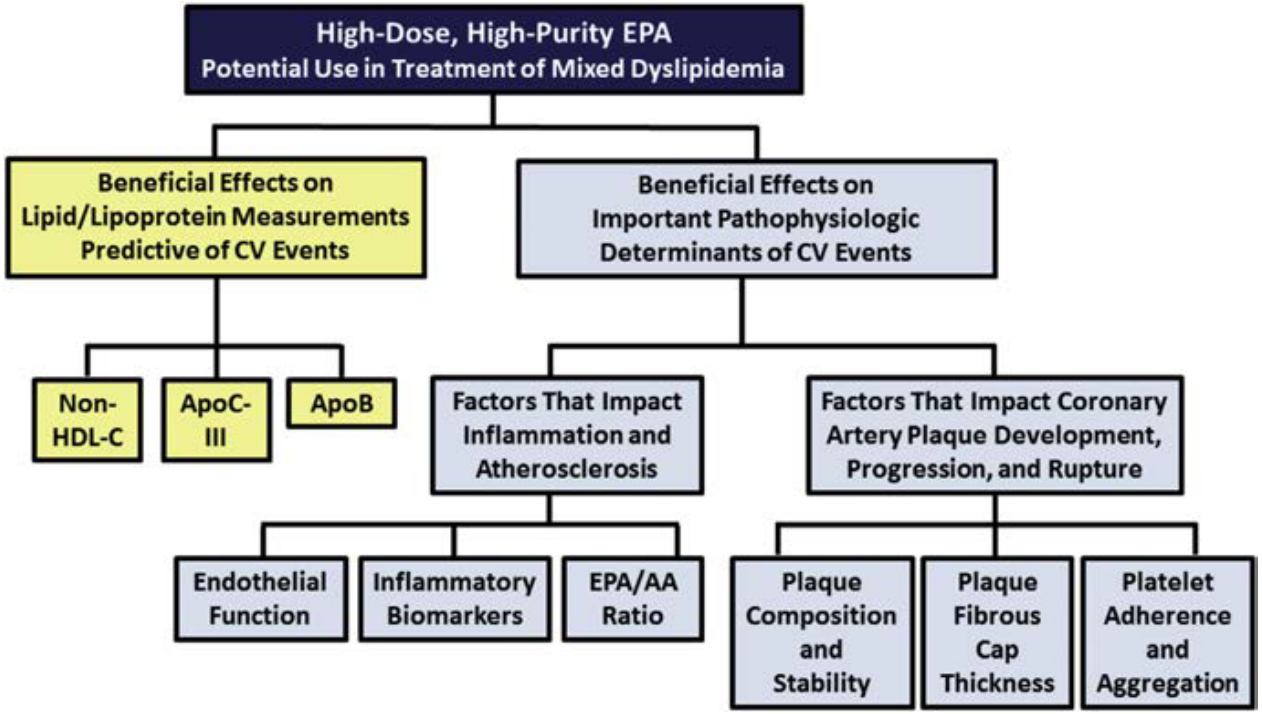
Thus, based on the submitted data, absence of specific clinically relevant drug-drug-interactions can be assumed.

2.4.3. Pharmacodynamics

Mechanism of action

The possible mechanism of action in patients with hypertriglyceridemia at increased CV risk is unclear. As outlined below, AMR101 decreases TGs in a dose dependent manner. However, whether triglyceride lowering per se translates into a CV benefit is a matter of discussion. Several additional mechanisms of action have been discussed in the publicly available literature. Among these are an impact on the regulation of NO and ONOO-1, reduction of reactive oxygen species, inhibition of lipid peroxidation, improvement of endothelial function and restoration of endothelium-dependent vasodilation, effects on differentiation of monocytes into macrophages relevant for atherogenic processes, effects on inflammatory processes, plaque stabilization and incorporation of EPA into platelet membranes that may reduce platelet aggregation. A multimodal concept of the potential mechanisms of action has been published (Figure 3). The applicant has provided additional data indicating a primary action of EPA on the atherosclerotic process.

Figure 3. Potential beneficial effects of eicosapentaenoic acid (EPA) on clinical cardiovascular (CV) end points. Apo, apolipoprotein; AA, arachidonic acid; non-HDL-C, non-high-density lipoprotein cholesterol (from K.M. Borow et al.; Atherosclerosis 242 (2015) 357).



Primary and Secondary pharmacology

Primary pharmacology

Effects of AMR101 on the key lipid and inflammatory parameters has been investigated in the MARINE, and MARINE OLE, in ANCHOR and in the pivotal REDUCE IT trial in adult patients with hypertriglyceridaemia.

In MARINE there was a consistent and dose dependent reduction in TG levels from baseline to week 12 and an increase with placebo (mineral oil). LDL-C decreased numerically slightly, with AMR101 and placebo. Non HDL-C and VLDL-C decreased at a dose of 4 gr AMR101 daily and increased in the placebo

arm. Lp-PLA2 decreased at 4 gr. AMR101 with little change in the placebo arm. ApoB decreased at 4 gr AMR101 and increased in the placebo arm. For hsCRP a decrease was observed with 4 gr an increase with placebo, and to a lesser degree with 2 gr. AMR101. Total cholesterol, VLDL-TG and to some degree HDL-C decreased with AMR101 4g. A smaller reduction was seen for VLDL-TG for AMR101 2 gr with little change for the other parameters. With placebo an increase in TC and VLDL-TG was seen and no change for HDL-C.

The results in ANCHOR were consistent with the following exceptions:
LDL increased in the placebo group and to a minor degree with AMR101 (both doses). Lp-PLA2 showed a moderate increase in the placebo arm. HDL-c slightly increased with Placebo with little change in both AMR101 treatment groups.

An overview over the results for Lipid parameters as observed in MARINE is shown in Table below.

Table Median Baseline and Percent Change From Baseline To Week 12 in Lipid Parameters-ITT Population (MARINE)

Parameter	Placebo (N=75)		Vazkepa 4 g/day (N=76)		Vazkepa 2 g/day (N=73)		Median		p-value	
	BL	% Change	BL	% Change	BL	% Change	Vazkepa 4 g/day vs. Placebo	Vazkepa 2 g/day vs. Placebo	Vazkepa 4 g/day vs. Placebo	Vazkepa 2 g/day vs. Placebo
TG[1] (mmol/L)	7.9	9.7	7.7	-26.6	7.4	-7.0	-33.1	-19.7	<0.0001	0.0051
LDL-C (mmol/L)	2.2	-3.0	2.3	-4.5	2.2	-2.5	-2.3	5.2	0.6768	0.3022
Non-HDL-C (mmol/L)	5.9	7.8	5.8	-7.7	5.4	0.0	-17.7	-8.1	<0.0001	0.0182
VLDL-C[2] (mmol/L)	3.2	13.7	3.2	-19.5	3.1	0.0	-28.6	-15.3	0.0005[3]	0.1152[3]
Lp-PLA$_2$[2] (ng/mL)	253.0	-2.4	246.0	-17.1	235.0	-5.1	-13.6	-5.1	0.0006[3]	0.2367[3]
Apo B[2] (g/L)	1.2	4.3	1.2	-3.8	1.2	2.1	-8.5	-2.6	0.0019[3]	0.2367[3]
hsCRP (mg/L)	1.8	33.3	2.2	-2.5	2.0	25.1	-36.0	-10.1	0.0012	0.4028
TC (mmol/L)	6.6	7.7	6.6	-7.3	6.1	0.7	-16.3	-6.8	<0.0001	0.0148
HDL-C (mmol/L)	0.7	0.0	0.7	-3.5	0.7	0.0	-3.6	1.5	0.2174	0.5225
VLDL-TG (mmol/L)	6.1	7.8	5.9	-25.2	5.5	-6.4	-25.8	-17.3	0.0023	0.0733

% Change = Median Percent Change from Baseline; Apo B = apolipoprotein B; BL = Baseline (mg/dL); HDL-C = high-density lipoprotein cholesterol; hsCRP = high sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; Lp-PLA$_2$ = lipoprotein-associated phospholipase A$_2$; non-HDL-C = non-high-density lipoprotein cholesterol; TC = total cholesterol; TG = triglyceride; VLDL-C = very low-density lipoprotein cholesterol; VLDL-TG = very low-density lipoprotein triglycerides. Medians are Hodges-Lehmann medians; p-values are from the Wilcoxon rank-sum test.

1 Fasting TG level was the primary efficacy endpoint

2 VLDL-C, Lp-PLA$_2$, and Apo B were secondary efficacy endpoints

3 Adjusted p-values from applying Hommel's multiple comparison procedure to the p-value from the treatment comparison between 4 or 2 g/day Vazkepa with placebo are reported.

An overview over the results for Lipid parameters as observed in ANCHOR is shown in Table 20.

Table Median Baseline and Percent Change from Baseline To Week 12 in Lipid Parameters-ITT Population (ANCHOR)

Parameter	Placebo (N=227)		Vazkepa 4 g/day (N=226)		Vazkepa 2 g/day (N=234)		Median		p-value	
	BL	% Change	BL	% Change	BL	% Change	Vazkepa 4 g/day vs. Placebo	Vazkepa 2 g/day vs. Placebo	Vazkepa 4 g/day vs. Placebo	Vazkepa 2 g/day vs. Placebo
TG[a] (mmol/L)	2.9	5.9	3.0	-17.5	2.9	-5.6	-21.5	-10.1	<0.0001	0.0005
LDL-C[b] (mmol/L)	2.2	8.8	2.1	1.5	2.1	2.4	-6.2	-3.6	0.0067	0.0867
Non-HDL-C[b] (mmol/L)	3.3	9.8	3.3	-5.0	3.3	2.4	-13.6	-5.5	0.0001[c]	0.0140[c]
VLDL-C[b] (mmol/L)	1.1	15.0	1.1	-12.1	1.1	1.6	-24.4	-10.5	0.0001[c]	0.0170[c]
Lp-PLA_2[b] (ng/mL)	185.0	6.7	180.0	-12.8	190.0	-1.8	-19.0	-8.0	0.0001[c]	0.0004[c]
Apo B[b] (g/L)	0.9	7.1	0.9	-2.2	0.9	1.6	-9.3	-3.8	0.0001[c]	0.0170[c]
hsCRP (mg/L)	2.2	17.1	2.2	-2.4	1.9	10.3	-22.0	-6.8	0.0005	0.2894
TC (mmol/L)	4.3	9.1	4.3	-3.2	4.4	2.1	-12.0	-4.8	<0.0001	0.0019
HDL-C (mmol/L)	1.0	4.8	1.0	-1.0	1.0	0.0	-4.5	-2.2	0.0013	0.1265
VLDL-TG (mmol/L)	2.1	8.9	2.1	-19.2	2.1	-2.1	-26.5	-11.3	<0.0001	0.0049

% Change = Median Percent Change from Baseline; Apo B = apolipoprotein B; BL = Baseline; HDL-C = high-density lipoprotein cholesterol; hsCRP = high sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; Lp-PLA_2 = lipoprotein-associated phospholipase A_2; non-HDL-C = non-high-density lipoprotein cholesterol; TC = total cholesterol; TG = triglyceride; VLDL-C = very low-density lipoprotein cholesterol; VLDL-TG = very low-density lipoprotein triglycerides. Medians are Hodges-Lehmann medians; p-values are from the Wilcoxon rank-sum test.

a Fasting TG level was the primary efficacy endpoint

b LDL-C, non-HDL-C. VLDL-C, Lp-PLA_2, and Apo B were secondary efficacy endpoints

c Adjusted p-values from applying Hommel's multiple comparison procedure to the p-value from the treatment comparison between 4 or 2 g/day Vazkepa with placebo are reported.

It is unclear, to which degree mineral oil as a comparator is inert. The increase in hsCRP cannot be easily explained by variability or regression to the mean effects. LDL-C increased in ANCHOR and in the pivotal REDUCE-IT trial but not in MARINE. Possibly, regression to the mean effects based on the differences in LDL-C related inclusion criteria in the three studies contributed to the differential LDL-C pattern. Based on the information derived from dose response (4 g vs. 2 g) and from change from baseline, AMR101 reduced TGs, VLDL-C, VLDL-TG, Lp-PLA2, and to some degree non-HDL-C, ApoB. There was a decrease in TC and hsCRP when 4 g is compared with 2 g but not when compared with baseline.

The effect of AMR101 on TG was dose dependent and pronounced. This effect was preserved over one year as demonstrated in the MARINE OLE (open label extension) study (see below, supportive studies).

Secondary pharmacology

There is considerable uncertainty of the pharmacodynamic mechanism leading to the clinical efficacy of EPA. Therefore, definite division in primary and secondary pharmacology is not possible and it is referred to the primary pharmacology section above.

Relationship between plasma concentration and effect

There was a linear correlation between plasma/erythrocyte EPA content and TG lowering effect based on the assessment of placebo control, AMR101 2g daily and 4 g daily. Among the PD effects presented the TG lowering effect was most pronounced and therefore, there is a rationale to use it to assess the PK/PD correlation. In addition, in a post hoc analysis a correlation between plasma/erythrocyte EPA concentration and clinical efficacy on MACE has been observed. The relative contribution of the TG lowering effect and the relevance of different proposed mechanisms of action are unknown. It is therefore not possible to finally conclude on the clinical relevance of the PK/PD correlation provided.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

EPA is an essential omega-3 fatty acid, included in standard diet in different amounts. Marine fish is the primary natural dietary source of EPA.

Absorption and elimination in the plasma is slow (tmax ~ 5 h, t1/2 more than 3 days). Accordingly, EPA concentration in plasma and tissues increases to steady state within a period of approximately one month. The increase in EPA after dosing with Vazkepa constitutes only a minor fraction of the total

systemic fatty acid pool. EPA did constitute 3.4-3.6 mol % of the total molar fatty acid concentration in plasma after 12 weeks with 4 g/day Vazkepa, versus 0.4-0.5 % at baseline. Similar results were seen in red blood cells (RBC).

The majority of EPA in plasma is esterified into phospholipids (PL), triacylglycerols (TAG) or triglycerides and cholesteryl esters (CE), with incorporation of EPA in RBC and tissues. The most prominent degradation pathway is β-oxidation.

There was an about 15% higher exposure in patients ≥75 year age not considered relevant for efficacy. Whether the slightly higher exposure contributed in part to the increase in bleeding events in the higher age groups may not be clarified based on the data available.

Possible drug-drug-interactions (DDI) have been addressed. No clinically relevant DDI could be identified.

The multi-factorial mechanisms of action contributing to the icosapent ethyl effects include improved lipid and lipoprotein profiles, such as a reduction in triglyceride levels without raising low density lipoprotein cholesterol (LDL-C) levels compared to placebo, likely through reduced production and faster clearance of triglycerides and decreased production of very low-density lipoprotein (VLDL) particles and increased clearance of LDL particles. In addition, anti-inflammatory effects of EPA may result from displacement of pro-inflammatory arachidonic acid (AA), directing catabolism away from eicosanoids (2-series prostaglandins and thromboxanes, and 4-series leukotrienes) to non- or anti-inflammatory mediators. EPA may also exert systemic anti-inflammatory and antioxidant effects as reflected by reductions in various biomarkers including C-reactive protein (CRP) and lipoprotein phospholipase A2 (Lp-PLA2), and oxidised LDL compared to placebo. EPA may inhibit platelet activation and aggregation and reduce mean platelet volume and count, thereby exerting both anti-platelet and anti-thrombotic effects.

The applicant has provided additional analyses from the REDUCE-IT trial indicating a correlation between EPA concentration and efficacy on MACE. These data from post hoc analyses are not considered conclusive mainly due to sparse sampling and a key impact of imputation rules on the overall results. The exact mechanism for cardiovascular risk reduction remains unclear. This limits target-oriented determination of PD parameters. Therefore, determining only some PD parameters is acceptable. Available data suggest that 4 g Vazkepa / day is an effective dose. Further PD data e.g. on hypertriglyceridaemia are addressed in phase 3 studies and are discussed in the clinical efficacy section.

Pharmacodynamics and PK/PD correlation

The assessment of the PD effects of AMR101 is to some degree hampered by uncertainties related to the comparator mineral oil used in the PD studies (MARINE and ANCHOR) and in the pivotal study (REDUCE-IT). Mineral oil may not be entirely inert but the relevance of possible negative effects of mineral oil on CV outcome in the pivotal REDUCE-IT trial are limited. It was hypothesized that substance specific actions and indirect effects (e.g. reduced absorption of drugs like statins) may affect lipids, lipoproteins and markers of inflammation. If so, in comparison to mineral oil effects may be overestimated. However, as discussed in the context of the pivotal REDUCE-IT trial below, even under hypothetical worst-case assumptions, most of the effects observed on lipid parameters and on clinical efficacy on MACE has to be attributed to Vazkepa. Consistently, there was a dose response from 2 g to 4 gr AMR101 in the PD studies for several of the above-mentioned parameters. Based on an assessment of the difference between the effect of 4 gr

and of 2 gr AMR101 reduced TGs, VLDL-C, VLDL-TG, Lp-PLA2, and to some degree non-HDL-C and ApoB. There was a decrease in TC and hsCRP when 4 gr is compared with 2 gr but not when compared with baseline.

The effect on TGs was preserved over one year as demonstrated in the MARINE OLE (open label extension) study. The long-term data provide some reassurance regarding an absence of a relevant increase in LDL-C induced by AMR101. Overall, the effects on the lipid profile appear to be favourable. A clear correlation between dose, concentration in plasma/erythrocytes and TG lowering effect was demonstrated.

Whereas these PD effects are clearly established, the relevance of these effects for the CV prevention indication is less clear. TG lowering on its own has not been consistently been associated with a CV risk reduction. Many different possible mechanisms of actions have been proposed in the literature. The applicant has provided data indicating beneficial effects of EPA on the atherosclerotic process based on imaging studies which allow direct visualisation of drug effect on plaque burden, stability and rupture, as well as thin-cap fibroatheroma and macrophage accumulation. However, it is not clear, why plaque stabilising effects of EPA would be associated with a lag time of more than one year before efficacy on MACE events are seen as was the case in REDUCE-IT. Ultrasound studies have indicated smaller coronary atherosclerotic plaque or lipid volume in subjects on EPA therapy than in those not on EPA therapy. Overall, at present the contribution of each of different proposed mechanisms of actions remains unclear.

2.4.5. Conclusions on clinical pharmacology

The CHMP considered Vazkepa to be approvable from the clinical pharmacology point of view.

2.5. Clinical efficacy

Vazkepa (AMR101, Ethyl-EPA) was intended for reduction of cardiovascular (CV) risk as an adjunct to statin therapy in adult patients with elevated triglyceride (TG) levels and other risk factors for cardiovascular disease (CVD). The proposed by the applicant daily dose in adults was 4 capsules per day taken with food.

The CHMP approved the following indication for Vazkepa:

Vazkepa is indicated to reduce the risk of cardiovascular events in adult statin-treated patients at high cardiovascular risk with elevated triglycerides (≥150 mg/dL) and

- *established cardiovascular disease, or*
- *diabetes, and at least one other cardiovascular risk factor.*

For study details including cardiovascular risk factors and results with respect to effects on cardiovascular events see section 5.1.

The recommended daily oral dose is 4 capsules taken as two 998 mg capsules twice daily.

Table 2 summarizes the studies relevant for the application in CV prevention. REDUCE-IT is the pivotal trial for this application, ANCHOR, MARINE and MARINE OLE (open label extension study) are considered supportive.

Table Phase 3 Randomised, Placebo-Controlled, Clinical Studies Conducted with Vascepa

	REDUCE-IT (AMR-01-01-0019) NCT01492361	**ANCHOR (AMR-01-01-0017) NCT01047501**	**MARINE (AMR-01-01-0016) NCT01047683**
	Pivotal	**Supportive**	**Supportive**
Patient population	Patients with elevated TG (≥1.5 and <5.6 mmol/L [≥135 and <500 mg/dL][1]) on statin therapy and at high risk for CVD[4]	Patients with hypertriglyceridaemia (TG ≥2.3 and <5.6 mmol/L [≥200 and <500 mg/dL]) on statin therapy[6]	Patients with severe hypertriglyceridaemia (TG ≥5.6 and ≤22.6 mmol/L [≥500 and ≤2000 mg/dL])
LDL-C at inclusion	1.06 to 2.59 mmol/L (41 to 100 mg/dL)	1.03 to 2.97 mmol/L (40 to 115 mg/dL)[6]	-
Clinical Endpoints	CV events	TG reduction	TG reduction
Trial Design	Randomised, double-blind, placebo-controlled, multi-centre	Randomised, double-blind, placebo controlled, multi-centre	Randomised, double-blind, placebo-controlled
Trial Duration	Median 4.9 years (event-driven)	12-week double-blind period.	12-week double-blind period followed by 40-week OLE
Dose regimen	4 g/day Vascepa, placebo	2 or 4 g/day Vascepa, placebo	2 or 4 g/day Vascepa, placebo (4 g/day Vascepa in OLE)
Randomisation	1:1	1:1:1	1:1:1
Stratification	CV risk (secondary or primary-prevention[5], use or no use of ezetimibe, and geographic region)	Patients were stratified by type of statin (atorvastatin, rosuvastatin, or simvastatin), the presence of diabetes, and gender	Stratified according to baseline TG level, gender and use of statin therapy at baseline.
Statin Use	All patients	All patients	~25% of patients
Planned	7990	648	240
Randomised/ Completed	8179/7314 (Vascepa 4089/3684 Placebo 4090/3630)	702/663 Vascepa 4 g/day 233/221 Vascepa 2 g/day 236/225 Placebo 233/217	229/215 Vascepa 4 g/day 77/74 Vascepa 2 g/day 76/70 Placebo 76/71
Geographic Location	Global[2]	US only	Global[3]
Status	Completed	Completed	Completed

CV=cardiovascular, CVD=cardiovascular disease, LDL-C = low-density lipoprotein cholesterol, OLE=open-label extension, TG=triglyceride, UIS = United States.
To convert the values for TG to mmol/L, multiply by 0.01129.

	REDUCE-IT (AMR-01-01-0019) NCT01492361	ANCHOR (AMR-01-01-0017) NCT01047501	MARINE (AMR-01-01-0016) NCT01047683
	Pivotal	**Supportive**	**Supportive**
1.	Note that the original protocol stipulated a lower end of the fasting TG level of ≥1.52 mmol/L (135 mg/dL), reflecting a 10% allowance from the target lower fasting TG level of ≥1.69 mmol/L (150 mg/dL); this 10% allowance was included due to the variability in TG levels. Protocol Amendment 1 (16 May 2013) increased the lower end of fasting TG levels from ≥1.52 mmol/L (135 mg/dL) to ≥2.26 mmol/L (200 mg/dL) without a variability allowance to increase enrolment of patients with TG levels at or above 2.26 mmol/L (200 mg/dL).		
2.	United States, the Netherlands, Ukraine, Russian Federation, South Africa, Poland, India, Canada, Romania, Australia, and New Zealand		
3.	Included sites in United States, South Africa, The Netherlands, Germany, Finland, Italy, Russia, Ukraine, and India		
4.	at least 45 years old with documented CVD (secondary prevention group) OR at least 50 years old with diabetes and with at least one additional risk factor for CVD (primary prevention group)		
5.	in approximately 30% of enrolled patients		
6.	To facilitate enrolment, a protocol amendment was implemented after approximately 1/2 of patients were randomised: the haemoglobin A1c exclusion criterion was increased from 9.0% to >9.5%; based on known within patient variability for TG and LDL cholesterol, entry criteria were expanded so the mean of the 2 TG-qualifying values was ≥2.09 mmol/L (185 mg/dL) with ≥1 of the 2 values ≥2.26 mmol/L (200 mg/dL); and the upper limit of the LDL-C entry criteria was increased by 15% to 2.97 mmol/L (≤115 mg/dL)		

Table Listing of Clinical Studies (Target Indication):

Type of Study	Study Identifier (Location in MAA)	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dose Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Target Indications								

Type of Study	Study Identifier (Location in MAA)	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dose Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy	AMR-01-01-0017 (ANCHOR) (5.3.5.1)	Efficacy and safety; Changes in TG	Double-Blind, Randomized, Placebo-Controlled	AMR101 2 g or 4 g/day oral	702	Patients with High Triglycerides	12 weeks	Complete; Full
Efficacy	AMR-01-01-0016 (MARINE) (5.3.5.1)	Efficacy and safety; Changes in TG	Double-Blind, Randomized, Placebo-Controlled, with Open-Label Extension	AMR101 2 g or 4 g/day oral	229	Patients with Very High Triglycerides	12 weeks – double-blind treatment period[a]	Complete; Full
Safety and efficacy	AMR-01-01-0016 (MARINE OLE) (5.3.5.1)	Safety	Open-Label Extension	AMR101 4 g/day oral	210	Patients with Very High Triglycerides	40-week open label extension	Complete; Full
Efficacy	AMR-01-01-0019 (REDUCE-IT) (5.3.5.1)	Efficacy and safety; Cardiovascular Risk Reduction	Double-Blind, Randomized, Parallel-Group, Placebo Controlled	AMR101 4 g/day oral	8179	Patients with High Triglycerides and at risk for CVD	4.9-year median follow-up duration	Complete; Full

TG= triglyceride

a. All patients rolled over into open-label extension received AMR101 capsules 4 g/day

The following studies in other indications were included in the dossier. These studies are not relevant for the assessment of efficacy in the proposed CV prevention indication and therefore are not discussed here.:

- Patients with Huntington's Disease: 3 Studies: LA01.01.0005, AN01.01.0011, AN01.01.0012

- Patients with Schizophrenia: 1 Study: LA01.01.0001

- Patients with Depression: 3 Studies: LA01.01.0002, LA01.01.0006, LA01.01.0008A

- Patients with Age-Associated Memory Impairment: 1 Study: AN01.01.0014

2.5.1. Dose response studies and main clinical study

In the REDUCE-IT study a daily dose of AMR101 of 4 g (2 g BID with food) was investigated. No data are available on the correlation between dose and efficacy on hard CV clinical endpoints.

The dose selection was mainly based on results from ANCHOR and MARINE/MARINE OLE. Prior to MARINE and ANCHOR, more than 1000 patients had been exposed to AMR101 at doses up to 4 g per day in the randomised, double-blind periods of Amarin-sponsored studies (see above). More than 700 patients had received continuous treatment with AMR101 1 g per day and 2 g per day (most patients received 2 g per day). The Applicant states that AMR101 was well tolerated in these studies. ANCHOR and MARINE studies investigated efficacy of two dose levels (1 and 2 g BID, i.e. 2g and 4 g daily dose taken with food). MARINE OLE was an open label extension study investigating a daily dose of AMR101 4 g over 40 weeks. In these studies AMR101 resulted in a statistically significant reduction of TG compared with placebo. A larger reduction in TG and some other lipid and lipoprotein parameters was seen with AMR101 4 g/day than with AMR101 2 g/day. Data on PK/PD correlation based on these two doses indicated a linear correlation between percent change from baseline to Week 12 in fasting TG versus percent change in EPA concentration in plasma and red blood cells for the ITT population at least up to a daily dose of 4 gr.

Based on these data 4 g/day (2 g BID) to be taken with food (i.e., with or at the end of their morning and evening meals) was chosen as the only dose to be investigated in REDUCE-IT. The choice of the 4 g daily AMR101 dose appears to be reasonable when assuming that the TG lowering effect is relevant for efficacy which is not clear. While information about efficacy of lower doses on CV endpoints is missing, not including a lower dose treatment arm in the REDUCE-IT trial was not considered as an issue of concern with respect to efficacy. With respect to safety it is unclear, whether AEs like haemorrhagic events and atrial fibrillation would have been observed with similar frequency at a lower dose level.

Main study

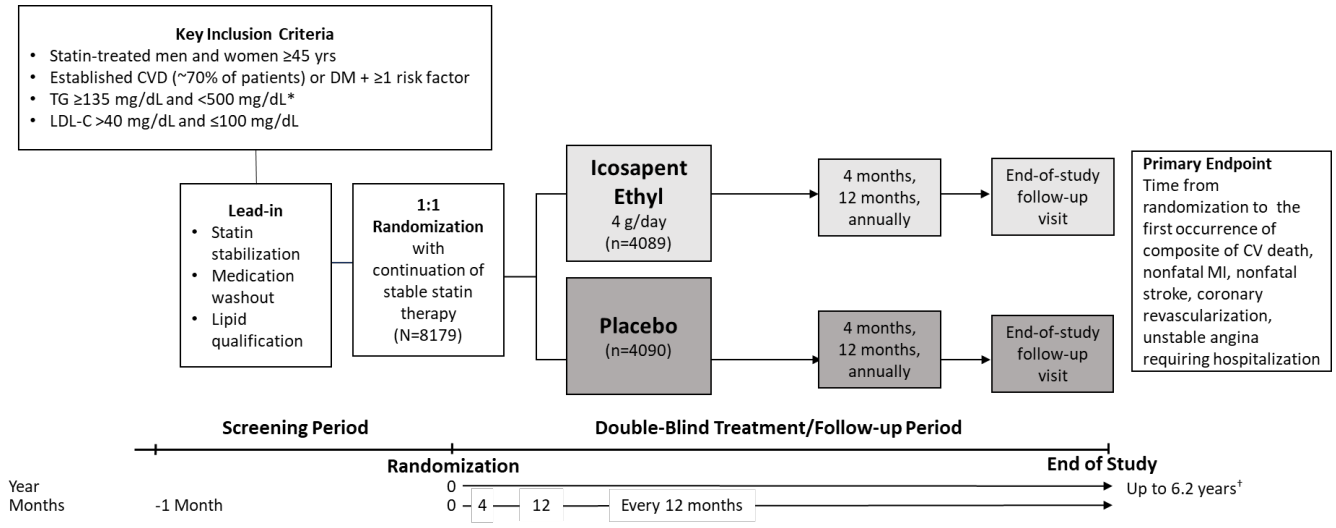
STUDY AMR-01-01-0019 (REDUCE-IT)

A Multi-Center, Prospective, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Effect of AMR101 on Cardiovascular Health and Mortality in Hypertriglyceridemic Patients with Cardiovascular Disease or at High Risk for Cardiovascular Disease: REDUCE-IT (Reduction of Cardiovascular Events with EPA – Intervention Trial)

Methods

It was a multi-center, multi-national, prospective, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the effect of 2 g of AMR101 twice daily (BID) (4 g/day) for preventing CV events in statin-treated patients with moderately elevated TG levels and other CVD risk factors. The study was event driven. A total of approximately 7990 patients were planned to be enrolled (i.e., randomized) in the study to either receive AMR101 or placebo in a 1:1 ratio (approximately 3995 patients per treatment group) to observe an estimated 1612 primary endpoint events. An overview over the study design is shown in Figure 9-1.

Figure 9-1 From the REDUCE-IT CSR:



*Due to the variability of triglycerides, a 10% allowance from the lower qualifying target of ≥150 mg/dL existed in the initial protocol, which permitted patients to be enrolled with qualifying triglycerides ≥135 mg/dL. Protocol amendment 1 (May 2013) changed the lower limit of acceptable triglycerides from 135 mg/dL to 200 mg/dL, with no variability allowance.

†Median trial follow-up duration was 4.9 years (minimum 0.0, maximum 6.2 years).

Abbreviations: CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; icosapent ethyl = AMR101; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; TG = triglycerides; yrs = years.
Source: Modified from Bhatt DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. 2019;380(1):11-22.

Study Participants

Key inclusion criteria (not exhaustive)

Men and women at age ≥ 45 years (risk category 1) or 50 years (risk category 2) with the following characteristics:

Inclusion criteria related to lipid status:

1. Original protocol: fasting TG level of ≥135 mg/dL (1.53 mmol/L) and <500 mg/dL (5.64 mmol/L).

After amendment 1 (16 May 2013): fasting TG level of ≥200 mg/dL (2.26 mmol/L) and <500 mg/dL (5.64 mmol/L).

2. LDL-C >40 mg/dL (1.04 mmol/L) and ≤100 mg/dL (2.60 mmol/L) and on stable therapy with a statin (with or without ezetimibe) for at least 4 weeks (i.e. no change in dose for 28 days) prior to the LDL-C and TG baseline qualifying measurements for randomization. In case of a change or de novo initiation of statin/ezetimibe, a stabilization period of at least 28 days was needed prior to the qualifying lipid measurements (TG and LDL-C.

Inclusion criteria related to cardiovascular risk:

3. Either having established CVD (in CV risk category 1) or at high risk for CVD (in CV risk category 2). The CV risk categories were defined as follows:

CV Risk Category 1 (Secondary Prevention Cohort): men and women ≥45 years of age with one or more of the following:

− Documented **coronary artery disease** (**CAD**) according to predefined criteria

− Documented **cerebrovascular or carotid disease** according to predefined criteria

− Documented **peripheral arterial disease** according to predefined criteria

CV Risk Category 2 (Primary Prevention Cohort): Men and women ≥ 50 years of age with diabetes mellitus (Type 1 or Type 2) requiring treatment with medication and one or more of the following at Visit 1:
▪ Men ≥55 years of age or women ≥65 years of age.
▪ Cigarette smoker or stopped smoking within 3 months before Visit 1.
▪ Hypertension (blood pressure ≥140 mmHg systolic or ≥90 mmHg diastolic) or on antihypertensive medication.
▪ HDL-C ≤40 mg/dL for men or ≤50 mg/dL for women.
▪ hsCRP >3.00 mg/L (0.3 mg/dL).
▪ Renal dysfunction: creatinine clearance (CrCL) >30 and <60 mL/min (>0.50 and <1.00 mL/sec).
▪ Retinopathy, defined as any of the following: non-proliferative retinopathy, pre-proliferative retinopathy, proliferative retinopathy, maculopathy, advanced diabetic eye disease, or a history of photocoagulation.
▪ Micro- or macroalbuminuria.
▪ ABI <0.9 without symptoms of intermittent claudication (patients with ABI <0.9 with symptoms of intermittent claudication were included in CV risk category 1).

Key exclusion criteria (not exhaustive)

1. Severe (New York Heart Association class IV) heart failure.

2. Any life-threatening disease expected to result in death within the next 2 years (other than CVD).

3. Active severe liver disease

4. HbA1c >10.0% (or >86 mmol/mol IFCC units)

5. Poorly controlled hypertension

6. Planned coronary intervention

All patients were on statin therapy, whereas PCSK9 inhibitors were not allowed, efficacy has therefore not been investigated add on this substance class.

Treatments

Double-blind investigational products:

• AMR101 1 g capsules

• Placebo capsules (to match AMR101 1 g capsules)

The daily dose of study drug was 4 capsules per day taken orally as two capsules on two occasions per day (two capsules given BID) with food.

AMR101 capsule fill contained icosapent ethyl and tocopherol and placebo capsule fill contained light mineral oil and tocopherol. The same capsule shell was used for both AMR101 and placebo and contained gelatin, non-crystalizing sorbitol, glycerin, water and maltitol.

Objectives, outcomes and endpoints

The **primary objective** of this study was, in patients at LDL-C goal while on statin therapy, with established CVD or at high risk for CVD and elevated TG (fasting TG ≥135 mg/dL and <500 mg/dL [≥1.53 mmol/L and <5.64 mmol/L]), to evaluate the effect of 4 g/day AMR101 on the time from randomization to the first occurrence of any component of the composite of the following major CV events:

• CV death
• Nonfatal myocardial infarction (MI) (including silent MI)
• Nonfatal stroke
• Coronary revascularization
• Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization

The **key secondary objective** of this study was:

• To evaluate the effect of therapy on the time from randomization to the first occurrence of the composite of CV death, nonfatal MI (including silent MI), or nonfatal stroke

Other secondary and tertiary objectives were predefined.

Randomisation and blinding (masking)

It was a double blind study. Measures to keep blinding were in place.

Patients were assigned in a blinded manner according to a computer-generated randomization scheme to one of two treatment groups at a 1:1 ratio via the IWRS.

Randomization was stratified by CV risk category, use of ezetimibe (yes/no), and by geographical region (Westernized, Eastern European, and Asia Pacific). Two CV risk categories were defined, as follows:

• CV Risk Category 1 (Secondary Prevention Cohort): patients with established CVD defined in the inclusion criteria

• CV Risk Category 2 (Primary Prevention Cohort): patients with diabetes and at least one additional risk factor for CVD, but no established CVD

Patients with diabetes and established CVD were included in CV risk category 1. Stratification was accounted for and recorded in the IWRS at the time of enrollment. Approximately 70% of the planned 7990 randomized patients were planned to be in the CV risk category 1, and approximately 30% of randomized patients were planned to be in the CV risk category 2.

Statistical methods

All statistical analyses and data summaries were generated according to the statistical analysis plan (SAP) and the SAP Addendum, both finalized prior to database lock and final unblinding.

The primary efficacy analysis was performed on the ITT population including all randomized patients. For the primary endpoint, all observed data that were positively adjudicated by the Clinical Endpoint Committee (CEC), including data after discontinuation of study drug for patients who discontinued study drug prematurely, were included in the primary analysis. Patients who experienced no primary endpoint event were censored at the date of their last visit/phone contact or date of non-CV death.

Kaplan-Meier estimates were used to summarize the time to the first event of the primary endpoint. The log-rank test, stratified by stratification variables at randomization (CV risk category, use of ezetimibe, and geographical region) was used to compare the time-to-event between treatment groups. The hazard ratio (HR) comparing the two treatment groups along with the 95% confidence interval (CI) were calculated from a stratified Cox proportional hazards model.

The 2 sided alpha level for the primary analysis was adjusted to 0.0437 from 0.05 to account for the two interim analyses based on a group sequential design with O'Brien-Fleming boundaries generated using the Lan DeMets alpha-spending function. The interim analysis results of the study were monitored by an independent DMC.

The time to first occurrence of each of the five component events of the primary endpoint, each of the secondary endpoints, and time-to-event tertiary endpoints were analyzed by the same methods described for the primary endpoint.

For the analysis of all secondary endpoints, the Type 1 error was controlled by testing each endpoint sequentially, starting with the key secondary endpoint. Testing was done at a significance level of 0.0437 consistent with that used for the primary endpoint.

Subgroup analyses of the primary and key secondary endpoints were performed as described for the primary endpoint. Subgroup analyses results are presented in forest plots. A p-value for testing the interaction terms <0.15 was considered significant.

As a sensitivity analysis, alternative censoring rules were applied. In addition, recurrent event analysis was performed considering events as count data, a stratified Cox proportional hazards model was constructed for the primary endpoint to evaluate the treatment effect adjusting for important baseline covariates, and tipping point analyses were performed to assess the potential impact of missing data that were caused by early termination from the study.

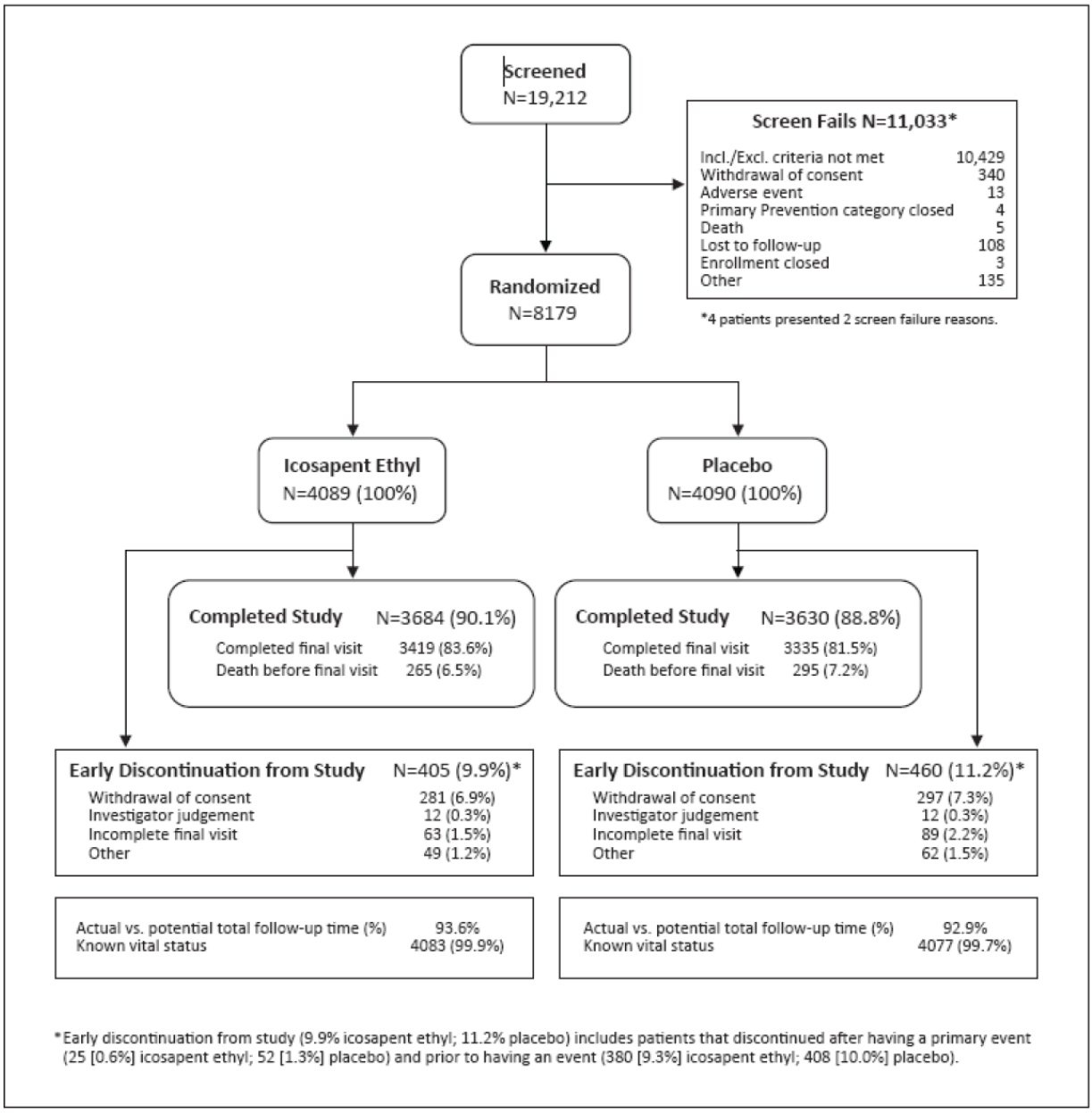
For measurements of lipids, lipoproteins, and inflammatory markers, the Wilcoxon rank-sum test was used for treatment comparisons of the percent change from baseline, and medians and quartiles were provided for each treatment group. The medians of the differences between the treatment groups and 95% CIs were estimated with the Hodges-Lehman method. In addition, shift tables were generated.

Results

Participant flow

A summary of patient disposition is displayed in Figure 10-1.

Figure 10-1: Patient Disposition



Abbreviations: icosapent ethyl = AMR101; incl./excl. = inclusion/exclusion; vs. = versus.
Source: Table 14.1.3.1 and Table 14.1.2.

Recruitment

A total of approximately 7990 patients were planned to be enrolled (i.e., randomized) in the study to either receive AMR101 or placebo in a 1:1 ratio (approximately 3995 patients per treatment group) to observe an estimated 1612 primary endpoint events. A total of 473 sites enrolled and/or followed patients in 11 countries in 3 geographic regions. A total of 19,212 patients were screened, 8179 patients were randomized, 7314 completed the final visit (Vazkepa 4089/3684, Placebo 4090/3630).

Baseline data

Patient demographics and baseline characteristics are summarized in Table 11-1, overall and by treatment group. Overall, the majority of patients were male (71.2% [5822/8179]) and white (90.2% [7379/8179]). The mean age of patients was 63.4 years (range 44 to 92 years), with 46.0% (3763/8179) of patients aged ≥65 years. Mean height, weight, and BMI were 171.3 cm, 93.0 kg, and 31.6 kg/m2, respectively. Overall, 22.2% (1816/8179) of patients were renally impaired at baseline (eGFR <60 mL/min/1.73m2). The demographics and baseline characteristics across the ITT, mITT, and PP populations were comparable.

Parameter Statistic	AMR101 (N=4089)	Placebo (N=4090)	Overall (N=8179)	P-value[1]
Diabetes, n (%)				0.7627
No diabetes at baseline	1695 (41.5)	1694 (41.4)	3389 (41.4)	
Type 1 diabetes	27 (0.7)	30 (0.7)	57 (0.7)	
Type 2 diabetes	2366 (57.9)	2363 (57.8)	4729 (57.8)	
Both Type 1 and Type 2 diabetes	1 (0.0)	0 (0.0)	1 (0.0)	
Missing	0 (0.0)	3 (0.1)	3 (0.0)	
Type 1 or 2[4]	2394 (58.5)	2393 (58.5)	4787 (58.5)	0.9622
BMI <25 kg/m^2	134 (5.6)	138 (5.8)	272 (5.7)	
BMI ≥25 to <30 kg/m^2	681 (28.4)	676 (28.2)	1357 (28.3)	
BMI ≥30 kg/m^2	1571 (65.6)	1567 (65.5)	3138 (65.6)	
BMI missing	8 (0.3)	12 (0.5)	20 (0.4)	
Hypertension[5], n (%)				0.9706
Yes	3541 (86.6)	3543 (86.6)	7084 (86.6)	
No	548 (13.4)	547 (13.4)	1095 (13.4)	
Metabolic Syndrome[6], n (%)				0.0988
Yes	3792 (92.7)	3753 (91.8)	7545 (92.2)	
No	297 (7.3)	337 (8.2)	634 (7.8)	
Impaired Glucose Metabolism[7], n (%)				0.1570
Yes	1454 (35.6)	1517 (37.1)	2971 (36.3)	
No	2630 (64.3)	2571 (62.9)	5201 (63.6)	
Missing	5 (0.1)	2 (0.0)	7 (0.1)	

Abbreviations: BMI = body mass index; CRF = case report form; eGFR = estimated glomerular filtration rate; ITT = Intent-to-Treat; Max = maximum; Min = minimum; SD = standard deviation.

Note: Percentages were based on the number of patients randomized to each treatment group in the ITT population (N) except as noted below.

1 To assess balance between treatment groups, p-values were reported from a chi-square test for categorical variables and a t-test for continuous variables. Missing categories were excluded from any comparisons.

2 Age (years) was at randomization.

3 eGFR <60 mL/min/1.73m^2.

4 Percentages were based on the number of patients with Type 1 or Type 2 diabetes.

5 Hypertension as identified on the CRF "Cardiovascular History."

6 For the diagnosis of metabolic syndrome, refer to Appendix D of Protocol Amendment 2 (Appendix 16.1.1).

7 Impaired glucose metabolism was based on Visit 2 fasting blood glucose of 100 to 125 mg/dL.

Source: Table 14.1.8.1.

Parameter Statistic	AMR101 (N=4089)	Placebo (N=4090)	Overall (N=8179)	P-value[1]
Diabetes, n (%)				0.7627
No diabetes at baseline	1695 (41.5)	1694 (41.4)	3389 (41.4)	
Type 1 diabetes	27 (0.7)	30 (0.7)	57 (0.7)	
Type 2 diabetes	2366 (57.9)	2363 (57.8)	4729 (57.8)	
Both Type 1 and Type 2 diabetes	1 (0.0)	0 (0.0)	1 (0.0)	
Missing	0 (0.0)	3 (0.1)	3 (0.0)	
Type 1 or 2[4]	2394 (58.5)	2393 (58.5)	4787 (58.5)	0.9622
BMI <25 kg/m^2	134 (5.6)	138 (5.8)	272 (5.7)	
BMI ≥25 to <30 kg/m^2	681 (28.4)	676 (28.2)	1357 (28.3)	
BMI ≥30 kg/m^2	1571 (65.6)	1567 (65.5)	3138 (65.6)	
BMI missing	8 (0.3)	12 (0.5)	20 (0.4)	
Hypertension[5], n (%)				0.9706
Yes	3541 (86.6)	3543 (86.6)	7084 (86.6)	
No	548 (13.4)	547 (13.4)	1095 (13.4)	
Metabolic Syndrome[6], n (%)				0.0988
Yes	3792 (92.7)	3753 (91.8)	7545 (92.2)	
No	297 (7.3)	337 (8.2)	634 (7.8)	
Impaired Glucose Metabolism[7], n (%)				0.1570
Yes	1454 (35.6)	1517 (37.1)	2971 (36.3)	
No	2630 (64.3)	2571 (62.9)	5201 (63.6)	
Missing	5 (0.1)	2 (0.0)	7 (0.1)	

Abbreviations: BMI = body mass index; CRF = case report form; eGFR = estimated glomerular filtration rate; ITT = Intent-to-Treat; Max = maximum; Min = minimum; SD = standard deviation.
Note: Percentages were based on the number of patients randomized to each treatment group in the ITT population (N) except as noted below.
1 To assess balance between treatment groups, p-values were reported from a chi-square test for categorical variables and a t-test for continuous variables. Missing categories were excluded from any comparisons.
2 Age (years) was at randomization.
3 eGFR <60 mL/min/1.73m^2.
4 Percentages were based on the number of patients with Type 1 or Type 2 diabetes.
5 Hypertension as identified on the CRF "Cardiovascular History."
6 For the diagnosis of metabolic syndrome, refer to Appendix D of Protocol Amendment 2 (Appendix 16.1.1).
7 Impaired glucose metabolism was based on Visit 2 fasting blood glucose of 100 to 125 mg/dL.
Source: Table 14.1.8.1.

Cardiovascular Disease History

Reported CV disease history and risk factors are summarized in Table 11-2, overall and by treatment group, for the ITT population. Overall, the most common incidences of reported CV disease history or other prior conditions influencing CV risk were hypertension (86.6% [7084/8179]), Type 2 diabetes (57.8% [4730/8179]), and MI (46.7% [3819/8179]).

The most frequently reported CV history findings were coronary artery disease (12.8% [1045/8179]), angina pectoris (11.6% [947/8179]), and atrial fibrillation (8.7% [713/8179]).

Table 11-2: Reported Cardiovascular Disease History and Risk Factors, Overall and by Treatment Group (ITT Population)

Category Term	AMR101 (N=4089) n (%)	Placebo (N=4090) n (%)	Overall (N=8179) n (%)
Prior Atherosclerotic Cardiovascular Disease	2816 (68.9)	2835 (69.3)	5651 (69.1)
Prior Atherosclerotic Coronary Artery Disease and Related Morbidities	2387 (58.4)	2393 (58.5)	4780 (58.4)
Ischemic dilated cardiomyopathy	137 (3.4)	109 (2.7)	246 (3.0)
Myocardial infarction	1938 (47.4)	1881 (46.0)	3819 (46.7)
Unstable angina	1017 (24.9)	1015 (24.8)	2032 (24.8)
Prior Atherosclerotic Cerebrovascular Disease and Related Morbidities	641 (15.7)	662 (16.2)	1303 (15.9)
Carotid disease	343 (8.4)	372 (9.1)	715 (8.7)
Ischemic stroke	267 (6.5)	242 (5.9)	509 (6.2)
Transient ischemic attack	194 (4.7)	181 (4.4)	375 (4.6)
Prior Atherosclerotic Peripheral Arterial Disease	387 (9.5)	388 (9.5)	775 (9.5)
Ankle brachial index <0.9 without symptoms of intermittent claudication	97 (2.4)	76 (1.9)	173 (2.1)
Peripheral arterial disease	377 (9.2)	377 (9.2)	754 (9.2)
Prior Non-Atherosclerotic Cardiovascular Disease	3649 (89.2)	3645 (89.1)	7294 (89.2)
Prior Structural Cardiac Disorders	827 (20.2)	866 (21.2)	1693 (20.7)
Congestive heart failure	703 (17.2)	743 (18.2)	1446 (17.7)
Hypertrophic cardiomyopathy	23 (0.6)	20 (0.5)	43 (0.5)
Non-ischemic dilated cardiomyopathy	35 (0.9)	29 (0.7)	64 (0.8)
Non-rheumatic valvular heart disease	150 (3.7)	163 (4.0)	313 (3.8)
Rheumatic valvular heart disease	17 (0.4)	9 (0.2)	26 (0.3)
Prior Cardiac Arrhythmias	229 (5.6)	243 (5.9)	472 (5.8)
Atrio-ventricular block above first degree	51 (1.2)	54 (1.3)	105 (1.3)
Sick sinus syndrome	30 (0.7)	32 (0.8)	62 (0.8)
Supra-ventricular tachycardia other than atrial fibrillation/atrial flutter	74 (1.8)	77 (1.9)	151 (1.8)
Sustained ventricular tachycardia	34 (0.8)	34 (0.8)	68 (0.8)
Torsades de pointes	1 (0.0)	3 (0.1)	4 (0.0)
Ventricular fibrillation	61 (1.5)	65 (1.6)	126 (1.5)
Prior Non-Cardiac/Non-Atherosclerotic Vascular Disorders	3568 (87.3)	3566 (87.2)	7134 (87.2)
Arterial embolism	12 (0.3)	9 (0.2)	21 (0.3)
Deep vein thrombosis	70 (1.7)	60 (1.5)	130 (1.6)
Hypertension	3541 (86.6)	3543 (86.6)	7084 (86.6)
Hypotension	45 (1.1)	33 (0.8)	78 (1.0)
Pulmonary embolism	31 (0.8)	42 (1.0)	73 (0.9)
Non-ischemic stroke	79 (1.9)	84 (2.1)	163 (2.0)
Hemorrhagic stroke	18 (0.4)	22 (0.5)	40 (0.5)
Stroke of unknown origin	63 (1.5)	62 (1.5)	125 (1.5)

Other Prior Conditions or Investigations Influencing Cardiovascular Risk	3044 (74.4)	3055 (74.7)	6099 (74.6)
Prior Metabolic Disorders	2480 (60.7)	2515 (61.5)	4995 (61.1)
Diabetes type 1	28 (0.7)	30 (0.7)	58 (0.7)
Diabetes type 2	2367 (57.9)	2363 (57.8)	4730 (57.8)
Metabolic syndrome	507 (12.4)	540 (13.2)	1047 (12.8)
Baseline Investigations	1783 (43.6)	1707 (41.7)	3490 (42.7)
Renal Disorders	470 (11.5)	429 (10.5)	899 (11.0)
Creatinine clearance >30 and <60 mL/min	309 (7.6)	286 (7.0)	595 (7.3)
Macroalbuminuria	34 (0.8)	24 (0.6)	58 (0.7)
Microalbuminuria	146 (3.6)	134 (3.3)	280 (3.4)
Proteinuria	75 (1.8)	63 (1.5)	138 (1.7)
Abnormal Lipids	1496 (36.6)	1419 (34.7)	2915 (35.6)
High HDL-C (≥60 mg/dL)	187 (4.6)	187 (4.6)	374 (4.6)
Low HDL-C (<40 mg/dL)	1327 (32.5)	1259 (30.8)	2586 (31.6)
Triglycerides >1000 mg/dL	76 (1.9)	72 (1.8)	148 (1.8)
hsCRP >3 mg/L	236 (5.8)	252 (6.2)	488 (6.0)
Other Morbidities	173 (4.2)	173 (4.2)	346 (4.2)
Pancreatitis	14 (0.3)	9 (0.2)	23 (0.3)
Retinopathy	161 (3.9)	167 (4.1)	328 (4.0)
Carotid Stenosis (%)			
n	316	346	662
Mean (SD)	59.0 (21.04)	56.9 (22.99)	57.9 (22.09)
Median	60.0	59.0	59.5
Min, Max	0.0, 100.0	0.0, 100.0	0.0, 100.0

Abbreviations: HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; ITT = Intent-to-Treat; Max = maximum; Min = minimum; SD = standard deviation.
Note: Percentages were based on the number of patients randomized to each treatment group in the ITT population (N). This summary was based on data collected from the "Cardiovascular History" case report form. Two outliers of carotid stenosis (%) with a value over 100% were excluded from the analysis. Carotid stenosis (%) data reported in categorical format of >x% and <y% were analyzed as x% and y%, respectively, and reported as x% to y% was analyzed as an average of x% and y%.
Source: Table 14.1.12.1.

Numbers analysed

A summary of analysis populations is presented in Table 10-3. The ITT population, which is identical to the Safety population, is the primary population for the analysis of efficacy and safety data; all 8179 randomized patients are included in the ITT population.

Table 10-3: Analysis Populations (Randomized Patients; N=8179)

Analysis Populations, n (%)	AMR101	Placebo	Overall
ITT[1]	4089 (100)	4090 (100)	8179 (100)
mITT[2]	4083 (99.9)	4077 (99.7)	8160 (99.8)
PP[3]	3360 (82.2)	3299 (80.7)	6659 (81.4)
Safety[1]	4089 (100)	4090 (100)	8179 (100)

Abbreviations: ITT = Intent-to-Treat; mITT = modified Intent-to-Treat; PP = Per-Protocol.
Note: Percentages were based on the number of patients randomized to each treatment group in the ITT population (N).
1 The ITT and Safety populations included all randomized patients.
2 The mITT population included all randomized patients who received study drug.
3 The PP population included all mITT patients without any major protocol deviations, who had ≥80% compliance while on treatment, and a minimum treatment duration of 90 days.
Source: Table 14.1.4.

A total of 473 sites enrolled and/or followed patients in 11 countries in 3 geographic regions (United States, the Netherlands, Ukraine, Russian Federation, South Africa, Poland, India, Canada, Romania,

Australia, and New Zealand). There were two patients (both in the Netherlands) inadvertently randomized twice, each under two separate patient numbers. Patient 19-716-037 was later randomized as 19-725-089 and Patient 19-735-004 was later randomized as 19-735-013.

Outcomes and estimation

Primary Endpoint Analysis

5-fold MACE: CV death, nonfatal MI, nonfatal stroke, coronary revascularisation, unstable angina caused by myocardial ischemia and associated with emergent hospitalisation.

The results of the analysis of the primary endpoint are summarized in Table 11-5 for the ITT population, and the associated Kaplan-Meier curve is displayed in Figure 11-1. The median follow-up duration for the primary endpoint was 4.7 and 4.5 years for the AMR101 and placebo groups, respectively.

A primary endpoint event occurred in 17.2% (705/4089) of patients in the AMR101 group, as compared with 22.0% (901/4090) of patients in the placebo group (HR of 0.752 [95% CI: 0.682 to 0.830; p=0.00000001]; relative risk reduction [RRR] of 24.8% and number needed to treat [NNT] of 21).

Table 11-5: Stratified Analysis of Time to the Primary Composite Endpoint from Date of Randomization (ITT Population)

Endpoint Statistic	AMR101 (N=4089)	Placebo (N=4090)
Primary Composite Endpoint, n (%)[1]	705 (17.2)	901 (22.0)
Treatment Comparison[2]		
P-value from Log-Rank Test	0.00000001	
HR (95% CI) AMR101/Placebo	0.752 (0.682 – 0.830)	
Components Contributing to Primary Endpoint, n (%)[3]		
CV Death[4]	137 (3.4)	149 (3.6)
Nonfatal MI[5]	205 (5.0)	280 (6.8)
Nonfatal Stroke	80 (2.0)	105 (2.6)
Coronary Revascularization	189 (4.6)	244 (6.0)
Hospitalization for Unstable Angina	94 (2.3)	123 (3.0)

Abbreviations: CI = confidence interval; CV = cardiovascular; ECG = electrocardiogram; HR = hazard ratio; ITT = Intent-to-Treat; MI = myocardial infarction.

Note: The number of patients with event (n) is the number of patients in the ITT population within each treatment group (N).

1 Primary composite endpoint includes CV death, nonfatal MI, nonfatal stroke, coronary revascularization, and hospitalization for unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing.

2 Log-Rank test statistic and p-value are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

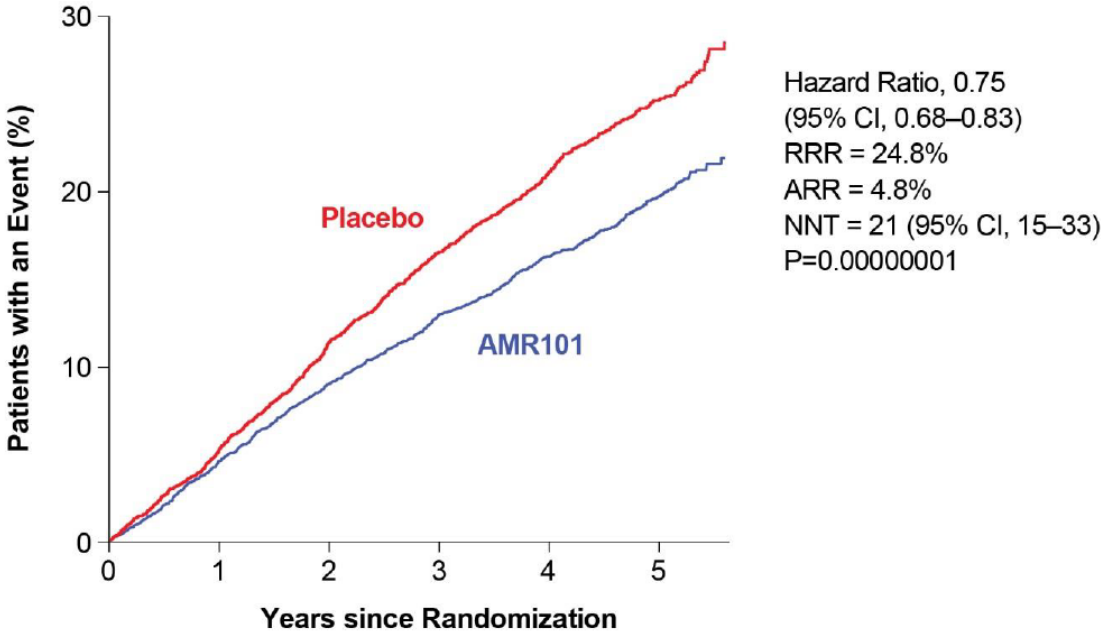
3 Based on a patient's first post-randomization occurrence of the event contributing to the primary endpoint.

4 CV death includes adjudicated CV deaths and deaths of undetermined causality.

5 Nonfatal MI includes silent MI, which was assumed to occur on the date of the first post-randomization ECG tracing indicative of a silent MI.

Source: Table 14.2.1.11.1 and Table 14.2.1.12.1.

Figure 11-1: Kaplan-Meier Curve of Time to Primary Composite Endpoint from Date of Randomization (ITT Population)



No. at Risk						
Placebo	4090	3743	3327	2807	2347	1358
AMR101	4089	3787	3431	2951	2503	1430

Abbreviations: ARR = absolute risk reduction; CI = confidence interval; ITT = Intent-to-Treat; NNT = number needed to treat; No. = number; P = p-value; RRR = relative risk reduction.
Source: Figure 14.2.1.1.1.

Key Secondary Composite Endpoint Analysis

The key secondary composite endpoint was the time from randomization to the first occurrence of the composite of CV death, nonfatal MI (including silent MI), or nonfatal stroke (i.e., hard MACE endpoint). The results of the analysis of the key secondary endpoint are summarized in Table 11-6 for the ITT population, and the associated Kaplan-Meier curve is displayed in Figure 11-2. The median follow-up duration for the key secondary endpoint was 4.8 and 4.7 years for the AMR101 and placebo groups, respectively. A key secondary endpoint event occurred in 11.2% (459/4089) of patients in the AMR101 group, as compared with 14.8% (606/4090) of patients in the placebo group (HR of 0.735 [95% CI: 0.651 to 0.830; p=0.0000006]; RRR of 26.5% and NNT of 28).

Table 11-6: Stratified Analysis of Time to the Key Secondary Composite Endpoint from Date of Randomization (ITT Population)

Endpoint Statistic	AMR101 (N=4089)	Placebo (N=4090)
Key Secondary Composite Endpoint, n (%)[1]	459 (11.2)	606 (14.8)
Treatment Comparison[2]		
P-value from Log-Rank Test	0.0000006	
HR (95% CI) AMR101/Placebo	0.735 (0.651 – 0.830)	
Components Contributing to Key Secondary Endpoint, n (%)[3]		
CV Death[4]	149 (3.6)	167 (4.1)
Nonfatal MI[5]	230 (5.6)	325 (7.9)
Nonfatal Stroke	80 (2.0)	114 (2.8)

Abbreviations: CI = confidence interval; CV = cardiovascular; ECG = electrocardiogram; HR = hazard ratio; ITT = Intent-to-Treat; MACE = major adverse coronary event; MI = myocardial infarction.

Note: The number of patients with event (n) is the number of patients in the ITT population within each treatment group (N).

1 The key secondary composite (i.e., hard MACE) endpoint includes CV death, nonfatal MI, and nonfatal stroke.

2 Log-Rank test statistic and p-value are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

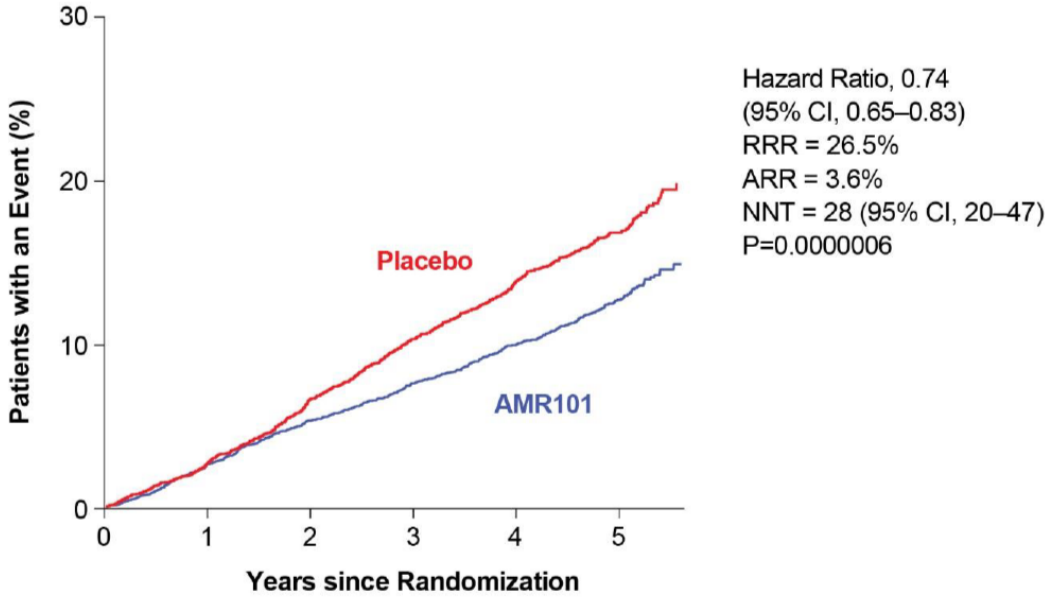
3 Based on a patient's first post-randomization occurrence of the event contributing to the key secondary endpoint.

4 CV death includes adjudicated CV deaths and deaths of undetermined causality.

5 Nonfatal MI includes silent MI, which was assumed to occur on the date of the first post-randomization ECG tracing indicative of a silent MI.

Source: Table 14.2.1.21.1 and Table 14.2.1.22.1.

Figure 11-2: Kaplan-Meier Curve of Time to Key Secondary Composite Endpoint from Date of Randomization (ITT Population)



No. at Risk

Placebo	4090	3837	3500	3002	2542	1487
AMR101	4089	3861	3565	3115	2681	1562

Abbreviations: ARR = absolute risk reduction; CI = confidence interval; ITT = Intent-to-Treat; NNT = number needed to treat; No. = number; P = p-value; RRR = relative risk reduction.

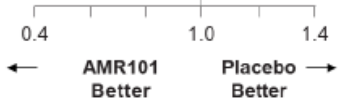
Source: Figure 14.2.2.1.

Individual Components of the Primary and Key Secondary Endpoints

A forest plot of the analyses of the individual components of the primary and key secondary endpoints, each analyzed as independent endpoints (e.g., time to first occurrence of nonfatal MI, regardless of the time to first occurrence of any other endpoints for the same patient), is presented in Figure 11-3.

Figure 11-3: Forest Plot of Analyses of Individual Components of the Primary and Key Secondary Endpoints (ITT Population)

Endpoint	Hazard Ratio (95% CI)	AMR101 n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	p-Value
Primary Composite (ITT)		705/4089 (17.2)	901/4090 (22.0)	0.752 (0.682, 0.830)	<0.0001
Key Secondary Composite		459/4089 (11.2)	606/4090 (14.8)	0.735 (0.651, 0.830)	<0.0001
Cardiovascular Death		174/4089 (4.3)	213/4090 (5.2)	0.803 (0.657, 0.981)	0.03
Nonfatal Myocardial Infarction		237/4089 (5.8)	332/4090 (8.1)	0.697 (0.590, 0.823)	<0.0001
Nonfatal Stroke		85/4089 (2.1)	118/4090 (2.9)	0.708 (0.536, 0.936)	0.01
Coronary Revascularization		376/4089 (9.2)	544/4090 (13.3)	0.664 (0.583, 0.758)	<0.0001
Hospitalization for Unstable Angina		108/4089 (2.6)	157/4090 (3.8)	0.679 (0.531, 0.868)	0.002



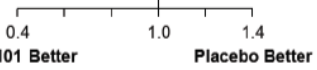
Abbreviations: CI = confidence interval; MI = myocardial infarction; ITT = Intent-to-Treat.
Source: Table 14.2.1.12.1 and Figure 14.2.7.3.1.

Other Secondary Endpoint Analyses

Other secondary endpoints were the time from randomization to the first occurrence of each of the events described below. If the primary and key secondary endpoints were statistically significant, the remaining secondary endpoints were to be tested in the hierarchical order as depicted in Figure 11-4. All of these other secondary endpoint events occurred in a lower percentage of patients in the AMR101 group than in the placebo group. The results were statistically significant for each secondary endpoint event, with the exception of total mortality, the final secondary endpoint in the hierarchy.

Figure 11-4: Forest Plot of Analyses of Other Secondary Endpoint Events (ITT Population)

Endpoint	Hazard Ratio (95% CI)	AMR101 n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	P-value
Primary Composite (ITT)		705/4089 (17.2%)	901/4090 (22.0%)	0.752 (0.682–0.830)	<0.0001
Key Secondary Composite (ITT)		459/4089 (11.2%)	606/4090 (14.8%)	0.735 (0.651–0.830)	<0.0001
Cardiovascular Death or Nonfatal Myocardial Infarction		392/4089 (9.6%)	507/4090 (12.4%)	0.753 (0.660–0.859)	<0.0001
Fatal or Nonfatal Myocardial Infarction		250/4089 (6.1%)	355/4090 (8.7%)	0.688 (0.585–0.808)	<0.0001
Urgent or Emergent Revascularization		216/4089 (5.3%)	321/4090 (7.8%)	0.653 (0.550–0.776)	<0.0001
Cardiovascular Death		174/4089 (4.3%)	213/4090 (5.2%)	0.803 (0.657–0.981)	0.0315
Hospitalization for Unstable Angina		108/4089 (2.6%)	157/4090 (3.8%)	0.679 (0.531–0.868)	0.0018
Fatal or Nonfatal Stroke		98/4089 (2.4%)	134/4090 (3.3%)	0.720 (0.555–0.934)	0.0129
Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke		549/4089 (13.4%)	690/4090 (16.9%)	0.772 (0.690–0.864)	<0.0001
Total Mortality		274/4089 (6.7%)	310/4090 (7.6%)	0.870 (0.739–1.023)	0.0915



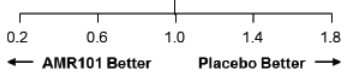
Abbreviations: CI = confidence interval; CV = cardiovascular; ECG = electrocardiogram; ITT = Intent-to-Treat; MI = myocardial infarction.
Note: The number of patients with event (n) is the number of patients in the ITT population within each treatment group (N).
Log-Rank test statistic and p-value are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.
Endpoint events are based on a patient's first post-randomization occurrence of the specified endpoint event.
CV death includes adjudicated CV deaths and deaths of undetermined causality.
Nonfatal MI includes silent MI, which was assumed to occur on the date of the first post-randomization ECG tracing indicative of a silent MI.
Source: Table 14.2.1.3.1 and Figure 14.2.7.3.1.

Subgroup Analyses

Analyses of the primary endpoint (Figure 11-16 to 11–19) and the key secondary endpoint (11-20 to 11-23) were performed for the following key subgroups of interest:

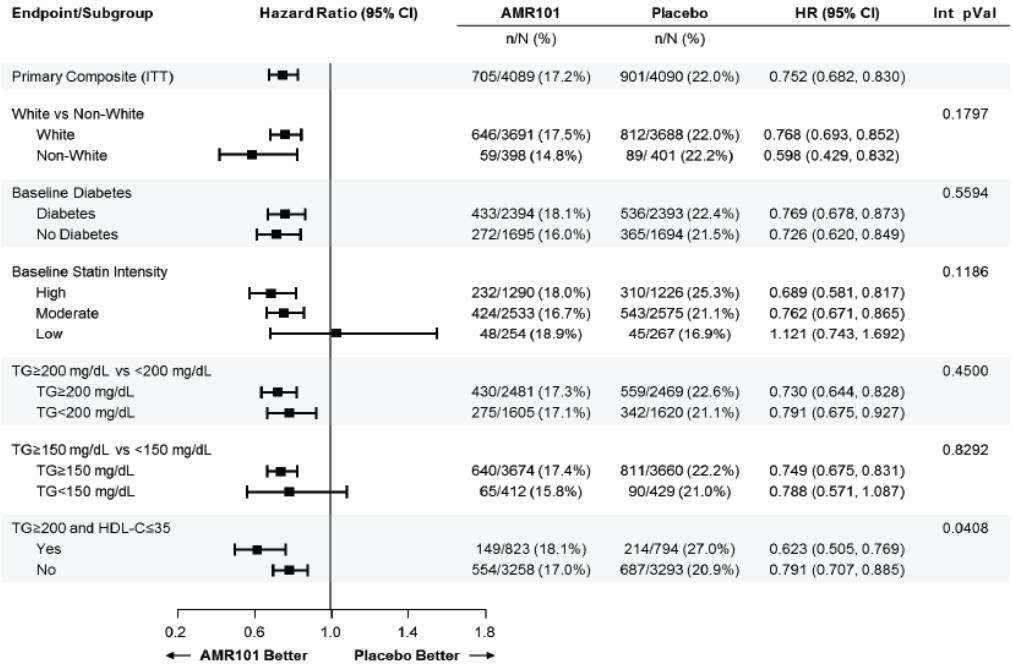
Figure 11-16: Forest Plot of Analyses of the Primary Endpoint by Subgroups (Geographic Region, Cardiovascular Risk Category, Baseline Ezetimibe Use, Sex, and Age Group) (ITT Population)

Endpoint/Subgroup	Hazard Ratio (95% CI)	AMR101 n/N (%)	Placebo n/N (%)	HR (95% CI)	Int pVal
Primary Composite (ITT)		705/4089 (17.2%)	901/4090 (22.0%)	0.752 (0.682, 0.830)	
Region					0.3046
Western		551/2906 (19.0%)	713/2905 (24.5%)	0.740 (0.662, 0.827)	
Eastern		143/1053 (13.6%)	167/1053 (15.9%)	0.842 (0.674, 1.053)	
Asia Pacific		11/130 (8.5%)	21/132 (15.9%)	0.491 (0.236, 1.020)	
Risk Category					0.1388
Secondary Prevention		559/2892 (19.3%)	738/2893 (25.5%)	0.726 (0.650, 0.810)	
Primary Prevention		146/1197 (12.2%)	163/1197 (13.6%)	0.876 (0.700, 1.095)	
Ezetimibe Use					0.6444
No		649/3827 (17.0%)	834/3828 (21.8%)	0.747 (0.675, 0.828)	
Yes		56/262 (21.4%)	67/262 (25.6%)	0.816 (0.572, 1.164)	
Sex					0.3264
Male		551/2927 (18.8%)	715/2895 (24.7%)	0.732 (0.655, 0.818)	
Female		154/1162 (13.3%)	186/1195 (15.6%)	0.818 (0.661, 1.013)	
Age Group					0.0037
<65 Years		322/2232 (14.4%)	460/2184 (21.1%)	0.650 (0.564, 0.750)	
≥65 Years		383/1857 (20.6%)	441/1906 (23.1%)	0.873 (0.761, 1.001)	



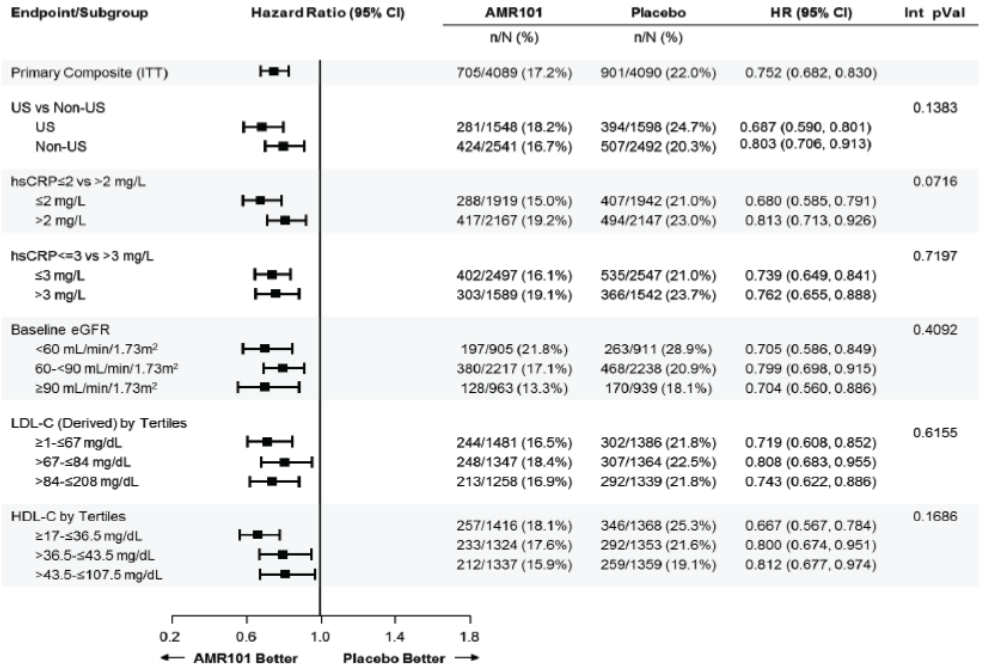
Abbreviations: CI = confidence interval; HR = hazard ratio; Int = interaction; ITT = Intent-to-Treat; pVal = p-value.
Source: Figure 14.2.7.12.1.

Figure 11-17: Forest Plot of Analyses of the Primary Endpoint by Subgroups (White vs Non-White, Baseline Diabetes, Baseline Statin Intensity, TG ≥200 vs <200 mg/dL, TG ≥150 vs <150 mg/dL, and TG ≥200 mg/dL and HDL-C ≤35 mg/dL) (ITT Population)



Abbreviations: CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; HR = hazard ratio; Int = interaction; ITT = Intent-to-Treat; pVal = p-value; TG = triglycerides; vs = versus.
Source: Figure 14.2.7.12.1.

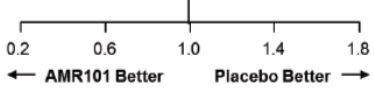
Figure 11-18: Forest Plot of Analyses of the Primary Endpoint by Subgroups (US vs Non-US, hsCRP ≤2 vs >2 mg/L, hsCRP ≤3 vs >3 mg/L, Baseline eGFR, LDL-C (Derived) by Tertiles, and HDL-C by Tertiles (ITT Population)



Abbreviations: CI = confidence interval; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; HR = hazard ratio; hsCRP = high-sensitivity C-reaction protein; Int = interaction; ITT = Intent-to-Treat; LDL-C = low-density lipoprotein cholesterol; pVal = p-value; US = United States; vs = versus.
Source: Figure 14.2.7.12.1.

Figure 11-19: Forest Plot of Analyses of the Primary Endpoint by Subgroups (Apo B by Tertiles, Non-HDL-C by Tertiles, and TG by Tertiles) (ITT Population)

Endpoint/Subgroup	AMR101 n/N (%)	Placebo n/N (%)	HR (95% CI)	Int pVal
Primary Composite (ITT)	705/4089 (17.2%)	901/4090 (22.0%)	0.752 (0.682, 0.830)	
ApoB by Tertiles				0.8785
≥17.5-≤76 mg/dL	241/1488 (16.2%)	298/1393 (21.4%)	0.731 (0.616, 0.866)	
>76-≤89 mg/dL	228/1297 (17.6%)	295/1302 (22.7%)	0.741 (0.623, 0.881)	
>89-≤207 mg/dL	228/1275 (17.9%)	301/1352 (22.3%)	0.780 (0.657, 0.927)	
Non-HDL by Tertiles				0.6001
≥60.5-≤109 mg/dL	227/1409 (16.1%)	274/1326 (20.7%)	0.744 (0.624, 0.888)	
>109-≤127.5 mg/dL	232/1363 (17.0%)	321/1387 (23.1%)	0.711 (0.600, 0.842)	
>127.5-≤244 mg/dL	246/1314 (18.7%)	306/1376 (22.2%)	0.806 (0.681, 0.954)	
Triglycerides by Tertiles				0.3311
≥81.25-≤190 mg/dL	233/1378 (16.9%)	291/1381 (21.1%)	0.789 (0.664, 0.938)	
>190-≥250 mg/dL	246/1370 (18.0%)	283/1326 (21.3%)	0.804 (0.677, 0.954)	
>250-≤1401 mg/dL	226/1338 (16.9%)	327/1382 (23.7%)	0.675 (0.570, 0.800)	



Abbreviations: apo B = apolipoprotein B; CI = confidence interval; non-HDL-C = non-high-density lipoprotein cholesterol; HR = hazard ratio; Int = interaction; ITT = Intent-to-Treat; pVal = p-value; TG = triglycerides.
Source: Figure 14.2.7.12.1.

Tertiary Composite Efficacy Analyses

A summary of the stratified time to event analyses for each of the tertiary composite endpoints is presented in Table 11-10 and of additional tertiary endpoint events in Table 11-11.

Table 11-10: Stratified Analysis of Time to Tertiary Composite Endpoints from Date of Randomization (ITT Population)

Composite Endpoint, n (%)[2]	AMR101 (N=4089)	Placebo (N=4090)	Treatment Comparison[1] P-value from Log-Rank Test	Treatment Comparison[1] HR (95% CI) AMR101/Placebo
CV Death,[3] Nonfatal MI,[4] Nonfatal Stroke, Cardiac Arrhythmia, or Cardiac Arrest	589 (14.4)	701 (17.1)	0.0004	0.82 (0.73 – 0.91)
CV Death[3], Nonfatal MI,[4] Non-Elective Coronary Revascularization,[5] or Unstable Angina[6]	513 (12.5)	656 (16.0)	<0.0001	0.76 (0.68 – 0.85)
CV Death[3], Nonfatal MI,[4] Non-Elective Coronary Revascularization,[5] Unstable Angina,[6] Nonfatal Stroke, or PVD Requiring Intervention	683 (16.7)	852 (20.8)	<0.0001	0.77 (0.70 – 0.86)
CV Death[3], Nonfatal MI,[4] Non-Elective Coronary Revascularization,[5] Unstable Angina,[6] PVD Requiring Intervention, or Cardiac Arrhythmia	741 (18.1)	844 (20.6)	0.0019	0.86 (0.78 – 0.94)
Total Mortality or Newly Emergent CHF	393 (9.6)	431 (10.5)	0.1281	0.90 (0.78 – 1.03)
CV Death[3] or Newly Emergent CHF	306 (7.5)	346 (8.5)	0.0808	0.87 (0.75 – 1.02)

Abbreviations: CHF = congestive heart failure; CI = confidence interval; CV = cardiovascular; ECG = electrocardiogram; HR = hazard ratio; ITT = Intent-to-Treat; MI = myocardial infarction; PVD = peripheral vascular disease.

Note: The number of patients with event (n) is the number of patients in the ITT population within each treatment group (N).

1 Log-Rank test statistic and p-value are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

2 Based on a patient's first post-randomization occurrence of the event contributing to the composite endpoint.

3 CV death includes adjudicated CV deaths and deaths of undetermined causality.

4 Nonfatal MI includes silent MI, which was assumed to occur on the date of the first post-randomization ECG tracing indicative of a silent MI.

5 Represented as the composite of emergent or urgent classifications.

6 Determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization.

Source: Table 14.2.1.4.1 and Table 14.2.1.10.1.

Table 11-11: Stratified Analysis of Time to Additional Tertiary Endpoint Events from Date of Randomization (ITT Population)

Endpoint Event, n (%)[2]	AMR101 n/N (%)	Placebo n/N (%)	Treatment Comparison[1] P-value from Log-Rank Test	Treatment Comparison[1] HR (95% CI) AMR101/Placebo
Newly Emergent CHF	169/4089 (4.1)	176/4090 (4.3)	0.6260	0.95 (0.77 – 1.17)
Newly Emergent CHF Requiring Hospitalization	141/4089 (3.4)	144/4090 (3.5)	0.7810	0.97 (0.77 – 1.22)
Transient Ischemic Attack	64/4089 (1.6)	48/4090 (1.2)	0.1459	1.32 (0.91 – 1.92)
Amputation for PVD	22/4089 (0.5)	21/4090 (0.5)	0.9053	1.04 (0.57 – 1.89)
Carotid Revascularization	31/4089 (0.8)	26/4090 (0.6)	0.5399	1.18 (0.70 – 1.98)
Coronary Revascularization[3]	376/4089 (9.2)	544/4090 (13.3)	<0.0001	0.66 (0.58 – 0.76)
Emergent Revascularization	41/4089 (1.0)	65/4090 (1.6)	0.0158	0.62 (0.42 – 0.92)
Urgent Revascularization	181/4089 (4.4)	268/4090 (6.6)	<0.0001	0.66 (0.54 – 0.79)
Elective Revascularization	194/4089 (4.7)	278/4090 (6.8)	<0.0001	0.68 (0.57 – 0.82)
Salvage Revascularization	0/4089 (0.0)	2/4090 (0.0)	0.1563	0.00 (0.00 – 0.00)
Cardiac Arrhythmia Requiring Hospitalization of ≥24 Hours	188/4089 (4.6)	154/4090 (3.8)	0.0856	1.21 (0.97 – 1.49)
Cardiac Arrest	22/4089 (0.5)	42/4090 (1.0)	0.0105	0.52 (0.31 – 0.86)
Sudden Cardiac Death	61/4089 (1.5)	87/4090 (2.1)	0.0259	0.69 (0.50 – 0.96)
Ischemic Stroke	80/4089 (2.0)	122/4090 (3.0)	0.0020	0.64 (0.49 – 0.85)
Hemorrhagic Stroke	13/4089 (0.3)	10/4090 (0.2)	0.5507	1.28 (0.56 – 2.93)
New Onset Type 2 Diabetes[4]	65/1695 (3.8)	63/1697 (3.7)	0.8361	1.04 (0.73 – 1.47)
New Onset Hypertension[5]	13/4089 (0.3)	15/4090 (0.4)	0.6847	0.86 (0.41 – 1.80)
Peripheral Artery Disease	156/4089 (3.8)	159/4090 (3.9)	0.7604	0.97 (0.78 – 1.21)

Abbreviations: AE = adverse event; CEC = Clinical Endpoint Committee; CHF = congestive heart failure; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; ITT = Intent-to-Treat; MedDRA = Medical Dictionary for Regulatory Activities; PVD = peripheral vascular disease; SMQ = Standardised MedDRA Query.

Note: The number of patients with event (n) is the number of patients with the event in the ITT population within each treatment group (N).

1 Log-Rank test statistic and p-value are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

2 Based on a patient's first post-randomization occurrence of the specified endpoint event.

3 Coronary revascularization was defined as the composite of emergent, urgent, elective, and salvage revascularization.

4 Excludes patients with Type 1 or Type 2 diabetes at baseline.

5 As per the CEC Charter, new onset of hypertension was determined programmatically. To identify new onset of hypertension cases, the hypertension SMQ was used to search all AEs and negatively adjudicated endpoints. All patients who had hypertension reported on the "Cardiovascular History" page were excluded.

Source: Table 14.2.1.4.1 and Table 14.2.1.10.1.

Some of these events are discussed in more detail:

- Cardiac Arrhythmia Events Requiring Hospitalization of ≥24 Hours

As shown in Table 11-11, cardiac arrhythmia events requiring hospitalization of ≥24 hours occurred in 4.6% (188/4089) of patients in the AMR101 group, as compared with 3.8% (154/4090) of patients in the placebo group (HR of 1.21 [95% CI: 0.97 to 1.49]).

A summary of the stratified time to cardiac arrhythmia endpoint events analysis is presented in Table 11-12 for the ITT population.

Atrial fibrillation or atrial flutter events requiring hospitalization of ≥24 hours occurred in 3.1% (127/4089) of patients in the AMR101 group, as compared with 2.1% (84/4090) of patients in the placebo group (HR of 1.50 [95% CI: 1.14 to 1.98] p = 0.0037).

Table 11-12: Stratified Analysis of Time to Cardiac Arrhythmia Endpoint Events from Date of Randomization (ITT Population)

Endpoint Event, n (%)[2]	AMR101 (N=4089)	Placebo (N=4090)	Treatment Comparison[1] P-value from Log-Rank Test	Treatment Comparison[1] HR (95% CI) AMR101/Placebo
Cardiac Arrhythmia Requiring Hospitalization of ≥24 Hours	188 (4.6)	154 (3.8)	0.0856	1.21 (0.97 – 1.49)
Atrial Fibrillation or Flutter Requiring Hospitalization of ≥24 Hours	127 (3.1)	84 (2.1)	0.0037	1.50 (1.14 – 1.98)
Bradycardia/Heart Block Requiring Hospitalization of ≥24 Hours	28 (0.7)	40 (1.0)	0.1248	0.69 (0.42 – 1.11)
Ventricular Tachycardia or Ventricular Fibrillation Requiring Hospitalization of ≥24 Hours	35 (0.9)	37 (0.9)	0.7564	0.93 (0.59 – 1.48)
Other Tachycardia Requiring Hospitalization of ≥24 Hours	7 (0.2)	7 (0.2)	0.9819	0.99 (0.35 – 2.82)

Abbreviations: CI = confidence interval; CV = cardiovascular; HR = hazard ratio; ITT = Intent-to-Treat.
Note: The number of patients with event (n) is the number of patients with the event in the ITT population within each treatment group (N).
1 Log-Rank test statistic and p-value are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.
2 Based on a patient's first post-randomization occurrence of the endpoint event.
Source: Table 14.2.1.8.1.

Cardiac arrest events occurred in 0.5% (22/4089) of patients in the AMR101 group, as compared with 1.0% (42/4090) of patients in the placebo group (HR of 0.52 [95% CI: 0.31 to 0.86]). Sudden cardiac death events occurred in 1.5% (61/4089) of patients in the AMR101 group, as compared with 2.1% (87/4090) of patients in the placebo group (HR of 0.69 [95% CI: 0.50 to 0.96]).

Lipids and other Biomarkers

The effects on plasma biomarkers from baseline to years 1 or 2 are presented in Table 11-13. Plasma TG, non-HDL-C, LDL-C, HDL-C, and EPA were measured at Year 1; apo B and hsCRP were measured at Year 2. TG levels over time are presented in Figure 11-7 (ITT).

In the placebo arm some of these markers showed a trend to a numerical deterioration. Small numerical increases were observed for TG (+ 4.5 mg/dL), non-HDL-C (+ 12.0 mg/dL), LDL-C (+ 7.0 /+ 9.3 mg/dL (depending on the mode of calculation), apoB (+ 6.0 mg/dL), and hsCRP (+0.5 mg/L).

Significant reductions were observed with AMR101 compared to placebo in TG, LDL-C, non-HDL-C, apo B, and hsCRP. The effect on TGs was maximal at visit 3 and persisted up to the endo of the study.

In the AMR101 group, median percent decreases from baseline in approximated LDL-C (Hopkins) were observed at each time point assessed, with the difference from placebo being significant at each time point. Median percent change in approximated LDL-C (Hopkins) from baseline to one year was -1.2% (-1.1 mg/dL) for the AMR101 group and 10.9% (9.3 mg/dL) for the placebo group, for a median difference in percent change from baseline of -11.4% (Hodges- Lehmann estimate; p<0.0001).

Median percent change in approximated LDL-C (Hopkins) from baseline to the last study value was -1.2% (-1.0 mg/dL) for the AMR101 group and 6.5% (5.7 mg/dL) for the placebo group, for a median difference in percent change from baseline of -7.4% (Hodges-Lehmann estimate; p<0.0001).

Table 11-13: Effects on Plasma Biomarkers from Baseline to Years 1 or 2 (ITT Population)

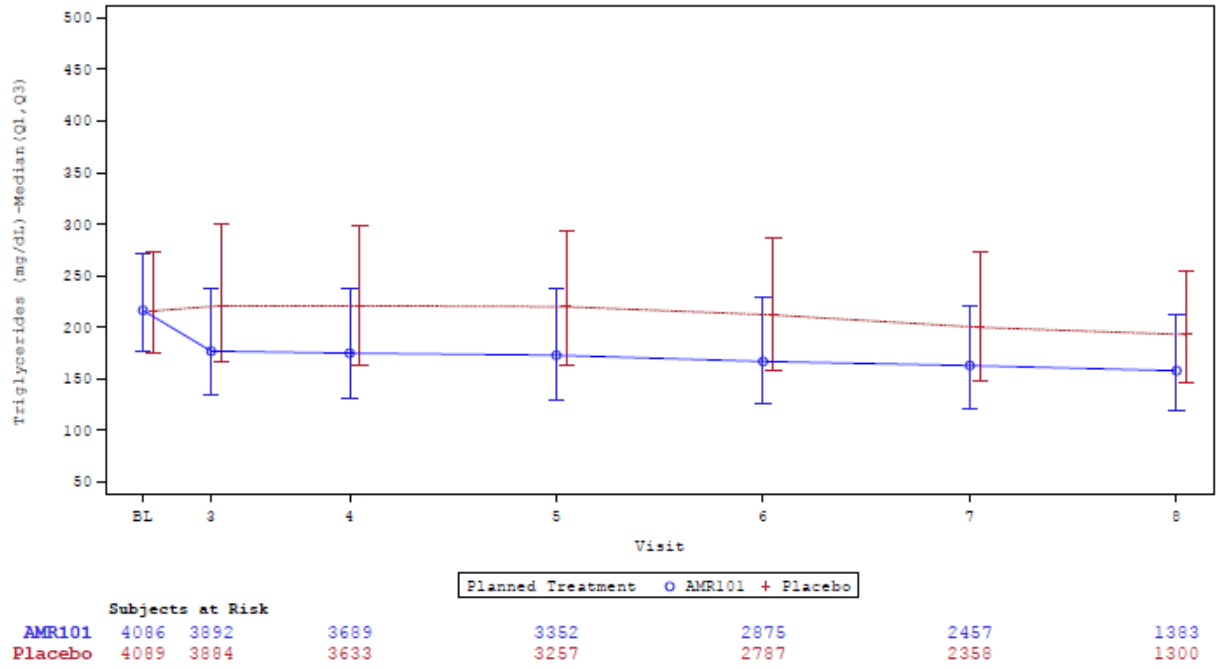
	AMR101 (N=4089) Median			Placebo (N=4090) Median			Median Between Group Difference at Year 1 or 2[4]		
Biomarker	Baseline	Year 1,2[4]	Change from Baseline	Baseline	Year 1,2[4]	Change from Baseline	Absolute Change from Baseline[1]	% Change from Baseline[1]	% Change P-value[2]
TG (mg/dL)	216.5	175.0	-39.0	216.0	221.0	4.5	-44.5	-19.7	<0.0001
non-HDL-C (mg/dL)	118.0	113.0	-4.0	118.5	130.0	12.0	-15.5	-13.1	<0.0001
LDL-C (mg/dL)[3]	74.0	77.0	2.0	76.0	84.0	7.0	-5.0	-6.6	<0.0001
LDL-C (Hopkins) (mg/dL)	85.8	85.3	-1.1	86.7	95.8	9.3	-9.6	-11.4	<0.0001
HDL-C (mg/dL)	40.0	39.0	-1.0	40.0	42.0	1.5	-2.5	-6.3	<0.0001
apo B (mg/dL)[4]	82.0	80.0	-2.0	83.0	89.0	6.0	-8.0	-9.7	<0.0001
hsCRP (mg/L)[4]	2.2	1.8	-0.2	2.2	2.8	0.5	-0.9	-39.9	<0.0001
Log hsCRP (mg/L)[4]	0.8	0.6	-0.1	0.8	1.0	0.3	-0.4	-22.5	<0.0001
EPA (µg/mL)	26.1	144.0	112.6	26.1	23.3	-2.9	114.9	385.8	<0.0001

Abbreviations: apo B = apolipoprotein B; EPA = eicosapentaenoic acid; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; ITT = Intent-to-Treat; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides.

1 Based on Hodges-Lehmann estimation.
2 P-value from Wilcoxon rank-sum test.
3 Derived as defined in Section 9.7.1.13.4.
4 Apo B, hsCRP, and log hsCRP were measured at Year 2; all other biomarkers presented were measured at Year 1.
5 "Log" denotes natural log.

Source: Tables 14.2.11.1.1, 14.2.11.2.1, 14.2.11.3.1, 14.2.11.5.1, 14.2.11.6.1, 14.2.11.7.1, 14.2.11.8.1, 14.2.11.14.1, and 14.2.11.16.1.

Figure 11-7: Plot of Median Triglycerides Over Time (ITT Population)

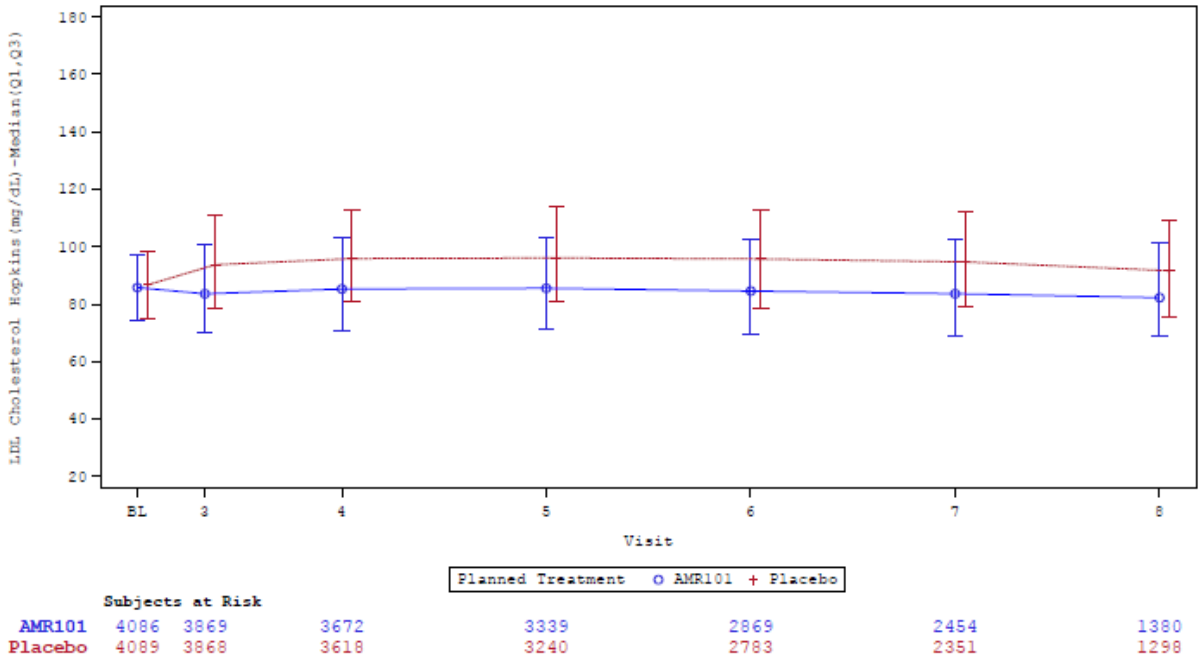


Abbreviations: ITT = Intent-to-Teat.

Source: Figure 14.2.8.1.1.

Median percent change in derived LDL-C from baseline to one year was 3.1% (2.0 mg/dL) for the AMR101 group and 10.2% (7.0 mg/dL) for the placebo group, for a median difference in percent change from baseline of -6.6% (Hodges-Lehmann estimate; p<0.0001).

Figure 11-8: Plot of Median LDL-C (Hopkins Approximation) Over Time (ITT Population)



Abbreviations: ITT = Intent-to-Treat; LDL-C = low-density lipoprotein cholesterol.
Source: Figure 14.2.8.1.4.

Total cholesterol increased from (median, mg/dL) 115.0 (Q1, Q3: 100.0, 131.0) to 118 (101.0, 137.0, visit 4, day 360) in the AMR101 group and from 117.0 (101.0, 133.0) to 126.0 (109.0, 146.0) in the Mineral oil group: Treatment difference -7.0 (-8.0, -6.0) p <.0001. (Table 14.2.11.10.1 of the Study report).

VLDL-C decreased from (median, mg/dL) 40.0 (31.0, 53.0) to 34.0 (25.0, 47.0) in the AMR101 group and increased from 41.0 (31.0, 52.0) to 44.0 (32.0, 59.0) in the mineral oil group: Treatment difference -10.0 ((-11.0, -9.0), p < .0001 (Table 14.2.11.11.1 of the Study report).

RLP-C Remnant lipoprotein cholesterol (RLP-C) decreased from (median, mg/dL) 30.9 (26.6, 36.8) to 27.0 (22.4, 34.2) in the AMR101 group and increased from 31.0 (26.7, 36.9) to 32.8 (26.2, 40.9) in the mineral oil group: Treatment difference -5.2 ((-5.6, -4.8) p <.0001).

hsTnT (High-sensitivity troponin) was 0.0 (0.0; 0.0) in both arms at baseline and at visit 4 (Table 14.2.11.12.1.)

EPA increased in the AMR101 group but remained largely unchanged in the placebo group (Table 11-13). HR for the time to the primary and to the key secondary efficacy endpoint did not indicate a correlation between Year 1 EPA tertiles and HR AMR101 vs. placebo (Table 14.2.14.1.1 and Table 14.2.14.2.1)

Table 14.2.14.1.1
Stratified Analysis of Time to the Primary Composite Endpoint from Date of Randomization by Tertile of Post-Baseline 1 Year EPA in AMR101 vs Placebo
ITT Population

EPA Analysis Method	AMR101 1 Year EPA Tertile vs Placebo	Subjects with Non-Missing Data: AMR101 (N=4089)	Placebo (N=4090)	HR (95% CI) [1]
EPA at One Year Post Baseline	AMR101 Upper Tertile vs Placebo (with EPA)	1058 (25.9%)	3155 (77.1%)	0.786 (0.667, 0.926)
	AMR101 Middle Tertile vs Placebo (with EPA)	1043 (25.5%)	3155 (77.1%)	0.675 (0.571, 0.798)
	AMR101 Lower Tertile vs Placebo (with EPA)	1049 (25.7%)	3155 (77.1%)	0.747 (0.637, 0.876)
	AMR101 (missin EPA) vs Placebo (missing EPA)	939 (23.0%)	935 (22.9%)	0.810 (0.656, 1.001)

[1] Hazard ratio and 95% CI for each subgroup are reported from a Cox proportional hazard model with treatment as a factor, and stratified by geographic region, CV risk category, and use of ezetimibe.

Table 14.2.14.2.1
Stratified Analysis of Time to the Key Secondary Composite Endpoint from Date of Randomization by Tertile of Post-Baseline 1 Year EPA in AMR101 vs Placebo
ITT Population

EPA Analysis Method	AMR101 1 Year EPA Tertile vs Placebo	Subjects with Non-Missing Data: AMR101 (N=4089)	Placebo (N=4090)	HR (95% CI) [1]
EPA at One Year Post Baseline	AMR101 Upper Tertile vs Placebo (with EPA)	1058 (25.9%)	3155 (77.1%)	0.796 (0.650, 0.974)
	AMR101 Middle Tertile vs Placebo (with EPA)	1043 (25.5%)	3155 (77.1%)	0.683 (0.556, 0.840)
	AMR101 Lower Tertile vs Placebo (with EPA)	1049 (25.7%)	3155 (77.1%)	0.691 (0.564, 0.848)
	AMR101 (missin EPA) vs Placebo (missing EPA)	939 (23.0%)	935 (22.9%)	0.771 (0.601, 0.990)

[1] Hazard ratio and 95% CI for each subgroup are reported from a Cox proportional hazard model with treatment as a factor, and stratified by geographic region, CV risk category, and use of ezetimibe.

There were no relevant differences in body weight and waist circumference over time and no differences between the groups.

Recurrent event analyses

Total CV events analysis was defined as the time from randomization to occurrence of the first and all recurrent major CV events, defined as CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, or unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization. A summary of total events in the primary and key secondary endpoints, including recurrent events on the same day, is presented in Table 11-7.

Table 11-7: Summary of Total Events in the Primary and Key Secondary Endpoints Including Recurrent Events on the Same Day (ITT Population)

Event, n (%)	AMR101 (N=4089)	Placebo (N=4090)	Total (N=8179)
Primary Endpoint Events	1185 (40.7)	1724 (59.3)	2909
≥1 event	705 (43.9)	901 (56.1)	1606
≥2 events	299 (39.2)	463 (60.8)	762
≥3 events	96 (35.3)	176 (64.7)	272
≥4 events	36 (27.9)	93 (72.1)	129
Others	49 (35.0)	91 (65.0)	140
Key Secondary Endpoint Events	590 (42.0)	816 (58.0)	1406
≥1 event	459 (43.1)	606 (56.9)	1065
≥2 events	96 (37.9)	157 (62.1)	253
≥3 events	20 (35.1)	37 (64.9)	57
≥4 events	6 (42.9)	8 (57.1)	14
Others	9 (52.9)	8 (47.1)	17

Abbreviations: ITT = Intent-to-Treat.
Note: Percentages of events in each category were calculated using the total number of events as the denominator.
Source: Table 14.2.4.1.1 and Table 14.2.4.2.1.

Summary of main study REDUCE-IT

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 (see later sections).

Table. Summary of efficacy for trial AMR-01-01-0019 (REDUCE-IT)

Title: A Multi-Center, Prospective, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Effect of AMR101 on Cardiovascular Health and Mortality in Hypertriglyceridemic Patients with Cardiovascular Disease or at High Risk for Cardiovascular Disease: REDUCE-IT (Reduction of Cardiovascular Events with EPA – Intervention Trial)			
Study identifier	AMR-01-01-0019		
Design	Multi-center, multi-national, prospective, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the effect of 2 g of AMR101 twice daily (BID) (4 g/day) for preventing CV events in statin-treated patients with moderately elevated TG levels and other CVD risk factors. The study was event driven.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Event driven, median follow-up 4.9 years Lead in 4 – 6 weeks not applicable
Hypothesis	Superiority of AMR101 4g over placebo (mineral oil)		
Treatments groups	AMR101		AMR101 2 x 2 g per day (4 gr daily dose)
	Placebo		Placebo: Paraffin oil (mineral oil) 2 x 1.86 g per day (3.72 g daily dose)
Endpoints and definitions	Primary endpoint	5 fold MACE	First event: • CV death • Nonfatal myocardial infarction (MI) (including silent MI) • Nonfatal stroke • Coronary revascularization • Unstable angina
	Key Secondary, most relevant	3 fold MACE	First event: • CV death • Nonfatal myocardial infarction (MI) (including silent MI) • Nonfatal stroke

	Secondary	Total mortality	Total mortality
Database lock	06 September 2018		
Results and Analysis			

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat, statin-treated patients with moderately elevated TG levels and other CVD risk factors including two groups: primary prevention and secondary prevention.		
Descriptive statistics and estimate variability	Treatment group	AMR101 4g daily dose	Placebo (mineral oil 3.72 g daily dose)
	Number of subject	4089	4090
	5 fold MACE	705 (17.2%)	901 (22.0%)
	3 fold MACE	459 (11.2%)	606 (14.8%)
	Total mortality	274 (6.7%)	310 (7.6%)
		HR	0.752
		(95% CI)	0.682 -0.830
		P-value	0.00000001
	Key Secondary	HR	0.735
		(95% CI)	0.651 -0.830
		P-value	0.0000006
	Total mortality	HR	0.870

		(95% CI)	0.739 – 0.864
		P-value	0.0915

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

The application is mainly based on one pivotal trial (REDUCE-IT). No analyses were provided across trials. This is appropriate.

Supportive studies

Two supportive studies were provided. Both studies aimed at investigating the effect of AMR101 at 2 doses (2gr daily and 4 gr daily, administered BID with wood in comparison with a placebo containing mineral oil) on lipid parameters and other parameters relevant for the characterisation of CV risk of patients.

AMR101 MARINE Study (AMR-01-01-0016) NCT01047683

A Phase 3, Multi-Center, Placebo-Controlled, Randomized, Double-Blind, 12-Week Study With an Open-Label Extension to Evaluate the Efficacy and Safety of AMR101 in Patients With Fasting Triglyceride Levels ≥500 mg/dL and ≤2000 mg/dL:

It was a multi-center, international, randomized, parallel group, placebo-controlled, 3 arm, double blind study. The primary objective of the study was to determine the efficacy of AMR101 2 g daily and 4 g daily, compared to placebo, in lowering fasting TG levels in patients with fasting TG levels ≥500 mg/dL and ≤2000 mg/dL (≥5.6 mmol/L and ≤22.6 mmol/L). It included a

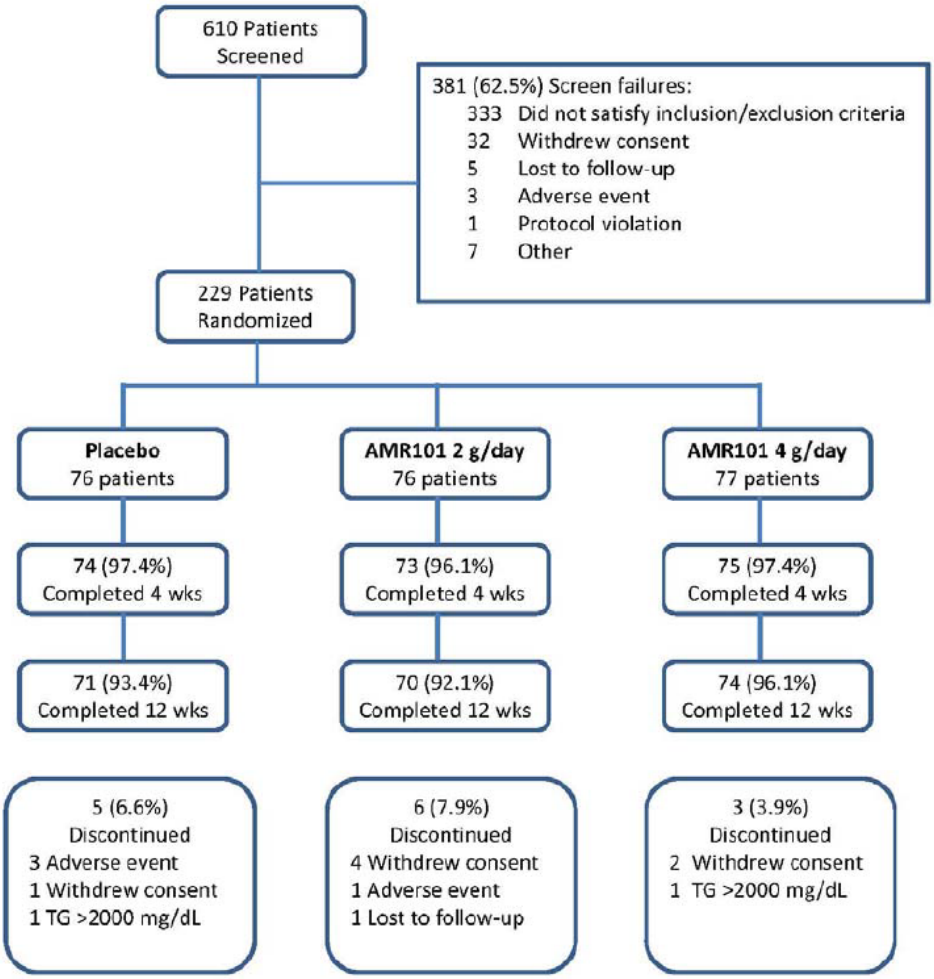
- 6- to 8-week screening/washout period (which included a diet and lifestyle stabilization period and a TG qualifying period),

- a 12-week double-blind treatment period (AMR101 2 g daily, AMR101 4 g daily, or placebo) and a

- 40-week open-label extension (OLE) period. All patients were to receive open-label AMR101 4 g daily. From Visit 7 (Week 12) until the end of the study, changes to the lipid-altering regimen were permitted (e.g., initiating, restarting, or raising the dose of statin or adding/restarting non-statin, lipid-altering medications), as guided by standard practice and prescribing information. After Visit 8 (Week 16), patients were to return to the site every 12 weeks until the last visit at Visit 11 (Week 52).

For methods and results of the OLE see below. The study design is depicted in Figure 1. Of the 229 patients assigned randomly to treatment, 76 were assigned to the placebo group, 76 were assigned to the AMR101 2 g group, and 77 were assigned to the AMR101 4 g group. Fourteen (6.1%) patients discontinued from the double-blind treatment period: 7 (3.1%) patients withdrew consent, 4 (1.7%) patients due to an adverse event, 2 (0.9%) patients with TG >2000 mg/dL, and 1 (0.4%) patient was lost to follow-up.

Figure 2. Patient Disposition – All Enrolled Patients

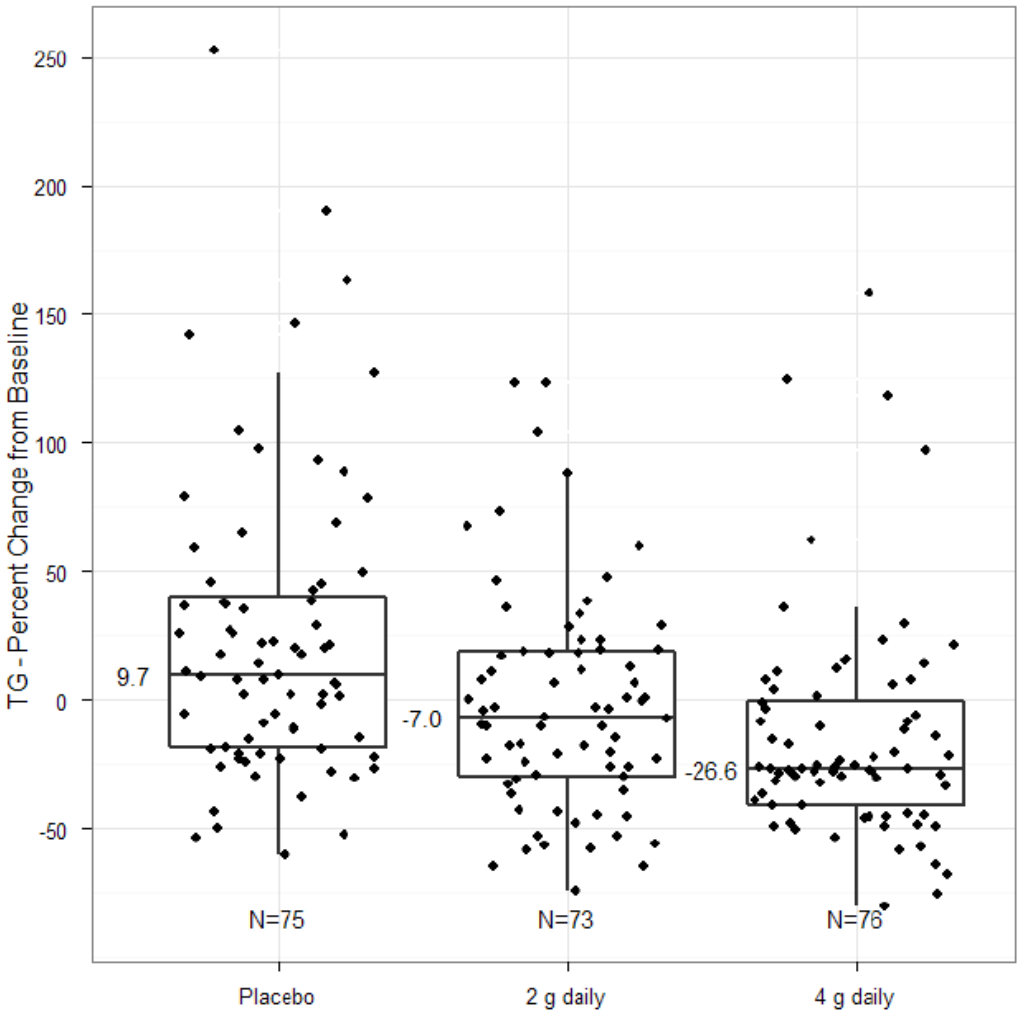


TG = triglyceride; wk = week.
Sources: Post-text Tables 14.1.1 and 14.1.2

Key results:

Figure 5 displays the median percent change in fasting TG from baseline to Week 12 endpoint for each treatment group in the ITT population.

Figure 5. Box-and-Whisker Plot of Median Percent Change in Fasting TG (mg/dL) From Baseline to Week 12 Endpoint – Intent-to-Treat Population



Each dot represents the percent change from baseline in TG for each patient. The horizontal line within each box and corresponding value represent the median percent change in TG from baseline to Week 12 endpoint. The bottom edge of each box represents Q1; the top edge of each box represents Q3. The whiskers extend to ≤1.5 × IQR from the box.
IQR = interquartile range; N = number of patients per treatment group; Q1 = first quartile; Q3 = third quartile; TG = triglyceride.
Source: Post-text Data Listing 16.2.6.1 (Note: This figure was provided by the Sponsor.)

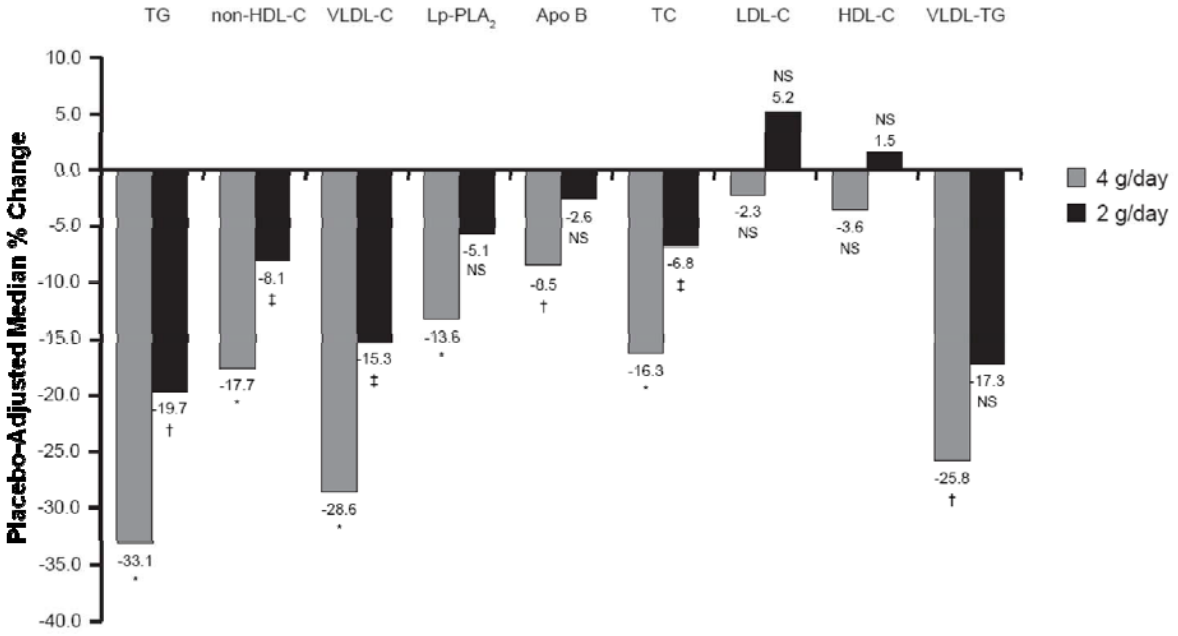
An overview of the results for Lipid parameters as observed in MARINE is shown in Table 25 and Figure 8. The results are discussed in more detail thereafter.

Table 25 **Median Baseline and Percent Change From Baseline To Week 12 in Lipid Parameters-ITT Population (MARINE)**

Parameter	Placebo (N=75)		Vascepa 4 g/day (N=76)		Vascepa 2 g/day (N=73)		Median		p-value	
	BL	% Change	BL	% Change	BL	% Change	Vascepa 4 g/day vs. Placebo	Vascepa 2 g/day vs. Placebo	Vascepa 4 g/day vs. Placebo	Vascepa 2 g/day vs. Placebo
TG[1] (mmol/L)	7.9	9.7	7.7	-26.6	7.4	-7.0	-33.1	-19.7	<0.0001	0.0051
LDL-C (mmol/L)	2.2	-3.0	2.3	-4.5	2.2	-2.5	-2.3	5.2	0.6768	0.3022
Non-HDL-C (mmol/L)	5.9	7.8	5.8	-7.7	5.4	0.0	-17.7	-8.1	<0.0001	0.0182
VLDL-C[2] (mmol/L)	3.2	13.7	3.2	-19.5	3.1	0.0	-28.6	-15.3	0.0005[3]	0.1152[3]
Lp-PLA$_2$[2] (ng/mL)	253.0	-2.4	246.0	-17.1	235.0	-5.1	-13.6	-5.1	0.0006[3]	0.2367[3]
Apo B[2] (g/L)	1.2	4.3	1.2	-3.8	1.2	2.1	-8.5	-2.6	0.0019[3]	0.2367[3]
hsCRP (mg/L)	1.8	33.3	2.2	-2.5	2.0	25.1	-36.0	-10.1	0.0012	0.4028
TC (mmol/L)	6.6	7.7	6.6	-7.3	6.1	0.7	-16.3	-6.8	<0.0001	0.0148
HDL-C (mmol/L)	0.7	0.0	0.7	-3.5	0.7	0.0	-3.6	1.5	0.2174	0.5225
VLDL-TG (mmol/L)	6.1	7.8	5.9	-25.2	5.5	-6.4	-25.8	-17.3	0.0023	0.0733

% Change = Median Percent Change from Baseline; Apo B = apolipoprotein B; BL = Baseline (mg/dL); HDL-C = high-density lipoprotein cholesterol; hsCRP = high sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; Lp-PLA$_2$ = lipoprotein-associated phospholipase A$_2$; non-HDL-C = non-high-density lipoprotein cholesterol; TC = total cholesterol; TG = triglyceride; VLDL-C = very low-density lipoprotein cholesterol; VLDL-TG = very low-density lipoprotein triglycerides.
Medians are Hodges-Lehmann medians; p-values are from the Wilcoxon rank-sum test.
1 Fasting TG level was the primary efficacy endpoint
2 VLDL-C, Lp-PLA$_2$, and Apo B were secondary efficacy endpoints
3 Adjusted p-values from applying Hommel's multiple comparison procedure to the p-value from the treatment comparison between 4 or 2 g/day Vascepa with placebo are reported.
Source: MARINE Table 14Marine_EU

Figure 8. Placebo-Adjusted Median Percent Change From Baseline to Week 12 Endpoint in Key Lipid and Lipoprotein Concentrations – Intent-to-Treat Population



* p <0.001
† p <0.01
‡ p <0.05
apo B = apolipoprotein B; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp-PLA$_2$ = lipoprotein-associated phospholipase A$_2$; non-HDL-C = non-high-density lipoprotein cholesterol; NS = not significant; TC = total cholesterol; TG = triglyceride; VLDL-C = very low-density lipoprotein cholesterol; VLDL-TG = very low-density lipoprotein triglycerides.
Sources: Post-text Tables 14.2.1, 14.2.6, 14.2.8, 14.2.10, 14.2.15, 14.2.17, 14.2.19, 14.2.21, and 14.2.23

AMR-01-01-0016 OLE. Open label extension study to the MARINE study

First Patient Entered Open-Label Extension Period: 21 May 2010

Completion Date of Open-Label Extension Period: 19 July 2011

Database Lock for Open-Label Extension Period: 26 August 2011

Patients who completed the 12-week double-blind treatment period were eligible to enter a 40-week open-label extension period at Visit 7 (Week 12). All patients were to receive open-label AMR101 4 g daily. From Visit 7 (Week 12) until the end of the study, changes to the lipid-altering regimen were permitted (e.g., initiating, restarting, or increasing the dose of statin or adding/restarting non-statin, lipid-altering medications), as guided by standard practice and prescribing information. After Visit 8 (Week 16), patients were to return to the site every 12 weeks until the last visit at Visit 11 (Week 52).

Duration of Treatment: 52 weeks: 12 weeks of double-blind treatment followed by 40 weeks of open-label treatment.

Number of Patients:

Planned (randomized): 240

Screened: 610

Randomized: 229

Completed double-blind treatment period: 215

Entered open-label extension period: 210

Did not continue into open-label extension period: 5

Discontinued from open-label extension period: 21

Completed open-label extension period: 189

No pre-specified efficacy hypothesis was tested in the open label extension period (40 weeks on AMR101 4g).

Table S1 presents the results for percent changes in key lipid and lipoprotein parameters from open-label baseline to Week 52 endpoint for the extension efficacy population by double-blind treatment group.

Table S1. Percent Change in Key Lipid and Lipoprotein Parameters From Open-Label Baseline to Week 52 Endpoint – Extension Efficacy Population

	Double-Blind Treatment Group								
	Placebo (N = 69)			AMR101 2 g (N = 70)			AMR101 4 g (N = 71)		
Parameter	n [1]	Baseline Median	Median Percent Change	n [1]	Baseline Median	Median Percent Change	n [1]	Baseline Median	Median Percent Change
TG	69	754.0	-35.5	70	615.5	-26.2	71	504.0	-15.9
VLDL-C	67	157.0	-37.4	66	118.0	-28.3	68	105.0	-11.0
Lp-PLA_2	63	261.0	-18.8	64	222.5	-9.3	65	198.0	1.3
Apo B	63	120.0	-5.1	64	117.0	0.4	65	122.0	4.0
TC	69	274.0	-14.0	70	242.0	-6.4	71	239.0	-0.4
HDL-C	69	27.0	0.0	70	28.5	0.0	71	26.0	8.3
LDL-C	67	75.0	24.1	66	93.5	15.1	68	88.0	21.7
Non-HDL-C	69	243.0	-14.1	70	214.0	-6.3	71	207.0	0.9
VLDL-TG	67	628.0	-39.2	66	530.5	-26.7	68	397.5	-18.6

For TG, open-label baseline was defined as the average of Visit 6 (Week 11) and Visit 7 (Week 12) measurements during the double-blind treatment period. If the measurement at 1 visit was missing, the other visit was used. If the measurements at both visits were missing, the last valid measurement during the double-blind treatment period was used as the baseline value. For all other parameters, open-label baseline was defined as the Visit 7 (Week 12) measurement during the double-blind treatment period. If missing, the last valid measurement during the double-blind treatment period was used as the baseline value.

1. Only patients with non-missing open-label baseline and Week 52 endpoint values were included.

Apo B = apolipoprotein B; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp-PLA_2 = lipoprotein-associated phospholipase A_2; non-HDL-C = non-high-density lipoprotein cholesterol; TC = total cholesterol; TG = triglyceride; VLDL-C = very low-density lipoprotein cholesterol; VLDL-TG = very low-density lipoprotein triglycerides.

Sources: Post-text Tables 14.2.1, 14.2.4, 14.2.7, 14.2.10, 14.2.13, 14.2.16, 14.2.19, 14.2.22, and 14.2.25

AMR101 ANCHOR Study (AMR-01-01-0017)

A Phase 3, Multi-Center, Placebo-Controlled, Randomized, Double-Blind, 12-Week Study to Evaluate the Effect of Two Doses of AMR101 on Fasting Serum Triglyceride Levels in Patients With Persistent High Triglyceride Levels (≥200 mg/dL and <500 mg/dL) Despite Statin Therapy:

The AMR101 ANCHOR Study

This Phase 3, multi-center study consisted of a 6- to 8-week screening/washout period (which included a diet and lifestyle stabilization period and an LDL-C and TG qualifying period) and a 12-week double-blind treatment period (AMR101 2 g daily, AMR101 4 g daily, or placebo).

The screening period included a 4- to 6-week diet and lifestyle stabilization period and washout period followed by a 2-week LDL-C and TG qualifying period. Patients taking non-statin, lipid-altering medications (niacin >200 mg daily, fibrates, fish oil, other products containing omega-3 fatty acids, or other herbal products or dietary supplements with potential lipid-altering effects) at the time of screening must have been able to safely discontinue them at screening. At the end of the 4-week diet and lifestyle stabilization period or the 6-week diet and stabilization and washout period, eligible patients entered the 2-week LDL-C and TG qualifying period and had their fasting LDL-C and TG levels measured at Visit 2 (Week -2) and Visit 3 (Week -1).

In order to enter the 12-week double-blind treatment period, patients must have had a mean fasting LDL-C level ≥40 mg/dL and ≤115 mg/dL (based on 2 qualifying visits) and fasting TG levels from 2 qualifying visits within the following ranges:

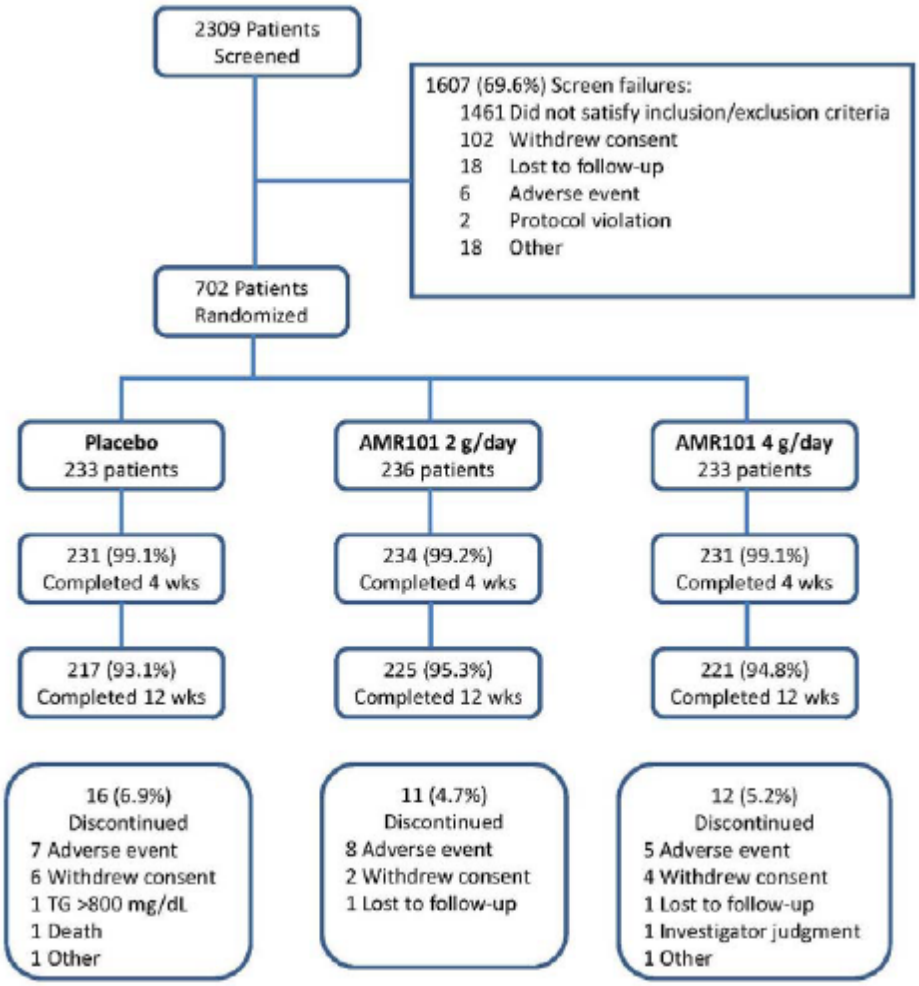
· Mean of the 2 values ≥185 mg/dL and at least 1 value ≥200 mg/dL and

• Mean of the 2 values <500 mg/dL.

Approximately 216 patients per treatment group were to be randomized in this study. Patients were stratified by type of statin (atorvastatin, rosuvastatin, or simvastatin), the presence of diabetes, and gender.

Figure 2 summarizes patient disposition during the double-blind treatment period. Of the 702 patients assigned randomly to treatment, 233 were assigned to the AMR101 4 g group, 236 were assigned to the AMR101 2 g group, and 233 were assigned to the placebo group. Thirty-nine (5.6%) patients discontinued from the double-blind treatment period: 20 (2.8%) patients due to an adverse event, 12 (1.7%) patients withdrew consent, 2 (0.3%) patients were lost to follow-up, 1 patient (0.1%) with a TG level >800 mg/dL, 1 (0.1%) patient due to investigator judgment, 1 (0.1%) patient died, and 2 (0.3%) patients withdrew for reasons other than those specified above. In total, 663 (94.4%) patients completed the double-blind treatment period of the study: 221 (94.8%) patients in the AMR1101 4 g group, 225 (95.3%) patients in the AMR101 2 g group, and 217 (93.1%) patients in the placebo group.

Figure 2. Patient Disposition – All Enrolled Patients



TG = triglyceride; wk = week.
Sources: Post-text Tables 14.1.1 and 14.1.2

An overview of the results on lipid parameters in the ITT population in ANCHOR is shown in Table 20 and Figure 6. The results are discussed in more detail thereafter.

Table 20 **Median Baseline and Percent Change from Baseline To Week 12 in Lipid Parameters-ITT Population (ANCHOR)**

Parameter	Placebo (N=227)		Vascepa 4 g/day (N=226)		Vascepa 2 g/day (N=234)		Median		p-value	
	BL	% Change	BL	% Change	BL	% Change	Vascepa 4 g/day vs. Placebo	Vascepa 2 g/day vs. Placebo	Vascepa 4 g/day vs. Placebo	Vascepa 2 g/day vs. Placebo
TG[a] (mmol/L)	2.9	5.9	3.0	-17.5	2.9	-5.6	-21.5	-10.1	<0.0001	0.0005
LDL-C[b] (mmol/L)	2.2	8.8	2.1	1.5	2.1	2.4	-6.2	-3.6	0.0067	0.0867
Non-HDL-C[b] (mmol/L)	3.3	9.8	3.3	-5.0	3.3	2.4	-13.6	-5.5	0.0001[c]	0.0140[c]
VLDL-C[b] (mmol/L)	1.1	15.0	1.1	-12.1	1.1	1.6	-24.4	-10.5	0.0001[c]	0.0170[c]
Lp-PLA$_2$[b] (ng/mL)	185.0	6.7	180.0	-12.8	190.0	-1.8	-19.0	-8.0	0.0001[c]	0.0004[c]
Apo B[b] (g/L)	0.9	7.1	0.9	-2.2	0.9	1.6	-9.3	-3.8	0.0001[c]	0.0170[c]
hsCRP (mg/L)	2.2	17.1	2.2	-2.4	1.9	10.3	-22.0	-6.8	0.0005	0.2894
TC (mmol/L)	4.3	9.1	4.3	-3.2	4.4	2.1	-12.0	-4.8	<0.0001	0.0019
HDL-C (mmol/L)	1.0	4.8	1.0	-1.0	1.0	0.0	-4.5	-2.2	0.0013	0.1265
VLDL-TG (mmol/L)	2.1	8.9	2.1	-19.2	2.1	-2.1	-26.5	-11.3	<0.0001	0.0049

% Change = Median Percent Change from Baseline; Apo B = apolipoprotein B; BL = Baseline; HDL-C = high-density lipoprotein cholesterol; hsCRP = high sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; Lp-PLA$_2$ = lipoprotein-associated phospholipase A$_2$; non-HDL-C = non-high-density lipoprotein cholesterol; TC = total cholesterol; TG = triglyceride; VLDL-C = very low-density lipoprotein cholesterol; VLDL-TG = very low-density lipoprotein triglycerides.
Medians are Hodges-Lehmann medians; p-values are from the Wilcoxon rank-sum test.

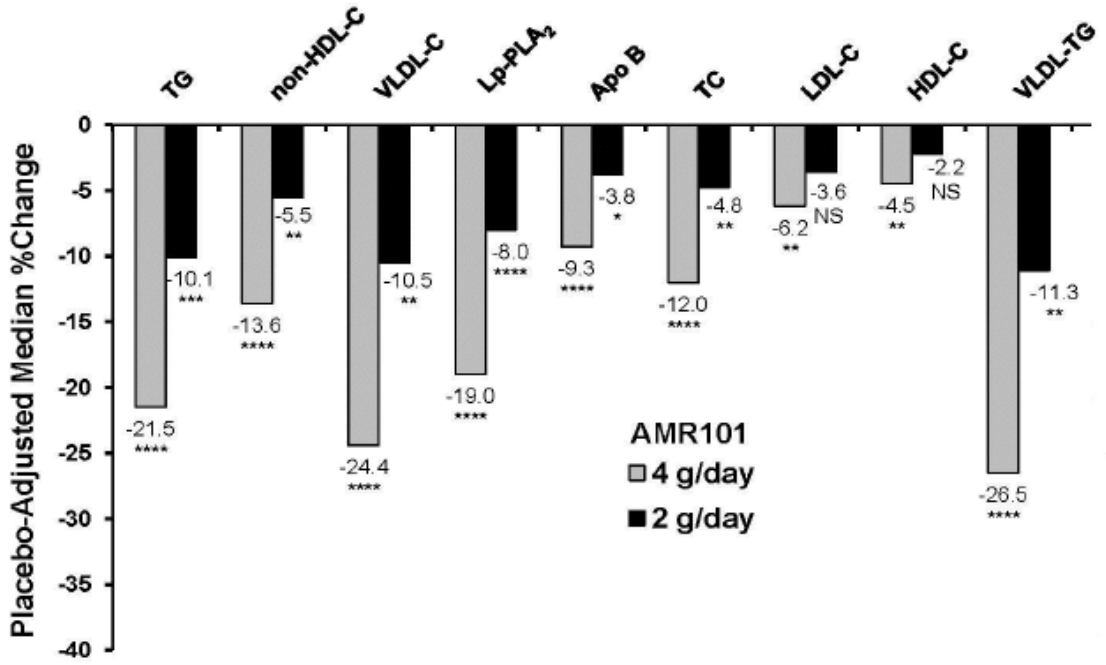
a Fasting TG level was the primary efficacy endpoint

b LDL-C, non-HDL-C. VLDL-C, Lp-PLA$_2$, and Apo B were secondary efficacy endpoints

c Adjusted p-values from applying Hommel's multiple comparison procedure to the p-value from the treatment comparison between 4 or 2 g/day Vascepa with placebo are reported.

Source: ANCHOR Table 14ANCHOR

Figure 6. Placebo-Adjusted Median Percent Change From Baseline to Week 12 Endpoint in Key Lipid and Lipoprotein Concentrations – Intent-to-Treat Population



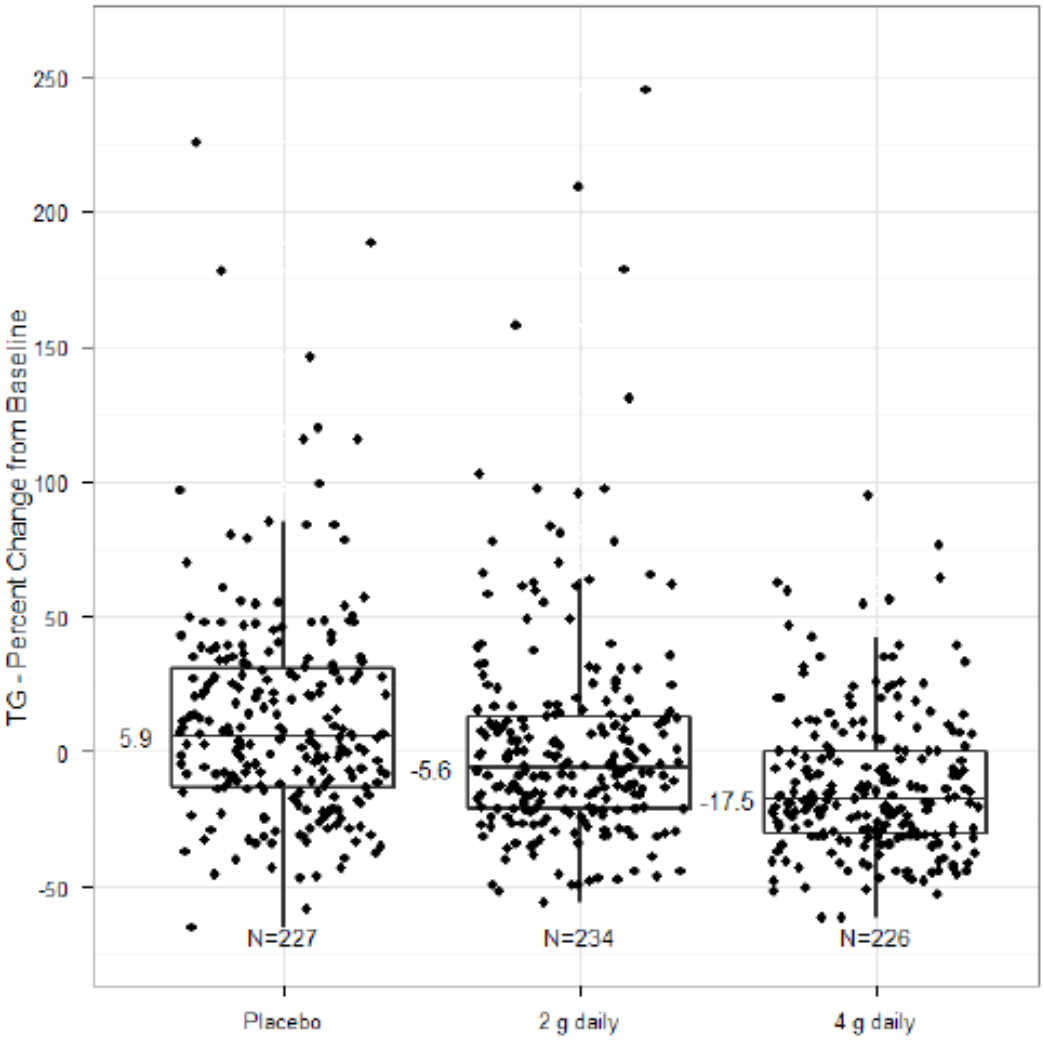
**** p <0.0001
*** p <0.001
** p <0.01
* p <0.05

apo B = apolipoprotein B; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp-PLA$_2$ = lipoprotein-associated phospholipase A$_2$; non-HDL-C = non-high-density lipoprotein cholesterol; NS = not significant; TC = total cholesterol; TG = triglyceride; VLDL-C = very low-density lipoprotein cholesterol; VLDL-TG = very low-density lipoprotein triglycerides.

Sources: Post-text Tables 14.2.1, 14.2.7, 14.2.9, 14.2.11, 14.2.13, 14.2.15, 14.2.19, 14.2.21, and 14.2.23.

Figure 3 displays the median percent change in fasting TG from baseline to Week 12 endpoint for each treatment group in the ITT population.

Figure 3. Box-and-Whisker Plot of Median Percent Change in Fasting TG (mg/dL) From Baseline to Week 12 Endpoint – Intent-to-Treat Population



Each dot represents the percent change from baseline in TG for each patient. The horizontal line within each box and corresponding value represent the median percent change in TG from baseline to Week 12 endpoint. The bottom edge of each box represents Q1; the top edge of each box represents Q3. The whiskers extend to ≤1.5 × IQR from the box. One value in the AMR101 4 g/day treatment group (564%) is not shown as it was an outlier and is outside of the y-axis range shown in the figure.
IQR = interquartile range; N = number of patients per treatment group; Q1 = first quartile; Q3 = third quartile; TG = triglyceride.
Source: Post-text Data Listing 16.2.6.1 (Note: This figure was provided by the Sponsor.)

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The CHMP approved Vazkepa in the following indication:

Vazkepa is indicated to reduce the risk of cardiovascular events in adult statin-treated patients at high cardiovascular risk with elevated triglycerides (≥150 mg/dL) and:

- *established cardiovascular disease, or*
- *diabetes, and at least one other cardiovascular risk factor*

For study details including cardiovascular risk factors and results with respect to effects on cardiovascular events see Section 5.1.

Dose finding studies

Dose selection was based on the efficacy of Vazkepa in reducing TG levels as investigated in two supportive controlled studies, ANCHOR and MARINE. Both were 3 arm, randomised, double-blind, placebo controlled, multi-centre studies with a 12-week double-blind period. MARINE was followed by a 40-week open label extension study. TG reduction was the primary endpoint in both studies, additional lipid parameters and serum markers were investigated as additional endpoints. In MARINE study, patients with severe hypertriglyceridaemia (TG ≥5.6 and ≤22.6 mmol/L [≥500 and ≤2000 mg/dL]) while in ANCHOR study patients with hypertriglyceridaemia (TG ≥2.3 and <5.6 mmol/L [≥200 and <500 mg/dL]) on statin therapy were included. In both studies 2 or 4 g/day Vazkepa or matching placebo (mineral oil) taken bid with food was administered. The studies included an evaluation of the correlation between EPA in plasma and red blood cells and the TG lowering effect at the two doses selected.

Main study REDUCE-IT

The application is mainly based on one pivotal trial the REDUCE IT trial. It was a Phase 3 randomised, placebo controlled event (cardiovascular events) driven study in patients with moderately elevated TG (≥1.5 and <5.6 mmol/L [≥135 and <500 mg/dL], after amendment 1: ≥2.26 mmol/L (200 mg/dL) and <500 mg/dL) on statin therapy and at high risk for CVD. Patients received 2 g of AMR101 twice daily (BID) (4 g/day) or matching placebo (mineral oil).

The primary objective of this study was to demonstrate the superiority of AMR101 compared to placebo in reducing the risk of major cardiovascular events (5 fold MACE: Composite of CV death, non-fatal MI (including silent MI), non-fatal stroke, coronary revascularisation, or unstable angina requiring emergent hospitalisation). The key secondary efficacy endpoint was time to 3-fold MACE (CV death, non-fatal MI (including silent MI), or non-fatal stroke) which is considered more relevant for the assessment of efficacy. Additional secondary CV endpoints were analysed in a predefined hierarchical order. Patients were included in two separate groups based on CV risk at baseline (intended ratio 70/30% Group 1/Group 2). CV Risk Category 1 (Secondary Prevention Cohort): men and women ≥45 years with documented coronary artery diseases (CAD), cerebrovascular or carotid disease, or peripheral arterial disease (PAD). CV risk category 2 (Primary Prevention Cohort): Men and women ≥ 50 years of age with diabetes mellitus (Type 1 or Type 2) and additional predefined risk factors (smoker, higher age, hypertension, renal dysfunction, retinopathy, micro- or macroalbuminuria, or Ankle brachial index (ABI) <0.9 without symptoms). Randomization was stratified by CV risk category, use of ezetimibe (yes/no), and by geographical region (Westernized, Eastern European, and Asia Pacific). Two protocol amendments were included after start of the study. The most relevant was the introduction of patients with higher level of TG as an inclusion criterion.

Numbers planned and analysed: A total of approximately 7990 patients were planned to be enrolled (i.e., randomized) in the study to either receive AMR101 or placebo in a 1:1 ratio (approximately 3995

patients per treatment group) to observe an estimated 1612 primary endpoint events. A total of 473 sites enrolled and/or followed patients in 11 countries in 3 geographic regions. A total of 19,212 patients were screened, 8179 patients were randomized/ 7314 completed the final visit (Vazkepa 4089/3684, Placebo 4090/3630). All efficacy analyses, including the primary analysis, were performed on the ITT population.

The statistical methods are generally acceptable.

The study was planned and started before the concept of estimand was introduced by the ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials. Nevertheless, although not explicitly specified using estimand terminology, including data after discontinuation of study drug for patients who discontinued study drug prematurely implies that a 'treatment policy' strategy was applied for the intercurrent event treatment discontinuation, which is appropriate. Censoring patients for non-CV death can either be seen as corresponding to targeting the hypothetical treatment effect that would have been observed if no non-CV deaths had occurred (under a missing at random assumption), or to targeting the effect while not having died for non-CV reasons. Both approaches have limitations regarding relevance and interpretability. Therefore, the secondary endpoint including total mortality in the composite endpoint instead of CV-death is of particular relevance.

The stratified log-rank test and the Cox proportional hazards model are standard methods for analysis of time to event data, also taking the stratified randomisation adequately into account. However, interpretation of the hazard ratio (HR) estimate resulting from the Cox model is not straightforward if the proportional hazards assumption is not fulfilled.

The measures to ensure confidentiality of interim analyses results to preserve the integrity of the study were adequate. The 95% confidence intervals that were calculated for the primary (and secondary) endpoints are nominal confidence intervals that are not consistent with the group sequential design of the study.

Sequential testing with alpha level 0.0437 does not necessarily ensure control of the family-wise type 1 error for secondary endpoints: The alpha level 0.0437 for final analysis was determined based on the information fractions (proportion of events) for the primary endpoint at the interim analyses, which are not the same as for the secondary endpoints. However, taking the actual results (p-values) into account, this is not considered an issue.

The sensitivity analyses cover adequately the assessment of analysis assumptions, as well as some sensitivity analyses target additional treatment effects of interest (estimands).

Overall the study was well conducted as planned, no concerns regarding compliance with GCP were detected during the assessment.

Efficacy data and additional analyses

In the REDUCE-IT study a daily dose of AMR101 of 4 g (2 g BID with food) was investigated. No data are available on the correlation between dose and efficacy on hard CV clinical endpoints.

The dose selection was mainly based on results from ANCHOR and MARINE/MARINE OLE. Prior to MARINE and ANCHOR, more than 1000 patients had been exposed to AMR101 at doses up to 4 g per day in the randomised, double-blind periods of Amarin-sponsored studies. ANCHOR and MARINE studies investigated efficacy of two dose levels (1 and 2 g BID, i.e. 2g and 4 g daily dose taken with food). MARINE OLE was an open label extension study investigating a daily dose of AMR101 4 g over 40 weeks. In these studies AMR 101 resulted in statistically significant reductions of TG compared with placebo. A larger reduction in TG and other lipid, lipoprotein, and inflammatory markers was seen with

AMR101 4 g/day than with AMR101 2 g/day. Data on PK/PD correlation based on these two doses were provided in ANCHOR and MARINE showing a correlation between dose, percent change in EPA levels in plasma end red blood cells and TG lowering effect. In addition, a post hoc analysis indicating a correlation between clinical outcome and EPA exposure in REDUCE-IT was provided.

Based on these considerations the choice of the 4 g daily AMR101 dose (2 g bid with food) in REDUCE-IT appears to be reasonable, although the contribution of the TG lowering effect to efficacy is unclear. While information about efficacy of lower doses on CV endpoints is missing, not including a lower dose treatment arm in the REDUCE-IT trial is not a key issue of concern in terms of efficacy.

The patient characteristics were balanced between the 2 treatment arms. Overall, the majority of patients were male (71.2% [5822/8179]) and white (90.2% [7379/8179]). The mean age of patients was 63.4 years (range 44 to 92 years), with 46.0% (3763/8179) of patients aged ≥65 years. Mean height, weight, and BMI were 171.3 cm, 93.0 kg, and 31.6 kg/m2, respectively. 22.2% (1816/8179) of patients were renally impaired at baseline (eGFR <60 mL/min/1.73m2). 69.1% of the patients had prior atherosclerotic CV disease, most of these had CAD (58.4%), and history of MI (46.7%).

The most common incidences of reported CV disease history or other prior conditions influencing CV risk were hypertension (86.6% [7084/8179]), Type 2 diabetes (57.8% [4730/8179]), and MI (46.7% [3819/8179]). The most common incidences of reported CV disease history or other prior conditions influencing CV risk were hypertension (86.6% [7084/8179]), Type 2 diabetes (57.8% [4730/8179]), and MI (46.7% [3819/8179]). Only few patients with T1DM were included.

Primary efficacy result

Primary endpoint: 5-fold MACE: CV death, nonfatal MI, nonfatal stroke, coronary revascularisation, unstable angina caused by myocardial ischemia and associated with emergent hospitalisation. A primary endpoint event occurred in 17.2% (705/4089) of patients in the AMR101 group, as compared with 22.0% (901/4090) of patients in the placebo group (HR of 0.752 [95% CI: 0.682 to 0.830; p=0.00000001]; relative risk reduction [RRR] of 24.8% and number needed to treat [NNT] of 21). The median follow-up duration for the primary endpoint was 4.7 and 4.5 years for the AMR101 and placebo groups, respectively. No statistically significant difference was seen after 1 year between the treatment arms. All 5 components of the primary composite endpoint contributed to the overall statistically significant result. In a landmark analysis a significantly lower risk of major adverse CV events with AMR101 than with placebo (HR of 0.799 [95% CI: 0.693 to 0.920; p=0.0017]) was observed at the 2-year landmark.

Key secondary composite endpoint analysis (3-fold MACE: CV death, nonfatal MI, nonfatal stroke)

The key secondary endpoint is considered most important for the assessment of efficacy. The median follow-up duration for the key secondary endpoint was 4.8 and 4.7 years for the AMR101 and placebo groups, respectively. A key secondary endpoint event occurred in 11.2% (459/4089) of patients in the AMR101 group, as compared with 14.8% (606/4090) of patients in the placebo group (HR of 0.735 [95% CI: 0.651 to 0.830; p=0.0000006]; RRR of 26.5% and NNT of 28). Similar to the primary endpoint result, there was a lag time of about 1.5 years before differences between the groups became apparent.

Results for the individual components of the primary and key secondary endpoint

All components contributed to the overall result (results for first event in each class are shown, AMR101 vs. placebo, events (%), HR (95% CI), p value)):

- CV death: 174 (4.3%) vs. 213 (5.2%), HR 0.803 (0.657, 0.981, p = 0.03),

- Nonfatal myocardial infarction: 237 (5.8%) vs. 332 (8.1%), HR 0.697 (0.590; 0.823, p < 0.0001),
- Nonfatal stroke: 85 (2.1%) vs. 118 (2.9%), HR 0.708 (0.536, 0.936, p = 0.01),
- Coronary revascularisation: 376 (9.2%) vs. 544 (13.3%), HR 0.664 (0.583 0.758, p < 0.0001),
- Hospitalization for unstable angina: 108 (2.6%) vs. 157 (3.8%), HR 0.679 (0.531, 0.868, p = 0.002).

Other secondary endpoints

Statistically significant reductions in time to event (first event, ITT) were observed for the following secondary endpoints (predefined hierarchical testing): CV death or nonfatal MI; fatal of nonfatal MI; urgent or emergent revascularization; CV death; hospitalization for unstable angina; fatal or nonfatal stroke; total mortality, nonfatal MI or nonfatal stroke (AMR101 vs. placebo, events (%), HR (95% CI), p value): 549 (13.4%) vs. 690 (16.9%), HR 0.772 (0.690, 0.864, p <.0001). For total mortality the numerical difference between the two groups did not reach statistical significance: 274 (6.7%) vs. 310 (7.6%), HR 0.870 (0.739, 1.023) p = 0.0915.

Overall, the results for the primary endpoint were consistent for most of the predefined subgroups.

Region, Ezetimibe use, Sex, hsCRP, eGFR, LDL-C, HDL-C, Apo-B, Non-HDL-C and Triglycerides at baseline had no significant impact on efficacy as determined by the primary endpoint. A significant p value for interaction was observed for age < 65 and ≥ 65 years with lower efficacy at the higher age group.

Although not significant (p value for interaction 0.1388), overall efficacy tended to be lower in the primary prevention cohort:

Primary prevention: 146/1197 (12.2%) vs. 163/1197 (13.6%), HR 0.876 (0.700, 1.095)

Secondary Prevention: 559/2892 (19.3%) vs. 738/2893 (25.5%), HR 0.726 (0.650, 0.810)

Post hoc exploratory analyses indicated relevant efficacy in patients at high and very high CV risk. Efficacy in cohort 2 was less clear in patients with less than three risk factors and at lower age (below 55/65 years m/f). These patients overall had a lower CV risk. As over-interpretation of exploratory analyses needs to be avoided, such analyses were not specifically included in the wording of the indication. A statement in the wording of the indication that patients should be "at high cardiovascular risk" sufficiently covers uncertainties around efficacy in such patients at lower baseline risk. The applicant has amended the proposed indication accordingly.

Results for additional tertiary composite CV composites combining CV death and other CV events and of several additional tertiary endpoints were consistent with the results for the primary and key secondary analysis.

Cardiac arrhythmia events requiring hospitalization of ≥24 hours occurred in 4.6% (188/4089) of patients in the AMR101 group, as compared with 3.8% (154/4090) of patients in the placebo group (HR of 1.21 [95% CI: 0.97 to 1.49]). **Atrial fibrillation or atrial flutter** events requiring hospitalization of ≥24 hours occurred in 3.1% (127/4089) of patients in the AMR101 group, as compared with 2.1% (84/4090) of patients in the placebo group (HR of 1.50 [95% CI: 1.14 to 1.98] p = 0.0037).

Plasma TG, non-HDL-C, LDL-C, HDL-C, and EPA were measured at Year 1; apo B and hsCRP were measured at Year 2. In the placebo arm some of these markers showed a trend to a numerical

deterioration. Small numerical increases were observed for TG (+ 4.5 mg/dL), non-HDL-C (+ 12.0 mg/dL), LDL-C (+ 7.0 /+ 9.3 mg/dL (depending on the mode of calculation)), apo B (+ 6.0 mg/dL), and hsCRP (+0.5 mg/L). Significant reductions were observed with AMR101 compared to placebo in TG, LDL-C, non-HDL-C, apo B, and hsCRP. The effect on TGs was maximal at visit 3 and persisted up to the end of the study.

A key issue discussed with the Applicant is **the potentially negative impact of the comparator** (mineral oil) on CV events. The mechanism of action of AMR101 is not entirely clear. TG lowering therapy has not consistently been associated with a parallel reduction in CV events in the past and it is conceivable that multiple mechanisms of action contribute to the difference in the event rate between the AMR101 and the placebo arm. Mineral oil (paraffin oil) was chosen as placebo, but it is not clear that mineral oil in fact is entirely inert. Some of the markers relevant for prognosis showed a trend toward deterioration in the mineral oil arm. Small numerical increases were observed for TG, non-HDL-C, LDL-C, apoB, and hsCRP. Change from baseline in systolic BP showed a small difference between the groups. To which degree this just represented the natural course of the disease, was due to variability and regression of the mean effects or represented a negative effect of mineral oil is not entirely clear.

In a first step a worst-case scenario was proposed to identify the maximally conceivable negative impact of the comparator in order to assess whether under such assumptions efficacy remained clinically relevant. The scenario was based on the following assumptions as derived from associations as published: an increase in LDL-C by 7 – 9.3 mg/dl may translate into an increase in MACE events by about 4 – 5%. An increase in Apo B by 6.0 mg/dL may translate into an increase in CAD by about 5%, and in major cardiovascular disease risk by 4%. An increase in hsCRP by 0.5 mg may translate into an increase by 4 – 5% in ischemic stroke and coronary artery disease and an increase by 11% in vascular deaths. A difference in systolic blood pressure by 0.6 – 1.5 mmHg may translate into a difference in CV event rates by about 2%. Based on the worst-case assumption that all of these effects were independent, additive and due to mineral oil, CV events increased by at the most 15%. However, it is clear that this scenario is largely over-pessimistic. E.g. the impact of LDL-C and ApoB on CV outcome are not additive but overlapping. It was further assumed that all of the changes vs. baseline were due to mineral oil and did not represent the natural course of the disease or design features of the study. Such an assumption may also not hold true. Some studies indicate that the predictive value of hsCRP for CV events may be lower in patients on statin treatment than in statin naïve patients. However, for hsCRP the worst-case scenario was based on data from the emerging risk factors collaborations that were adjusted for several CV risk factors including cholesterol levels. It is acknowledged that there is considerable uncertainty about the predictive value for the specific group of patients included in REDUCE-IT and it is most likely not appropriate just to add the presumed hsCRP associated risk to the LDL-C/ApoB associated risk. The small effect on blood pressure may be additive on its own. When taking the overlap of LDL-C and Apo-B into account the possible negative impact is very likely to be smaller than about 10%. This would translate into a Vazkepa mediated RRR on MACE (3 point MACE) events of more than 16.5%, which clearly is clinically relevant. Even this assumption is likely to be over-pessimistic. In the Amarin sponsored studies, increases in LDL-C were only seen in those two studies with an upper threshold for LDL-C as an inclusion criterion indicating the possibility of regression to the mean effects rather than true PD effects. Increases in LDL-C have also been observed in the control arms in other studies not using mineral oil as a comparator where upper limits of LDL-C were among the selection criteria. Therefore, the observed increase in LDL-C may have been at least in part due to the design of REDUCE-IT. Furthermore, as outlined by the Applicant, the hypothetical worst-case scenario does not take into account that there were also beneficial effects in the mineral oil arm (increase in HDL-C) that could counterbalance a putative negative effect.

The Applicant has provided covariate-based analyses of the study results. These analyses indicated for most of the biomarkers a much lower impact on CV outcome than estimated based on population-based association data from the literature. Based on these calculations the applicant concluded that the possible effect of mineral oil on biomarkers should not make up for more than 0.3 - 3% of CV events (3-point MACE).

It is worth considering that mineral oil may interact with the absorption of drugs like statins that are relevant for the CV prevention. Effects on the absorption of antihypertensive drugs, non VIT K anticoagulants or thrombocyte inhibitors are unknown. The Applicant provided additional analyses indicating that efficacy of statins and of anticoagulants was not related to physicochemical properties of the drugs which would have been expected if mineral oil had a relevant impact on absorption. Bleeding patterns were also not related to physicochemical properties of anticoagulants or antiplatelet drugs. However, the latter analyses were hampered by the relevant increase in bleeding with Vazkepa and a pronunciation of bleeding events when Vazkepa was concomitantly administered with anticoagulants or antiplatelet drugs. The issue is further discussed in the safety part.

The Applicant claimed that there was **a correlation between EPA levels and CV outcome** further supporting the assumption of a treatment related effect. Analyses of the data as provided initially indicated that those patients on active treatment that did not achieve EPA levels above 100 µg/mL (about 1/3 of the patients) had a considerably higher rate of CV events than patients on placebo. This unexpected observation was sufficiently explained by an inappropriate definition of imputation rules assuming that steady state was not reached before the first measurement of EPA blood concentrations (usually at year 1). When changing this assumption in line with PK data indicating that steady state is reached by about day 14 the negative apparent imbalance disappeared. Low EPA blood levels in almost 30% of patients on treatment could at least in part be explained by a lower compliance. In these patients the MACE event rate was not different from the event rate in the overall placebo group. Taking the uncertainties about missing data, sparse sampling and the high impact of the definition of imputation rules on the results into account, the analyses indicating an association between EPA concentrations and efficacy are not considered robust.

In summary, for the key secondary analysis (3-point MACE) Vazkepa showed a risk reduction by 26.5% when compared to mineral oil. Upon request, the potential negative impact of mineral oil on CV outcome has been analysed by the Applicant in detail. Whether the assumption of the Applicant of a potential negative effect of mineral oil on CV outcome (MACE) of up to 0.3 - 3% holds true or a higher value may be more realistic that – in a worst case scenatio - is not above 10% in a worst case scenario, the remaining benefit of Vazkepa on CV outcome remains unambiguously clinically relevant. Even under very conservative assumptions, treatment with Vazkepa was associated with a risk reduction for MACE (3 point MACE) of at least 16.5%. This worst-case scenario may considerably overestimate a putative negative impact of long term treatment with mineral oil on CV events.

After amending the wording of the indication by including reference to high CV risk and specifying age as a CV risk factor in section 5.1 in the study description the proposed target population appropriately reflects the study population with respect to baseline cardiovascular (CV) risk and triglyceride (TG) levels, for which a positive benefit-risk balance has been demonstrated. According to the Applicant´s calculations based on the placebo event rate the average 10 year risk for CV death was 12.2% in the overall study population. This indicates that overall patients in REDUCE-IT were not only at high risk (≥ 5% and <10% for 10-year risk of fatal CVD) but a substantial proportion was even at very high risk (≥ 10% for 10-year risk of fatal CVD, according to 2019 ESC/EAS Guidelines for the management of dyslipidaemias, European Heart Journal (2020) 41, 111 – 188, Table 4). Regarding patients in Risk category 1 the cited guideline considers all patients with documented ASCVD as having a very high risk.

For patients in Risk category 2 ("primary prevention") the calculated risk for CV death was 8.3%. Analyses provided indicated that a large number of these patients were also at a very high risk since several inclusion criteria for risk category 2 were in line with the above-mentioned ESC definitions for very high risk. (e.g. DM with target organ damage" or patients with diabetes and another major risk factors). Analyses provided indicated that absolute risk reduction was lower in patients at high risk than in those at very high risk, but relative efficacy of Vazkepa was similar in both groups.

The applicant stated that reference to "statin-treated patients" would better reflect inclusion criteria than reference to "maximally tolerated" statin therapy which was initially requested by the CHMP in line with the recommendations of clinical guidelines. This is acceptable.

Additional analyses indicated that hsCRP had a prognostic and a positive predictive value in this context and therefore is appropriate as a risk factor to be included in section 5.1 of the SmPC.

The outcome and the final letters of the FDA based inspections have been provided, sensitivity analyses provided by excluding data at one center with some findings of the FDA indicated that inclusion of these data did not have an impact on the overall results.

2.5.3. Conclusions on the clinical efficacy

The CHMP considers the application is acceptable from the clinical efficacy viewpoint.

2.6. Clinical safety

Safety information regarding use of Vazkepa in patients with hypertriglyceridemia and high cardiovascular risk mainly comes from the pivotal Phase 3 study, REDUCE-IT, (Reduction of Cardiovascular Events with EPA – Intervention Trial; AMR-01-01-0019), which provides substantial evidence of the safety of Vazkepa in the proposed target patient population, i.e. statin-treated patients with elevated TG (fasting TG ≥135 mg/dL and <500 mg/dL) and high CV risk. Supportive evidence of the safety of Vazkepa in a relevant patient population is provided from the two Phase 3 studies: patients with hypertriglyceridemia and with persistent high fasting TG levels (≥200 and <500 mg/dL) despite statin therapy [ANCHOR (AMR-01-01-0017)], and patients with very high (≥500 mg/dL and ≤2000 mg/dL fasting TG levels [MARINE (AMR-01-01-0016)] (Table 1).

Additional safety data come from the two Phase 1 clinical pharmacology studies in healthy subjects (LA01.01.0009 and AMR-01-01-0018, Table 1) and three completed DDI studies (AMR-01-01-0020, AMR-01-01-0021, and AMR-01-01-0023).

In addition, eight clinical studies have been conducted in patients with central nervous system (CNS) disorders (three in Huntington's disease, three in depressions, one in memory impairment, and one in schizophrenia).

Table 1 of SCS (shortened): List of Studies supporting the Safety of Vazkepa

Study	Dose (g/day)	No. of Randomised Subjects	Treatment Duration
Clinical Pharmacology Studies			
LA01.01.0009: A Phase I Multiple Dose Pharmacokinetic Study of LAX-101 in Healthy Male Volunteers	Vazkepa 2 g	24	4 weeks

AMR-01-01-0018: Randomised, Open-Label, Multiple-Dose, Parallel, Comparative, Pharmacokinetic Study in Healthy Subjects after Oral Administration of Vazkepa 500 mg or Vazkepa 1000 mg Capsules	Vazkepa 2 g Vazkepa 4 g	36 12	28 days + 18 days of PK sampling
Phase 3 Clinical Studies in Cardiovascular/Hypertriglyceridemia			
AMR-01-01-0019 (REDUCE-IT): A Multi-Centre, Prospective, Randomised, Double-Blind, Placebo- Controlled, Parallel-Group Study to Evaluate the Effect of AMR101 on Cardiovascular Health and Mortality in Hypertriglyceridemic Patients with Cardiovascular Disease or at High Risk for Cardiovascular Disease	Vazkepa 4 g Placebo	4089 4090	Median duration of Vasc. and plc treatment: 4.5 and 4.2 years, resp.
AMR-01-01-0016 (MARINE): A Phase 3, Multi-Centre, Placebo-Controlled, Randomised, Double-Blind, 12-Week Study with an Open-Label Extension to Evaluate the Efficacy and Safety of Vazkepa in Patients with Fasting Triglyceride Levels ≥500 mg/dL and ≤2000 mg/dL	Vazkepa 2 g Vazkepa 4 g Placebo	76 77 76	12 weeks + 40 weeks open-label
AMR-01-01-0017 (ANCHOR): A Phase 3, Multi-Centre, Placebo-Controlled, Randomised, Double-Blind, 12-Week Study to Evaluate the Effect of Two Doses of AMR101 on Fasting Serum Triglyceride Levels in Patients with Persistent High Triglyceride Levels (≥200 mg/dL and <500 mg/dL) Despite Statin Therapy	Vazkepa 2 g Vazkepa 4 g Placebo	236 233 233	12 weeks
Clinical Studies in Central Nervous System Disorders			
LA.01.01.0001: A Multicentre, Double- Blind, Randomised, Parallel Group, Placebo Controlled, Dose Ranging Pilot Study of Ethyl Eicosapentaenoate (ETHYL- EPA) in Patients with Schizophrenia	Vazkepa 1 g Vazkepa 2 g Vazkepa 4 g Placebo	32 32 27 31	12 weeks
LA01.01.0002: A Multicentre, Double- Blind, Randomised, Parallel Group, Placebo-Controlled, Dose Ranging Pilot Study of Ethyl Eicosapentaenoate as Adjunct Therapy in Patients who Remain Depressed Following Treatment with Standard Antidepressant Therapy.	Vazkepa 1 g Vazkepa 2 g Vazkepa 4 g Placebo	17 18 17 18	12 weeks
LA01.01.0005: A Multicentre, Multinational, Double- Blind, Randomised, Parallel Group, Placebo Controlled Study of Ethyl Eicosapentaenoate in Patients with Huntington's Disease	Vazkepa 2 g Placebo	67 68	12 months + 12 months open-label
LA01.01.0006: A Multicentre, Double- Blind, Randomised, Parallel Group, Placebo Controlled Trial of LAX-101 (ethyl eicosapentaenoate) as Adjunct Therapy in Patients who Remain Depressed Following Treatment with Standard Antidepressant Therapy	Vazkepa 1 g Placebo	57 58	12 weeks + 12 months open-label
LA01.01.0008A: A Multicentre, Double- Blind, Randomised, Parallel Group, Placebo-Controlled, Dose Ranging Pilot Study of LAX-101 (ethyleicosapentaenoate) in Patients with a New or Recurrent Episode of Depression	Vazkepa 0.5g Vazkepa 1 g Vazkepa 2 g Placebo	19 20 18 20	6 weeks
AN01.01.0011: A Multi-Centre, Double- Blind, Randomised, Parallel Group, Placebo-Controlled Trial of Ethyl-EPA (Miraxion™) in Subjects with Mild to Moderate Huntington's Disease (HD)	Vazkepa 2 g Placebo	158 158	6 months + 6 months open-label

AN01.01.0012: A Multicentre, Multinational, Double- Blind, Randomised, Parallel-Group, Placebo- Controlled Trial of Ethyl-EPA (Ethyl-Icosapent) in Patients with Huntington's Disease	Vazkepa 2 g Placebo	147 143	6 months + 6 months open-label
AN01.01.0014: A Single Centre, Double- Blind, Randomised, Parallel Group, Placebo Controlled Dose-Ranging Pilot Study of Ethyl-EPA in Subjects with Age Associated Memory Impairment (AAMI)	Vazkepa 1 g Vazkepa 2 g Vazkepa 4 g Placebo	23 24 24 23	6 weeks

Patient exposure

In the REDUCE-IT trial, the median duration of Vazkepa and placebo treatment was 1614 days (4.5 years) and 1512 days (4.2 years), respectively. Overall, 12.3% (1010/8179) of patients received study drug for <1 year (i.e., <360 days) and 0.5% (37/8179) of patients received study drug for ≥6 years (≥2160 days); see table below.

Table 2 of SCS (shortened): Study Drug Exposure, REDUCE-IT (Safety Population)

Overall Treatment Duration (weeks)			
n	4083	4077	8160
Mean (SD)	193.6 (91.10)	185.8 (92.87)	189.7 (92.07)
Median	230.6	216.0	226.1
Q1, Q3	122.3, 268.1	106.9, 265.9	114.1, 267.1

Duration of treatment administration (n, %)			
>104- 208 weeks (4 years)	952 (23.3%)	977 (23.9%)	1929 (23.6%)
>208- 312 weeks (6 years)	2270 (55.5%)	2117 (51.8%)	4387 (53.6%)
>312 weeks (6 years)	8 (0.2%)	5 (0.1%)	13 (0.2%)

In the pooled hypertriglyceridemia phase 2 studies, mean exposure was 82 days (median 84 days) in all treatment groups, plc, Vazkepa 2g/d and Vazkepa 4g/d. For around 35% of the patients, treatment duration was more than 84 days. Total exposure was 69 subject-years in the plc and 70 subj-y. in each Vazkepa group (2 g and 4 g).

Adverse events

Overview

The following table provides an overview of AEs observed in the REDUCE-IT trial. The incidence of AEs and SAEs was rather high, but this was obviously due to underlying disease since there were no relevant differences between the Vazkepa and plc group in the frequency of all AEs or SAEs. This is also true for all sub-categories (drug-related AE, AE leading to discontinuation etc.).

Table 10 of SCS: Overview of Treatment-Emergent Adverse Events, Overall and by Treatment Group, REDUCE-IT (Safety Population)

	Vazkepa (N=4089) n (%)	Placebo (N=4090) n (%)	Overall (N=8179) n (%)
Patients with at least 1 TEAE, n (%)	3343 (81.8)	3326 (81.3)	6669 (81.5)
Severe TEAE	805 (19.7)	816 (20.0)	1621 (19.8)
Study Drug-Related TEAE[1]	514 (12.6)	499 (12.2)	1013 (12.4)
Serious TEAE	1252 (30.6)	1254 (30.7)	2506 (30.6)
Study Drug-Related Serious TEAE[1]	8 (0.2)	5 (0.1)	13 (0.2)
TEAE Leading to Withdrawal of Study Drug[2]	321 (7.9)	335 (8.2)	656 (8.0)
Study Drug-Related TEAE Leading to Withdrawal of Study Drug[1,2]	139 (3.4)	164 (4.0)	303 (3.7)
Serious TEAE Leading to Withdrawal of Study Drug[2]	88 (2.2)	88 (2.2)	176 (2.2)
Serious TEAE Leading to Death	94 (2.3)	102 (2.5)	196 (2.4)
Study Drug-Related Serious TEAE Leading to Withdrawal of Study Drug[1,2]	2 (0.0)	4 (0.1)	6 (0.1)

TEAE = treatment-emergent adverse event.
Note: A TEAE was defined as an event that first occurred or worsened in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. Percentages were based on the number of patients randomised to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints were not included.

1 Study drug related TEAE include those characterised as related, probably related, or possibly related.

2 Withdrawal of study drug excludes patients who were off drug but remained in the study for 30 days or more and restarted study drug.

The applicant also provided a pooled safety analysis of the two smaller studies in hypertriglyceridemia patients, ANCHOR and MARINE, see table below. The incidence of AEs was lower than in REDUCE-IT, probably because of the shorter study duration. All AEs, related AEs and AEs leading to discontinuation were numerically slightly more frequent in the plc group. Serious AEs were numerically more frequent in the Vazkepa group, but the number of events was low so that no firm conclusions can be drawn.

Table 11 of SCS: Overall Summary of Treatment-Emergent Adverse Events, Double-Blind Treatment Phase, Hypertriglyceridemia Placebo-Controlled Integrated Dataset (Safety Analysis Set)

	Placebo N=309 n (%)	**Vazkepa Pooled N=622 n (%)**	**Vazkepa 2 g N=312 n (%)**	**Vazkepa 4 g N=310 n (%)**
Patients with TEAE	151 (48.9)	285 (45.8)	142 (45.5)	143 (46.1)
Patients with Study Drug-Related TEAE	39 (12.6)	53 (8.5)	28 (9.0)	25 (8.1)
Patients with SAE	5 (1.6)	18 (2.9)	9 (2.9)	9 (2.9)
Patients with Study Drug-Related SAE	0	0	0	0
Patients with TEAE Leading to Discontinuation	10 (3.2)	14 (2.3)	9 (2.9)	5 (1.6)

AEs according to MedDRA Terms

The AE listing per organ class is provided below. Events occurring in 3% or more of the patients of a group are shown. Salient numerical imbalances between the treatment groups, Vazkepa and plc, were observed for the terms musculoskeletal pain, constipation, oedema peripheral and atrial fibrillation (highlighted by the assessor). These AEs were more frequent in the Vazkepa group. Vice versa, anemia

was more frequent among the plc patients. It should be noted that the plc treatment, mineral oil, can act as laxative; this may explain the higher rate of constipation in the Vazkepa group.

Table 12 of SCS: Treatment-Emergent Adverse Events Occurring at an Incidence of ⩾3% in Either Treatment Group, REDUCE-IT (Safety Population)

System Organ Class Preferred Term	Vazkepa (N=4089) n (%)	Placebo (N=4090) n (%)	Overall (N=8179) n (%)
Infections and infestations	1822 (44.6)	1774 (43.4)	3596 (44.0)
Nasopharyngitis	314 (7.7)	300 (7.3)	614 (7.5)
Upper respiratory tract infection	312 (7.6)	320 (7.8)	632 (7.7)
Bronchitis	306 (7.5)	300 (7.3)	606 (7.4)
Pneumonia	263 (6.4)	277 (6.8)	540 (6.6)
Influenza	263 (6.4)	271 (6.6)	534 (6.5)
Urinary tract infection	253 (6.2)	261 (6.4)	514 (6.3)
Sinusitis	169 (4.1)	166 (4.1)	335 (4.1)
Musculoskeletal and connective tissue disorders	1466 (35.9)	1406 (34.4)	2872 (35.1)
Back pain	335 (8.2)	309 (7.6)	644 (7.9)
Arthralgia	313 (7.7)	310 (7.6)	623 (7.6)
Osteoarthritis	241 (5.9)	218 (5.3)	459 (5.6)
Pain in extremity	235 (5.7)	241 (5.9)	476 (5.8)
Musculoskeletal pain	176 (4.3)	130 (3.2)	306 (3.7)
Myalgia	135 (3.3)	147 (3.6)	282 (3.4)
Muscle spasms	101 (2.5)	136 (3.3)	237 (2.9)
Gastrointestinal disorders	1350 (33.0)	1437 (35.1)	2787 (34.1)
Diarrhoea	367 (9.0)	453 (11.1)	820 (10.0)
Constipation	221 (5.4)	149 (3.6)	370 (4.5)
Nausea	190 (4.6)	197 (4.8)	387 (4.7)
Gastroesophageal reflux disease	124 (3.0)	118 (2.9)	242 (3.0)
General disorders and administration site conditions	1030 (25.2)	979 (23.9)	2009 (24.6)
Chest pain	273 (6.7)	290 (7.1)	563 (6.9)
Oedema peripheral	267 (6.5)	203 (5.0)	470 (5.7)
Fatigue	228 (5.6)	196 (4.8)	424 (5.2)
Non-cardiac chest pain	161 (3.9)	173 (4.2)	334 (4.1)
Nervous system disorders	1004 (24.6)	972 (23.8)	1976 (24.2)
Dizziness	235 (5.7)	246 (6.0)	481 (5.9)
Headache	171 (4.2)	180 (4.4)	351 (4.3)
Respiratory, thoracic, and mediastinal disorders	989 (24.2)	946 (23.1)	1935 (23.7)
Dyspnea	254 (6.2)	240 (5.9)	494 (6.0)
Cough	241 (5.9)	241 (5.9)	482 (5.9)
Metabolism and nutrition disorders	953 (23.3)	877 (21.4)	1830 (22.4)
Gout	171 (4.2)	127 (3.1)	298 (3.6)
Diabetes mellitus	169 (4.1)	173 (4.2)	342 (4.2)
Type 2 diabetes mellitus	147 (3.6)	133 (3.3)	280 (3.4)
Cardiac disorders	910 (22.3)	855 (20.9)	1765 (21.6)
Atrial fibrillation	215 (5.3)	159 (3.9)	374 (4.6)
Angina pectoris	200 (4.9)	205 (5.0)	405 (5.0)
Injury, poisoning, and procedural complications	748 (18.3)	697 (17.0)	1445 (17.7)
Fall	149 (3.6)	138 (3.4)	287 (3.5)
Vascular disorders	709 (17.3)	717 (17.5)	1426 (17.4)
Hypertension	320 (7.8)	344 (8.4)	664 (8.1)
Eye disorders	478 (11.7)	429 (10.5)	907 (11.1)
Cataract	233 (5.7)	208 (5.1)	441 (5.4)
Psychiatric disorders	372 (9.1)	362 (8.9)	734 (9.0)
Insomnia	124 (3.0)	111 (2.7)	235 (2.9)
Blood and lymphatic system disorders	321 (7.9)	372 (9.1)	693 (8.5)
Anaemia	191 (4.7)	236 (5.8)	427 (5.2)

Salient numerical imbalances among less frequent AEs in the REDUCE-IT trial are compiled in the following two tables (taken from Table 14.3.1.2.7 of CSR); the upper table shows events which were more frequent with Vazkepa and the lower shows AEs which were more frequent in the plc group. Beside supraventricular arrhythmias, Vazkepa increased the frequency of events of cardiac conduction disorders, hyperuricemia/gout, skin-related AEs and allergic conditions. The latter difference was mainly driven by the term "Hypersensitivity"; no further information is available.

In the plc group, a salient numerical increase in events of hyperglycaemia was observed. Furthermore, electrolyte disturbances (hyperkalaemia, hypomagnesaemia), ventricular arrhythmias, anaemia, hypothyroidism and intestine polyp were more frequent with plc than with Vazkepa.

Increased with Vazkepa

MedDRA Term	Vazkepa N=4089	Placebo N=4090
Purine and pyrimidine metabolism disorders	203 (5.0)	145 (3.5)
Gout	171 (4.2)	127 (3.1)
Hyperuricaemia	33 (0.8)	19 (0.5)
Vitamin D deficiency	94 (2.3)	67 (1.6)
Supraventricular arrhythmias	300 (7.3)	236 (5.8)
Atrial fibrillation	215 (5.3)	159 (3.9)
Cardiac conduction disorders	86 (2.1)	63 (1.5)
Bundle branch block right	33 (0.8)	12 (0.3)
Dermatitis and eczema	146 (3.6)	120 (2.9)
Rash	116 (2.8)	83 (2.0)
Allergic conditions	98 (2.4)	68 (1.7)

Increased with Plc

MedDRA Term	Vazkepa N=4089	Placebo N=4090
Large intestine polyp	90 (2.2)	118 (2.9)
Hyperglycaemic conditions NEC	91 (2.2)	117 (2.9)
Hyperglycaemia	71 (1.7)	93 (2.3)
Hyperkalaemia	32 (0.8)	55 (1.3)
Hypomagnesaemia	29 (0.7)	43 (1.1)
Ventricular arrhythmias and cardiac arrest	53 (1.3)	92 (2.2)
Ventricular extrasystoles	27 (0.7)	48 (1.2)
Low density lipoprotein increased	59 (1.4)	89 (2.2)
Anaemia	191 (4.7)	236 (5.8)
Iron deficiency anaemia	29 (0.7)	36 (0.9)
Hypothyroidism	59 (1.4)	74 (1.8)

In the two smaller studies in hypertriglyceridemia patients, ANCHOR and MARINE more patients in the Vazkepa than in the plc group had an event of arthralgia. Vice versa, UTI and GI disorders were more frequent in the plc group.

Safety information from published studies

In the Japan Eicosapentaenoic Acid Lipid Intervention Study (JELIS), a large randomised trial, revealed a higher incidence of adverse events (AEs); skin and gastrointestinal disorders, and haemorrhage (cerebral; fundal; epistaxis; subcutaneous) in the icosapent ethyl group than in the control group

(statin alone). The incidence of pain was decreased in the icosapent ethyl group. The number of laboratory abnormal values was higher in the icosapent ethyl group than in the control group, with a slightly higher incidence of increased aspartate aminotransferase (AST) values (0.6% versus 0.4%, p=0.03).

In addition, five published clinical studies with icosapent ethyl in other therapeutic areas (psychological distress, depression, schizophrenia and dyslexia) were identified. In general, TEAE associated with icosapent ethyl were mild gastrointestinal events that were not considered serious. One severe TEAE was reported in a diabetic patient. This patient had an allergic reaction attributed to icosapent ethyl, which was given as a supplement, and was characterised by a skin rash that was considered severe and resulted in discontinuation.

AEs of special interest

Bleeding

Doses of omega-3 marine oil in excess of 3 g daily have been linked with an increase in bleeding time. According to the applicant, these increases in bleeding time did not exceed normal limits.

Therefore, the applicant performed an analysis of bleeding-related AEs in the REDUCE-IT trial.

A statistically significantly higher incidence of bleeding events occurred in the Vazkepa group than in the placebo group (11.8% [482/4089] versus 9.9% [404/4090], respectively; p=0.0055). Serious bleeding events did not reach significance but trended toward higher incidence in the Vazkepa group versus the placebo group (2.7% [111/4089] versus 2.1% [85/4090], respectively; p=0.0605), while the rates of adjudicated haemorrhagic stroke were numerically different across treatment groups (0.49% vs. 0.29%, EPA vs. plc), this difference did not reach statistical significance. The incidences of serious GI bleeding, serious CNS bleeding, and serious anaemia were low overall and similar between the Vazkepa and placebo groups; see table below.

Table 23 of SCS: Overview of Pre-Specified Treatment-Emergent Adverse Events of Special Interest, Bleeding-Related Disorders, REDUCE-IT (Safety Population)

	Vazkepa (N=4089) n (%)	**Placebo (N=4090) n (%)**	**Overall (N=8179) n (%)**
Bleeding-related disorders[1]	482 (11.8)	404 (9.9)	886 (10.8)
Gastrointestinal bleeding	127 (3.1)	116 (2.8)	243 (3.0)
Central nervous system bleeding	20 (0.5)	12 (0.3)	32 (0.4)
Other bleeding	376 (9.2)	312 (7.6)	688 (8.4)

[1] Bleeding-related disorders were identified by the SMQs of "Gastrointestinal haemorrhage," "Central Nervous System haemorrhages and cerebrovascular conditions," and "Haemorrhage terms (excl laboratory terms)."

SAEs of bleeding in the REDUCE-IT study were further analysed. Overall, 2.7% of patients in the Vazkepa group and 2.1% of patients in the plc group had at least one SAE of bleeding. In most cases (1.5% Vasc. 1.1% plc) the serious bleeding occurred in the GI tract. Serious CNS bleeding was less frequent, 0.34% vs. 0.24%.

Since bleeding rate can be affected by concomitant medication, the applicant provided a summary of background medication. The use of all substance classes antiplatelet drugs was well balanced between the treatment groups; most important, this is also true for antiplatelet drugs. Thus, imbalances in baseline medication cannot be responsible for the increased bleeding risk in the Vazkepa group.

In order to address bleeding tendency also in the phase 2 trials performed in patients with hypertriglyceridemia, the applicant compiled all AEs which could indicate increased bleeding risk. An markedly increased incidence in the Vazkepa group was observed for anaemia (0.8% vs. 0, Vazkepa. vs. plc) and traumatic heamatoma (0.5% vs. 0). Notably, patients in the plc group more often took anticoagulant or antiplatelet medication than in the Vazkepa group.

Atrial fibrillation *(post hoc evaluation)*

Although not pre-specified as TEAE of special interest, atrial fibrillation and/or atrial flutter were explored, based on a treatment imbalance observed in the study. A summary of TEAE and SAE of atrial fibrillation/flutter is presented in the table below, along with positively adjudicated endpoints of atrial fibrillation/flutter requiring hospitalisation of ≥24 hours (endpoint events adjudicated by the Clinical Endpoint Committee [CEC]) as a comprehensive compilation of all documented post-randomisation occurrences of these atrial arrhythmias. Also positively adjudicated events were more frequent with Vazkepa than with plc (3.1% and 2.1% of patients in the Vazkepa and plc group, respectively). Reassuringly, the number of patients with serious events was low and was fairly balanced between the treatment groups.

Table 29 Summary of Atrial Fibrillation and Atrial Flutter, REDUCE-IT (ITT Population)

	Vazkepa (N=4089) n (%)	Placebo (N=4090) n (%)	P-Value
Atrial fibrillation/flutter[1] AE	236 (5.8)	183 (4.5)	0.0079
Serious atrial fibrillation/flutter[2]	22 (0.5)	20 (0.5)	0.7602
Positively adjudicated atrial fibrillation/flutter requiring ≥24 hours hospitalisation[3]	127 (3.1)	84 (2.1)	0.0037

1 Includes atrial fibrillation/flutter AE. The p-value was based on Fisher's exact test.
2 Includes atrial fibrillation/flutter AE meeting seriousness criteria. The p-value was based on Fisher's exact test.
3 Includes positively adjudicated atrial fibrillation/flutter requiring ≥24 hours hospitalisation clinical events by the Clinical Endpoint Committee. The p-value was based on stratified log-rank test.

Serious adverse event/deaths/other significant events

Deaths

Total mortality was lower in the Vazkepa group (274 subjects [6.7%] vs. 310 subjects [7.6%]); this was due to a decrease in CV mortality. For detailed discussion, see efficacy section.

Other SAEs

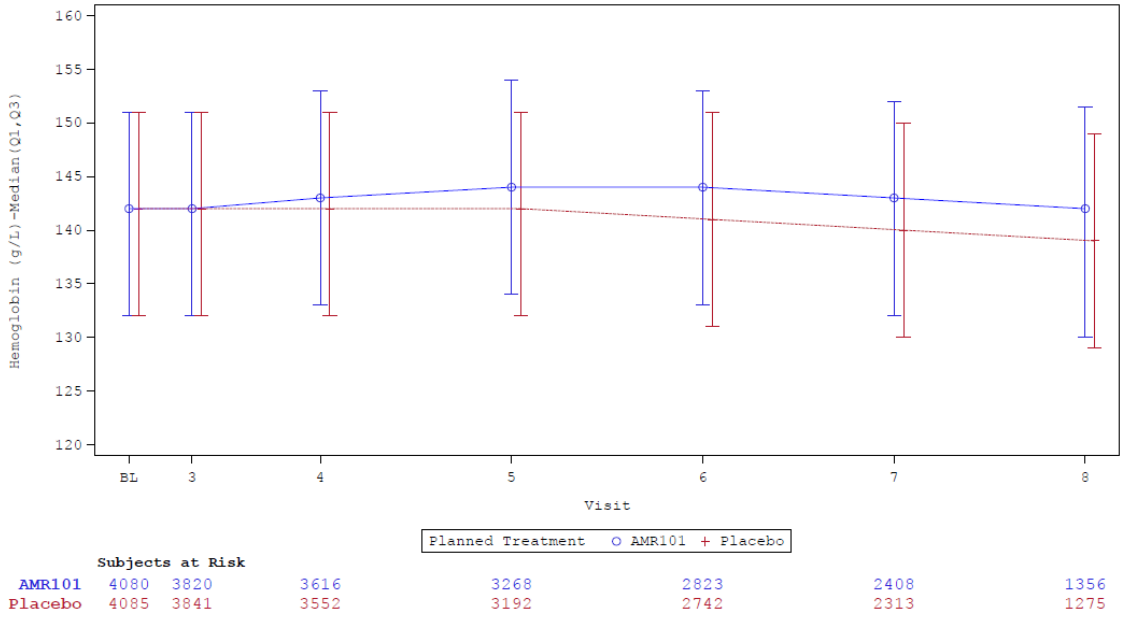
The total number of patients with an SAE was essentially equal in both treatment group, Vazkepa and plc, of the REDUCE-IT trial. Accordingly, no major differences became obvious in the incidences of SAEs affecting specific organ classes. In the smaller trials ANCHOR and MARINE, more patients in the Vazkepa than in the plc group experienced at least one SAEs, but the absolute number of events was low (18 subjects [2.9%] vs. 5 subjects [1.6%], Vazkepa vs. plc) so that no firm conclusions can be drawn.

Laboratory findings

Haematology

After around one year of treatment, the median haemoglobin values slightly increased in the patients of the Vazkepa group of REDUCE-IT as compared to plc patients; the difference between the groups did not further increase after around three years of treatment, see figure below.

Figure 12-1 of CSR: Plot of Median Haemoglobin Over Time (Safety Population)



In accordance with the median increase in Hb in the Vazkepa group, a lower number of events of Hb below LLN and a higher number of events of Hb above ULN was observed in this group, see table below. This table is taken from a shift analysis indicating how many study participants had altered values while having had normal basal values and vice versa. As an example, Visit 7 (after around 4 year's treatment) is shown since at this time point the number of patients on treatment was still sufficiently high (around 2400 per group) for meaningful conclusions.

Hemoglobin (g/L); Visit 7 - Day 1440 (from Tables 14.3.4.2.1 and 14.3.4.2.2 of CSR)

	Vazkepa	Plc
n	2408	2313
Mean (SD)	**141.81** (15.149)	**139.42** (15.259)
Change from Baseline:		
Mean (SD)	**0.64** (11.161)	**-2.69** (11.887)
Overall Post Baseline (low-normal-high at baseline)		
Low	59-**133**-0	57-**188**-0
Normal	84-2073-13	58-1963-20
High	0-**34**-14	1-**18**-9

Serum chemistry

In the following, the salient findings of serum chemistry in the REDUCE-IT study will be presented; furthermore, liver parameters will be shown since special emphasis was laid on them by the applicant to exclude events of drug-induced liver injury (DILI, so-called Hy's law cases). For completeness, also lipid parameters and inflammation markers will be mentioned although these were regarded as (tertiary) endpoints in the efficacy analysis.

Triglycerides, LDL-cholesterol, apo-B, CRP (from efficacy analysis)

There was a sharp decline in median serum triglyceride (TG) level within the first half year of treatment in the Vascspa group; thereafter, the median values remained rather constant and were below the median values of the plc group. LDL-cholesterol (LDL-C) remained essentially constant over time in the Vazkepa group and slightly increased within the first year of treatment in the plc group. Median CRP and apo-B levels slightly decreased from baseline within the first two years of treatment in the Vazkepa group. There was a more pronounced increase of these parameters in the plc group.

Liver parameters

There was no mean increase in serum ALT or AST levels in any treatment group. There were numerically more patients with elevated ALT after four or five years of treatment in the Vazkepa than in the plc group (868 [35%] and 742 [31%] cases in the Vazkepa and plc group, respectively after four years; baseline ALT was normal in these cases).

Markedly more patients in the Vazkepa than in the plc group had elevated bilirubin after four to five years of treatment, 205 [8.4%] vs. 67 [2.9%] subjects, Vazkepa vs. plc. This finding was paralleled by a slight increase of mean serum bilirubin over time in the Vazkepa group and a more pronounced decrease of bilirubin in the plc group, see table below (derived from Tables 14.3.4.3.1 and 14.3.4.3.2 of CSR).

Bilirubin (µmol/L)

	Vazkepa	Plc
n	2444	2343
Mean (SD)	**9.85** (5.182)	**7.65** (3.887)
Change from Baseline:		
Mean (SD)	**0.51** (3.757)	**-1.75** (3.755)
Overall Post Baseline (low-normal-high at baseline)		
High	0-**205**-92	0-**67**-39

Potential Hy's law cases

An increase of 3 x ULN in ALT or AST and an increase of 2 x ULN in total bilirubin was reported in one patient in each treatment group. An increase of 3 x ULN in ALT or AST, an increase of 2 x ULN in total bilirubin, and a decrease of ≤2 x ULN in alkaline phosphatase was reported in one patient in the Vazkepa group. During review of patient data in a blinded fashion over the course of the study, the same two patients were determined to have potentially met Hy's Law. For each patient, the elevated liver enzymes were characterised as not related to study drug and were not considered to be drug-induced liver injury cases. In considering whether these laboratory measures qualified as Hy's Law cases, criteria were evaluated as outlined in the FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation. According to the applicant, neither patient appear to have met all the requirements for Hy's Law.

Other salient findings

As above, measurements from Visit 7 (Day 1440, around four years of treatment) will be considered because of still a rather high number of patients under treatment at this time point (see tables below). Results from adjacent visits were similar. The values were taken from Tables 14.3.4.3.1 and 14.3.4.3.2 of CSR.

In the plc group, there was a marked mean increase over time in serum alkaline phosphatase (AP), Accordingly, the number of subjects with values above ULN was higher in the plc group compared to the Vazkepa group (396 subjects [16.8%] vs. 219 subjects [8.9%], plc vs. Vazkepa).

There was also a marked mean decrease from baseline in serum creatine kinase (CK) in the plc group and a less pronounced mean increase in the Vazkepa group; accordingly, the number of subject with CK above ULN was higher in the Vazkepa group.

A slightly higher number of subjects with increased sodium or urate levels was observed in the Vazkepa compared to the plc group.

Alkaline Phosphatase (U/L)

	Vazkepa	Plc
n	2456	2353
Mean (SD)	**74.66** (24.291)	**83.72** (29.970)
Change from Baseline:		
Mean (SD)	**-1.04** (25.768)	**8.85** (22.379)
Overall Post Baseline (low-normal-high at baseline)		
High	0-**219**-90	0-**396**-98

Creatine Kinase (U/L)

	Vazkepa	Plc
n	2445	2346
Mean (SD)	**135.95** (171.637)	**121.57** (89.391)
Change from Baseline:		
Mean (SD)	**3.99** (179.561)	**-10.39** (89.239)
Overall Post Baseline (low-normal-high at baseline)		
High	0-**905**-486	0-**728**-501

Sodium (mmol/L)

No difference in mean values between Vazkepa and plc

	Vazkepa	Plc
n	2457	2353
Overall Post Baseline (low-normal-high at baseline)		
Low	30-330-0	27-366-1
High	0-**245**-35	1-**175**-26

Urate (mmol/L)

No difference in mean values between Vazkepa and plc

	Vazkepa	Plc
n	2458	2353
Overall Post Baseline (low-normal-high at baseline)		
High	0-**742**-533	0-**581**-498

Vital signs

Heart rate, blood pressure, ECG

There were no relevant changes from baseline during the course of the study, and no meaningful differences between the treatment groups (Vazkepa and plc) of REDUCE-IT were observed in respect to heart rate, blood pressure and ECG parameters.

Body weight

The mean body weight of the participants slightly and steadily decreased during the course of the REDUCE-IT study, by 1.1 kg in the Vazkepa group and 2.1 kg in the plc group after five years of treatment in the safety population.

Safety in special populations

Age:

The applicant provided a safety evaluation stratified by the age categories <65 and ≥65 years. The percentage of patients experiencing at least one TEAE was generally larger in the elder subgroup as expected, but no relevant differences between the treatment groups became obvious.

Renal insufficiency:

In patients with renal impairment (eGFR<60 mL/min/1.73m^2 (see table below), a similar frequency of treatment emergent serious adverse events (SAEs) was observed with Vazkepa (40.2%) compared to placebo (39.3%). There were no drug-related SAEs for Vazkepa, versus one for placebo. Frequencies of drug-related treatment emergent adverse events (TEAEs) leading to withdrawal of study drug, SAEs leading to withdrawal of study drug, and SAEs leading to death were low and similar between the Vazkepa and placebo treatment groups.

A review of the individual TEAEs and SAEs in the sub-group with eGFR of <60 mL/min/1.73m^2 was similar to the overall safety profile for the entire Safety Population. As would be expected, frequencies of SAEs were higher in the sub-group with eGFR <60 mL/min/1.73 m^2 compared to subjects with ≥60 mL/min/1.73 m^2. A review of SAEs by system organ class (SOC) did not reveal any SOC with a marked imbalance between treatment groups for the sub-group of subjects with eGFR <60 mL/min/1.73 m^2.

Table 1 Overview of Treatment-Emergent Adverse Events by Baseline eGFR (ITT Population + Baseline eGFR)

Parameter	eGFR <60 mL/min/1.73m²		eGFR ≥60 mL/min/1.73m²	
	Vascepa (N=905)	Placebo (N=911)	AMR101 (N=3180)	Placebo (N=3177)
Subjects with at Least One TEAE, n (%)	794 (87.7)	778 (85.4)	2548 (80.1)	2546 (80.1)
Severe TEAE	241 (26.6)	237 (26.0)	564 (17.7)	578 (18.2)
Drug-related TEAE [1]	122 (13.5)	102 (11.2)	392 (12.3)	397 (12.5)
Serious TEAE	364 (40.2)	358 (39.3)	888 (27.9)	896 (28.2)
Drug-related serious TEAE [1]	0	1 (0.1)	8 (0.3)	4 (0.1)
TEAE Leading to Withdrawal of Study Drug [2]	107 (11.8)	94 (10.3)	214 (6.7)	241 (7.6)
Drug-Related TEAE Leading to Withdrawal of Study Drug [1,2]	37 (4.1)	38 (4.2)	102 (3.2)	126 (4.0)
Serious TEAE Leading to Withdrawal of Study Drug [2]	31 (3.4)	31 (3.4)	57 (1.8)	57 (1.8)
Serious TEAE Leading to Death	38 (4.2)	41 (4.5)	56 (1.8)	61 (1.9)
Drug-Related Serious TEAE Leading to Withdrawal of Study Drug [1,2]	0	1 (0.1)	2 (0.1)	3 (0.1)

Note: A treatment-emergent adverse event (TEAE) is defined as an event that first occurs or worsens in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study.
Percentages are based on the number of subjects randomised to each treatment group in the ITT population (N). Events that were positively adjudicated as clinical endpoints are not included.
[1] Drug-related TEAEs include those characterised as related, probably related, or possibly related.
[2] Withdrawal of study drug excludes subjects who were off drug in study (ODIS) for 30 days or more, and restarted study drug.

Hepatic impairment

A total of 517 patients (269 in the Vazkepa an d 248 in the plc group) were identified in the REDUCE-IT study who had signs of liver disease at the time of recruitment. Assumption of liver disease was based on history and on elevated serum liver parameters at baseline. A classification of the severity of liver impairment, e.g. by the Child-Pugh-Score, was not performed.

No relevant imbalances in total AE incidence between Vazkepa and plc became obvious in the subpopulation of subjects with hepatic disorders (222 subjects [82.5%] in the Vazkepa and 206 subjects [83.0%] in the plc group of this subpopulation suffered at least one TEAE). Regarding AEs per organ class or specific types of AEs, the picture was similar to that observed in the whole study population.

Immunological events

No special studies were performed. EPA is thought to affect inflammatory processes because it can serve as a precursor for prostaglandins and leukotrienes. AEs related to allergic conditions were numerically more frequent in the Vazkepa than in the plc group of the REDUCE-IT study (2.4% vs. 1.7%). Furthermore, dermatitis and eczema were numerically more frequent in the Vazkepa group (3.6% vs. 2.9%).

Safety related to drug-drug interactions and other interactions

No studies on safety related to drug-drug interaction were performed. For potential PK interactions see respective section above.

Discontinuation due to adverse events

Overall, 3.7% of study participants discontinued due to an AE. Discontinuation rate was slightly higher in the plc (mineral oil) group than in the Vazkepa group, 4.0% vs. 3.4%, plc vs. Vazkepa. This difference was mainly driven by diarrhoea (1.6% vs. 1.0%, plc vs. Vazkepa). Vice versa, nausea and arthralgia/arthritis were a more frequent reason for discontinuation in the Vazkepa group compared to plc. For further details, see table below.

Table 35 Study Drug-Related Treatment-Emergent Adverse Events Leading to Study Drug Withdrawal Occurring at an Incidence of ≥0.1% in Either Treatment Group, REDUCE-IT (Safety Population)

System Organ Class **Preferred Term**	**Vazkepa (N=4089) n (%)**	**Placebo (N=4090) n (%)**	**Overall (N=8179) n (%)**
Patients with at least 1 study drug related TEAE leading to study drug withdrawal	139 (3.4)	164 (4.0)	303 (3.7)
Gastrointestinal disorders	97 (2.4)	121 (3.0)	218 (2.7)
Diarrhoea	41 (1.0)	66 (1.6)	107 (1.3)
Nausea	16 (0.4)	11 (0.3)	27 (0.3)
Abdominal discomfort	6 (0.1)	6 (0.1)	12 (0.1)
Flatulence	6 (0.1)	6 (0.1)	12 (0.1)
Gastroesophageal reflux disease	5 (0.1)	3 (0.1)	8 (0.1)
Abdominal pain upper	4 (0.1)	5 (0.1)	9 (0.1)
Dyspepsia	4 (0.1)	5 (0.1)	9 (0.1)
Constipation	4 (0.1)	2 (0.0)	6 (0.1)
Gastric disorder	4 (0.1)	0 (0.0)	4 (0.0)
Eructation	3 (0.1)	4 (0.1)	7 (0.1)
Vomiting	3 (0.1)	4 (0.1)	7 (0.1)
Abdominal distension	3 (0.1)	3 (0.1)	6 (0.1)
Abdominal pain	1 (0.0)	3 (0.1)	4 (0.0)
Abnormal faeces	0 (0.0)	3 (0.1)	3 (0.0)
Skin and subcutaneous disorders	16 (0.4)	15 (0.4)	31 (0.4)
Rash	3 (0.1)	8 (0.2)	11 (0.1)
Pruritus generalised	3 (0.1)	0 (0.0)	3 (0.0)
Skin odor abnormal	3 (0.1)	0 (0.0)	3 (0.0)
Pruritus	1 (0.0)	3 (0.1)	4 (0.0)
Musculoskeletal and connective tissue disorders	13 (0.3)	10 (0.2)	23 (0.3)
Arthralgia	7 (0.2)	2 (0.0)	9 (0.1)
Arthritis	3 (0.1)	0 (0.0)	3 (0.0)
Muscle spasms	0 (0.0)	3 (0.1)	3 (0.0)
Immune system disorders	4 (0.1)	0 (0.0)	4 (0.0)
Hypersensitivity	3 (0.1)	0 (0.0)	3 (0.0)

Post marketing experience

Vazkepa was approved in the US in July 2012 and has been commercially available in the US since January 2013. Vazkepa was most recently approved for marketing in Lebanon and United Arab Emirates in March 2018 and July 2018, respectively. On 19 February 2016, FDA opened a Tracked Safety Issue for Vazkepa regarding liver injury, under the classification of "standard." As of 30 June

2016, FDA had determined that "no action is necessary at this time based on available information". Amarin continues to monitor all hepatic reports as events of special interest as part of the safety surveillance.

Over the first 7 years of post-approval safety surveillance (26 July 2012 to 25 July 2019), there were a total of 1204 unique reports of which 48 were serious reports. There has been one post marketing safety report resulting from the marketing of Vazkepa outside US, in Lebanon during this period. This report described elevation of triglycerides following initiation of therapy with Vazkepa.

The most frequently reported adverse reactions include arthralgia, product taste abnormal, blood triglycerides increased, diarrhoea, nausea and eructation. No action has been taken for safety reasons during this period.

Reports on serious events

During the period 26 July 2012 to 25 July 2019, there was a total of 48 expedited (15-day Alert) reports (i.e., serious and unlabelled) reporting 69 events. There were four reports with a fatal outcome during this period. Briefly, one report of death by suicide; one report of an accidental death by fire and two reports of death of unknown cause while taking Vazkepa were received. There were three serious adverse events assessed by the reporter as possibly related to Vazkepa and the events included coronary artery occlusion, neonatal respiratory distress disorder and elevated liver enzymes. Of these only the events of neonatal distress syndrome and elevated liver enzymes were also assessed by the applicant as possibly related. There were an additional 13 serious adverse events evaluated by the applicant to be possibly related to Vazkepa. These included two reports of choking/choking sensation, two reports of epistaxis and one report each of atrial fibrillation, diarrhoea, dyspnoea, hypersensitivity, loss of consciousness, nausea, presyncope, prostate cancer, and syncope.

Reports on non-serious events

The most common SOC was Gastrointestinal Disorders and the most frequently reported events included diarrhoea, nausea, eructation, abdominal pain, abdominal pain upper, abdominal discomfort, dyspepsia, dysphagia, abdominal distention, retching, flatulence, and vomiting. Among the Cardiac Disorders SOC, the most frequently reported terms were palpitations and atrial fibrillation.

Further findings from Periodic Adverse Drug Experience Reports (PADERs)

Upon a review of the provided PADERs, 19 cases reporting bleeding events were identified, out of which 7 were reported in the last PADER (from 26-Jul-2018 to 25-Jul 2019). In 9 from the 19 cases the respective bleeding event was assessed by the company to be possibly causally associated with Vazkepa and to be non-serious. Furthermore, several reports of events related to hepatic disorders were identified. A total 6 post-marketing cases of atrial fibrillation were identified by the Assessor. In all 6 cases a reasonable time relationship between the use of Vazkepa and the occurrence of atrial fibrillation is recognizable. Two of the 6 cases were reported as serious cases.

2.6.1. Discussion on clinical safety

Safety assessment of Vazkepa is mainly based on the results of the large phase 3 trial REDUCE-IT.

In general, Vazkepa was well tolerated. The incidence of any adverse events (AEs) and serious AEs was equally distributed between the treatment groups in REDUCE-IT. AEs leading to withdrawal of study drug were rather infrequent (in around 8% of patients) and numerically slightly higher in the plc group. In the pooled phase 2 trial ANCHOR and MARINE, AEs and SAEs were numerically less frequent in the Vazkepa than in the plc group.

A numerical increase in the incidence of specific, frequent AEs in the Vazkepa compared to the plc group was observed for the MedDRA terms musculoskeletal pain, constipation, peripheral oedema and atrial fibrillation (AF). Regarding constipation, it should be noted that the plc substance, mineral oil, is known to act as a laxative so that Vazkepa most likely does not increase constipation but plc decreases it. Vice versa, anaemia was more frequently observed in the plc than in the Vazkepa group.

A more detailed analysis of AF events revealed that the increase in incidence with Vazkepa predominantly occurred in patients with a history of AF. For these patients, a regular ECG monitoring was recommended in the SmPC to allow early diagnosis which may increase the chance of successful treatment of AF.

Diarrhoea was rather frequent in both treatment groups, affecting around 10% of patients. For the plc (mineral oil) group this is expected but the question remains whether Vazkepa also can induce diarrhoea. If so, the mechanism would be unclear. Mineral oil is thought to act as laxative because it is not absorbed in the gut, but the latter should not be the case for EPA. On the other hand, it is not clear whether Vazkepa or mineral oil (in the amount used as plc) caused diarrhoea at all; due to the rather long duration of the REDUCE-IT study, it cannot be excluded that diarrhoea of other causes occurred at least once in 10% of the participants. It is stated in the AE table in section 4.8 of the SmPC that c**onstipation** as adverse reaction of Vazkepa was recorded with frequency common. It is also mentioned (from post-marketing data) that Vazkepa is associated with diarrhoea. It is clarified in section 4.8 that the relative incidence of constipation in this study may have been confounded by a residual laxative effect for placebo, which comprised a subtherapeutic dose of light mineral oil (4 mL).

Among the less frequent AEs, there was a numerical increase in the Vazkepa compared to the plc group in respect to **hyperuricemia and gout, cardiac conduction disorders** such as bundle branch block, dermatitis, eczema and rash as well as for allergic conditions (mainly hypersensitivity). The latter could be related to EPA's effects on inflammation via metabolism via COX and LOX to prostaglandin and leukotriene derivates. The reason for the cardiac effects (atrial fibrillation, conduction disorders) is not known. A potential mechanism could be related to the fact that EPA can inhibit several cardiac ion channels in micromolar concentrations (see non-clinical part); however, it is not clear whether the circulating EPA concentrations are sufficient for relevant channel inhibition because EPA is highly bound to plasma proteins.

Regarding hyperuricemia and gout, a recommendation for regular determination of serum urate level during Vazkepa treatment is not considered necessary because AEs of gout were predominantly reported in patients with pre-existing gout. Thus, Vazkepa may increase the number of gout attacks, but in subjects with known gout the disease is regularly monitored anyway.

Increased incidence in the plc compared to the Vazkepa group of REDUCE-IT was observed for **hyperglycaemia** (58.5% of study participants had diabetes mellitus), for **electrolyte disturbances** (hyperkalaemia, hypomagnesaemia) and for AEs of ventricular arrhythmias. Further evaluation of hyperglycaemia events and glycaemic control in study participants with known diabetes did not reveal any relevant effects of Vazkepa on HbA1c level, fasting blood glucose and hypoglycaemia rate.

Bleeding events were regarded as AEs of special interest since prior experience with ω3 fatty acids containing oil. Bleeding-related AEs were slightly more frequent with Vazkepa than with plc in REDUCE-IT. This was also true for serious bleeding events and CNS bleeding (including subdural haematoma), but the number of these events was low. Increased bleeding risk could be associated with lower risk of thrombosis which in turn may contribute to the beneficial CV outcome as it is observed e.g. for ASA. The difference in bleeding rate between Vazkepa and plc was rather small. This is also true for patients taking antiplatelet drugs because this was the case for nearly 80% of participants in the REDUCE-IT study. The applicant conducted further analyses. It turned out that the bleeding risk is particularly

higher in patients concomitantly taking anti-coagulant or anti-platelet agents. A warning that patients taking icosapent ethyl along with antithrombotic agents, i.e., antiplatelet agents, including acetylsalicylic acid, and/or anticoagulants, may be at increased risk of bleeding and should be monitored periodically was included in the SmPC. The phase 2 studies were too small for meaningful conclusions on bleeding risk, but also in these studies bleeding events appeared to be more frequent in the Vazkepa group despite higher use of antiplatelet and anticoagulant medication in the plc group.

Some laboratory parameters (**haematology, serum chemistry**) were consistently altered by Vazkepa or mineral oil. In line with increased anaemia in the plc group, it was observed that mean haemoglobin levels increased vs. plc in the Vazkepa group in the first few years of treatment. Thereafter, the difference between the Vazkepa and plc group in Hb level remained constant. Notably, erythrocyte count did not change in accordance with the Hb change but remained virtually constant in both treatment groups. This implies increased Hb content per erythrocyte (although this was not determined in the study) with Vazkepa vs. plc. Increased Hb content per erythrocyte could be linked to deficiency of vitamin B_{12} or other nutrients so that either EPA or mineral oil could interfere with their absorption in gut. Otherwise, an effect on bone marrow is conceivable. The applicant discussed this possibility and considered it unlikely that mineral oil interferes with the intestinal absorption of nutrients. A main argument was that patients with signs for anaemia due to malabsorption were not over-represented in the mineral oil group.

There was a slight but steady increase in mean levels of **total bilirubin** in the Vazkepa-treated patients and a more pronounced decrease vs. baseline in subjects treated with plc (mineral oil). Accordingly, markedly more subjects in the Vazkepa than in the plc group had bilirubin levels above upper normal limit. A similar phenomenon was observed for **creatine kinase** (CK). The underlying biologic processes are unclear. The applicant could not provide a mechanistic explanation. These findings may indicate that mineral oil has some biological effects, but since the changes were small, they have no clinical relevance.

Vice versa, mean serum levels of **alkaline phosphatase** (AP) markedly increased over time during the study in the plc group (and slightly decreased in the Vazkepa group). Accordingly, AP above upper normal limit was more frequently observed in the plc group. The relevance of this finding is unclear, particularly because AP can originate from various different tissues so that it is even unclear which organ or tissue is affected by mineral oil treatment. The Applicant could not provide a mechanistic explanation. The Applicant doubted that mineral oil can exert biological actions at all because it becomes absorbed in very small amounts only; the described laboratory changes from baseline could be due to the underlying disease. On the other hand, a biological effect of mineral oil cannot fully be excluded since there are e.g. nutrient receptors on the surface of the intestinal mucosa which trigger release of gut hormones. These receptors could be a target for mineral oil although there are no clear hints for this in the published literature.

Mineral oil also caused changes in serum lipoproteins (increase of LDL-cholesterol and of apo-B) as well of increase in CRP. The changes were small, but this does not exclude relevant biological sum effect. It should be noted that the situation is similar for EPA. Its beneficial effects are thought to arise from the sum of many small effects on different organ systems, including e.g. lipid metabolism, inflammation, plaque stability and maybe coagulation. Thus, it is difficult to predict how large a potentially unfavourable effect of mineral oil on CV endpoints could be. Since Vazkepa was tested against mineral oil, it is unclear how large the remaining beneficial effect of EPA is when the unfavourable effect of mineral oil is subtracted. The Applicant argued that mineral oil is known to be safe and well-tolerated from its use as laxative. However, it is difficult to exclude any increased CV risk based on standard safety data.

Vital signs (heart rate, blood pressure and ECG) were not relevantly affected by Vazkepa or mineral oil. Regarding **body weight**, it was remarkable that there was no mean weight gain in the study participants during five years of treatment; to the contrary, weight loss of 1 kg and 2 kg in mean was observed for Vazkepa and plc, respectively. In the study population, like in the general population, body weight is expected to increase over the years. This may indicate that Vazkepa and mineral oil decreases appetite; alternatively, this was because the study participants (nearly 60% subjects had diabetes mellitus) strictly followed the lifestyle recommendations for diabetes such as diet and exercise. The applicant confirmed that no special reinforcement of life-style measures took place in the REDUCE-IT study. Rather, the participants followed the standard recommendations for subjects with increased weight, plasma lipids and CV risk. The applicant also pointed out that the mean age of the study participants was above 60 years and at this age, the annual body weight increase usually becomes lower or ceases completely.

In order to assess safety in **renally impaired patients**, the applicant performed an AE analysis stratified for subjects with eGFR at or above 60 mL/min vs. below 60 mL/min. As expected, patients with eGFR<60 experienced more AEs, irrespective of study treatment (Vazkepa or plc). No increased AE incidence vs. plc became obvious in the group of patients with moderate or severe renal impairment.

In order to address safety in patients with **hepatic disorders**, the Applicant defined criteria to identify patients with potential hepatic disorders at study entry. These criteria included patient history and laboratory values. Classification according to the severity of hepatic impairment, e.g. by the Child-Pugh score, was not performed. In the subgroup of patients with potential baseline hepatic disorder, the AE profile was not relevantly different from the total study population. Thus, no safety signals became obvious from this analysis.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

No major safety issues were identified with Vazkepa. Interpretation of the safety results is hampered by the fact that the direct and indirect biological effects of EPA probably affect many organ systems but are hardly understood, particularly how they are linked to the desired CV benefit. Furthermore, the substance used as placebo, mineral oil, had effects of its own. Therefore, it cannot always be decided whether observed changes in AE frequency or laboratory values reflect an effect of EPA or an effect of mineral oil. The application was considered acceptable from the clinical safety point of view.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Bleeding in patients on anti-thrombotic therapy Atrial fibrillation/flutter
Important potential risks	None

Summary of safety concerns	
Missing information	Use in pregnant and breast-feeding women

Pharmacovigilance plan

Table Part III.3.1: On-going and planned additional pharmacovigilance activities

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
- None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
- None				
Category 3 - Required additional pharmacovigilance activities				
- None				

Risk minimisation measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	**Routine risk minimisation activities**
Bleeding in patients on anti-thrombotic therapy	*SmPC section 4.4 and 4.8* *PL section 2 and 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Recommendation for periodic monitoring of patients receiving Vazkepa together with anti-thrombotic agents in SmPC section 4.4.* Other routine risk minimisation measures beyond the Product Information: Legal status: *Prescription only medicine*
Atrial fibrillation/flutter	*SmPC section 4.4 and 4.8* *PL section 2 and 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Recommendation to monitor for clinical evidence of atrial fibrillation or atrial flutter (e.g., dyspnoea, palpitations, syncope/dizziness, chest discomfort, change in blood pressure, or irregular pulse) and to perform electrocardiographic evaluation when clinically indicated in SmPC section 4.4.* Other routine risk minimisation measures beyond the Product Information: Legal status: *Prescription only medicine*
Missing information: Use in pregnant and breast-feeding women	*SmPC section 4.6 and 5.3* *PL section 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Not applicable* Other routine risk minimisation measures beyond the Product Information: Legal status: *Prescription only medicine*

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.4 (date of final sign off 18-Dec-2020) is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 26.07.2012. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant declared that icosapent ethyl (EPA) should be considered as new active substance as it has not been previously approved as active substance in a medicinal product in the Community and it differs significantly in properties with regards to pharmacodynamic effects and biomarkers of cardiovascular risk as compared to the EPA and mixtures of constituents included in the "omega-3-acid ethyl esters 90" previously authorised in the European Union (EU).

Medicinal products containing the active substance "omega-3-acid ethyl esters 90" have been authorised in the EU since the nineties (e.g. Omacor approved at daily doses from 2 g up to 4 g for the treatment of hypertriglyceridaemia). The active substance of Omacor is "omega-3-acid ethyl esters 90" and consists of a mixture including ethyl esters of the omega-3 series polyunsaturated fatty acids (ethyl esters of alpha-linolenic acid (C18:3 n-3), moroctic acid (C18:4 n-3), eicosatetraenoic acid (C20:4 n-3), timnodonic (eicosapentaenoic) acid (C20:5 n-3; EPA), heneicosapentaenoic acid (C21:5 n-3), clupanodonic acid (C22:5 n-3) and cervonic (docosahexaenoic) acid (C22:6 n-3; DHA)).

As EPA is part of approved medicinal products containing EPA and mixtures of constituents included in the "omega-3-acid ethyl esters 90" that are licenced for the treatment of hypertriglyceridemia it could not be concluded that EPA was not previously authorised in a medicinal product for human use in the European Union and that is from a chemical structure point of view not related to any other authorised substances.

Quality aspects

The active ingredient of the finished product is ethyl ester of eicosapentaenoic acid (ethyl-EPA). The assigned INN is icosapent ethyl. The active moiety of icosapent ethyl is eicosapentaenoic acid. The manufacturing process of icosapent ethyl involves the ethyl esterification of fish oil and multiple purification procedures (such as rectification/distillation and chromatography alone or combination of rectification/ distillation with chromatography) to produce icosapent ethyl active substance that contains not less than 96.0% icosapent ethyl.

Clinical aspects

The constituents of "omega-3-acid ethyl esters 90" (including both EPA and DHA) have different pharmacological effects compared to icosapent ethyl and the latter has some qualitative specificities as developed in the above section.

The content of EPA ethyl ester in Vazkepa is twice as high as in the "omega-3-acid ethyl esters 90" active substance (96% vs 43%). These characteristics of icosapent ethyl may impact on clinical effects as compared with EPA contained in "omega-3-acid ethyl esters 90".

Although the relative contribution of ethyl-EPA and ethyl-DHA and the other constituents of the active substance "omega-3-acid ethyl esters 90" has not been evaluated to support the MA, it is documented that the active moiety of icosapent ethyl, i.e., EPA, has different biological and pharmacodynamic effects than the constituents of "3-omega-acid ethyl esters 90", including both EPA and DHA. Most notably, whereas both EPA and DHA have been reported to reduce triglycerides (TG), DHA alone with EPA has been reported to be associated not only with reduction of TG levels, but also, importantly, with significant increases in low-density lipoprotein cholesterol (LDL-C) in subjects with lipid disorder.

Most importantly, icosapent ethyl differs significantly in properties with regards to efficacy compared to EPA and mixtures of constituents contained together in "omega-3-acid ethyl esters 90", as demonstrated in single pivotal trial REDUCE-IT. In REDUCE-IT trial icosapent ethyl significantly reduced the risk for the primary composite endpoint (time to first occurrence of cardiovascular death, myocardial infarction, stroke, coronary revascularisation, or hospitalisation for unstable angina; $p<0.0001$) and the key secondary composite endpoint (time to first occurrence of cardiovascular death, myocardial infarction, or stroke; $p<0.0001$). The beneficial effects of icosapent ethyl as demonstrated in the pivotal trial in patients with hypertriglyceridemia and increased CV risk on baseline statin therapy in the primary and secondary CV prevention represent a clinically meaningful benefit for the patients that has not been demonstrated with EPA and mixtures of constituents contained in "omega-3-acid ethyl esters 90" (see VITAL, ASCEND, STRENGTHT III, OMEMNI and JELIS studies – in the benefit-risk section of this AR). Therefore, it is considered that icosapent ethyl differs significantly in properties with regard to efficacy from substances previously authorised in the EU.

Conclusion

The CHMP considers, based on the available quality and clinical data, that the icosapent ethyl is considered to be a new active substance as it differs significantly in properties with regard to efficacy from EPA and mixtures of constituents contained in medicinal product(s) previously authorised within the European Union ("omega-3-acid ethyl esters 90").

2.10. Product information

2.10.1. 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.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Vazkepa (icosapent ethyl) is included in the additional monitoring list as It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Vazkepa is indicated to reduce the risk of cardiovascular events in adult statin-treated patients at high cardiovascular risk with elevated triglycerides (≥150 mg/dL) and

- *established cardiovascular disease, or*
- *diabetes, and at least one other cardiovascular risk factor.*

For study details including cardiovascular risk factors and results with respect to effects on cardiovascular events see section 5.1.

In the EU, cardiovascular diseases (CVD) cause over 1.8 million deaths each year, which accounts for 37% of all deaths (European Heart Network Report, 2017). In 2015, there were 6.1 million new cases of CVD in the EU and almost 49 million people were living with CVD in the EU. Half of these new CVD cases were due to ischaemic heart disease, while around 10% of new CVD cases were due to stroke.

Hypertriglyceridaemia (HTG) has been shown to be an independent risk factor for CVD. High TG levels are often associated with low HDL-C and high levels of small dense LDL particles. The burden of HTG is high, with about one-third of adult individuals having TG levels >1.7 mmol/l (150 mg/dL) (Bergheanu SC et al. Neth Heart J 2017; Catapano AL et al., Eur Heart J. 2016).

Prevalence of severe HTG (500 to 2,000 mg/dl) is rare (Christian JB et al. Am J Cardiol 2011) but elevated triglycerides at 150 mg/dL are a frequent observation. In Europe, the overall prevalence of hypertriglyceridemia (> 150 mg/dL) has been reported at 29.6% (Qiao Q, Group DS Diabetologia 2006), while the prevalence of hypertriglyceridemia in individuals with coronary artery disease ranges between 21.1 and 44.6 % (KotsevaK et al., Eur J Cardiovasc Prev Rehabil 2009.

Lp(a) is a specialised form of LDL and consists of an LDL-like particle and the specific apolipoprotein (apo) A. Elevated Lp(a) is an additional independent risk marker and genetic data made it likely to be causal in the pathophysiology of atherosclerotic vascular disease and aortic stenosis (Kronenberg F et al., J Int Med. 2013).

3.1.2. Available therapies and unmet medical need

In addition to available measures and therapies aiming at improvement of life style and other CV risk factors, current treatments for prevention of cardiovascular events in patients with elevated lipids include drugs that lower lipid levels include statins, PCSK9 inhibitors, selective cholesterol absorption inhibitors (e.g. ezetimibe), fibrates, niacin (nicotinic acid) and bile acid sequestrants (anion exchange resins). Considering that patients as included in the pivotal REDUCE-IT trial remain at high or very high risk for MACE events and CV death despite of optimal baseline therapy, there is an unmet medical need for additional therapeutic options.

3.1.3. Main clinical studies

The application is mainly based on one pivotal trial the REDUCE IT trial. It was a Phase 3 randomised, placebo controlled, cardiovascular events driven study in patients with moderately elevated TG (≥1.5 and <5.6 mmol/L [≥135 and <500 mg/dL], after amendment 1: ≥2.26 mmol/L (200 mg/dL) and <500 mg/dL) on statin therapy and at high risk for CVD. Patients received 2 g of icosapent ethyl twice daily (BID) (4 g/day) or matching placebo (mineral oil).

In addition to TG thresholds as an inclusion criterion, patients were included in two separate groups based on CV risk at baseline (intended ratio 70/30% Group 1/Group 2):

- CV Risk Category 1 (Secondary Prevention Cohort): men and women ≥45 years with documented coronary artery diseases (CAD), cerebrovascular or carotid disease, or peripheral arterial disease (PAD).
- CV risk category 2 (Primary Prevention Cohort): Men and women ≥ 50 years of age with diabetes mellitus (Type 1 or Type 2) and additional predefined risk factors (smoker, higher age, hypertension, renal dysfunction, retinopathy, micro- or macroalbuminuria, or Ankle brachial index (ABI) <0.9 without symptoms).

Randomization was stratified by CV risk category, use of ezetimibe (yes/no), and by geographical region (Westernized, Eastern European, and Asia Pacific).

3.2. Favourable effects

Primary endpoint: 5-fold MACE (CV death, nonfatal MI, nonfatal stroke, coronary revascularisation, unstable angina caused by myocardial ischemia and associated with emergent hospitalisation)

A primary endpoint event occurred in 17.2% (705/4089) of patients in the AMR101 group, as compared with 22.0% (901/4090) of patients in the placebo group (HR of 0.752 [95% CI: 0.682 to 0.830; p=0.00000001]; relative risk reduction [RRR] of 24.8% and number needed to treat [NNT] of 21). The median follow-up duration for the primary endpoint was 4.7 and 4.5 years for the AMR101 and placebo groups, respectively. The effect of AMR101 became observable after approximately 1.5 years of treatment. All 5 components of the primary composite endpoint contributed to the overall statistically significant result. In a landmark analysis a significantly lower risk of major adverse CV events with AMR101 than with placebo (HR of 0.799 [95% CI: 0.693 to 0.920; p=0.0017]) was observed at the 2-year landmark.

Key secondary composite endpoint analysis (3-fold MACE: CV death, nonfatal MI, nonfatal stroke)

The key secondary endpoint is considered most important for the assessment of efficacy. The median follow-up duration for the key secondary endpoint was 4.8 and 4.7 years for the AMR101 and placebo groups, respectively. A key secondary endpoint event occurred in 11.2% (459/4089) of patients in the AMR101 group, as compared with 14.8% (606/4090) of patients in the placebo group (HR of 0.735 [95% CI: 0.651 to 0.830; p=0.0000006]; RRR of 26.5% and NNT of 28). Similar to the primary endpoint result, there was a lag time of about 1.5 years before differences between the groups became apparent.

Results for the individual components of the primary and key secondary endpoint.

All components contributed to the overall result (results for first event in each class, AMR101 vs. placebo, events (%), HR (95% CI), p value)):

- CV death: 174 (4.3%) vs. 213 (5.2%), HR 0.803 (0.657, 0.981, p = 0.03),

- Nonfatal myocardial infarction: 237 (5.8%) vs. 332 (8.1%), HR 0.697 (0.590; 0.823, p < 0.0001),
- Nonfatal stroke: 85 (2.1%) vs. 118 (2.9%), HR 0.708 (0.536, 0.936, p = 0.01),
- Coronary revascularisation: 376 (9.2%) vs. 544 (13.3%), HR 0.664 (0.583 0.758, p < 0.0001),
- Hospitalization for unstable angina: 108 (2.6%) vs. 157 (3.8%), HR 0.679 (0.531, 0.868, p = 0.002).

Other secondary endpoints

Statistically significant reductions in time to event (first event, ITT) were observed for the following secondary endpoints (predefined hierarchical testing):

CV death or nonfatal MI; fatal of nonfatal MI; urgent or emergent revascularisation; CV death; hospitalization for unstable angina; fatal or nonfatal stroke; total mortality, nonfatal MI or nonfatal stroke (AMR101 vs. placebo, events (%), HR (95% CI), p value): 549 (13.4%) vs. 690 (16.9%), HR 0.772 (0.690, 0.864, p <.0001). For total mortality the numerical difference between the two groups did not reach statistical significance: 274 (6.7%) vs. 310 (7.6%), HR 0.870 (0.739, 1.023. p = 0.0915.

Overall, the results for the primary endpoint were consistent for most of the predefined subgroups.

Geographical region, ezetimibe use, sex, hsCRP, eGFR, LDL-C, HDL-C, Apo-B, Non-HDL-C and TG at baseline had no significant impact on efficacy as determined by the primary endpoint. A significant p value for interaction was observed for age < 65 and ≥ 65 years with lower efficacy at the higher age group. Although not significant (p value for interaction 0.1388), overall efficacy tended to be lower in the primary prevention cohort:

- Primary prevention: 146/1197 (12.2%) vs. 163/1197 (13.6%), HR 0.876 (0.700, 1.095)
- Secondary Prevention: 559/2892 (19.3%) vs. 738/2893 (25.5%), HR 0.726 (0.650, 0.810)

Results for additional tertiary composite CV composites combining CV death and other CV events and of several additional tertiary endpoints were consistent with the results for the primary and key secondary analysis.

3.3. Uncertainties and limitations about favourable effects

There are three main areas of uncertainty identified: (1) the choice of the comparator might have biased the results in favour of Vazkepa, (2) the mechanism of action is to some degree unclear and (3) there were uncertainties regarding the external validity of the study.

(1) Mineral oil as a comparator

Mineral oil (paraffin oil) was chosen as placebo, but it is not clear that mineral oil in fact is entirely inert. Some of the markers relevant for prognosis showed a trend toward deterioration in the mineral oil arm. Small numerical increases were observed for TG, non-HDL-C, LDL-C, apoB, and hsCRP. Change from baseline in systolic BP showed a small difference between the groups. Whether these observations just represented a natural course, were due to variability and regression to the mean effects, or represented a negative effect of mineral oil is not clear. Based on published literature, an increase in LDL-C by 7 – 9.3 mg/dl might translate into an increase in MACE events by about 4 – 5%, an increase in Apo B by 6.0 mg/dL, into an increase in CAD by about 5%, and in major cardiovascular disease risk by 4%, an increase in hsCRP by 0.5 mg into an increase by 4 – 5% in ischemic stroke and

coronary artery disease and an increase by 11% in vascular deaths. A difference in systolic blood pressure by 0.6 – 1.5 mmHg may translate into a difference in CV event rates by about 2%. Taking into consideration that such effects cannot be independently summed up, in a worst-case scenario attributing all of these effects to mineral oil, a putative negative impact of mineral oil on MACE should be below 10%. However, this is still an overestimation. Regression to the mean effects and the natural course of the disease may considerably have contributed to the increase in LDL-C and apoB. Furthermore, the scenario does not consider that the increase in HDL-C could be beneficial. Analyses taking physicochemical properties of drugs, efficacy and bleeding patterns into account did not indicate a major impact of mineral oil on absorption of statins, antiplatelet drugs and anticoagulants. However, e.g. the analyses of bleeding patterns were hampered by the fact that Vazkepa itself increases the risk of bleeding. Based on analyses as provided by the applicant, a putative negative effect of mineral oil should not account for more than 0.3 – 3% of MACE events. In summary, it is concluded that even when assuming the unlikely worst-case scenario, the remaining beneficial effect of Vazkepa on MACE events can be considered robust and meaningful.

(2) The mechanism of action was not clear

A dose dependent pronounced TG lowering effect has been demonstrated. However, TG lowering therapy has not consistently been shown to result in a CV benefit with other medicinal products. Numerous proposed mechanisms of action have been discussed in the public domain, including effects on platelet aggregation, anti-inflammatory actions, improvement in endothelial and vascular and plaque stabilizing effects. Some of these effects were described to be pronounced in the presence of statins. All patients in the study were on baseline statin therapy, however, subgroup analyses indicated that efficacy of Vazkepa possibly is lower in patients on low dose statin therapy. This does not necessarily indicate a positive interaction of Vazkepa with statins but rather may be related to the overall lower CV risk in patients receiving only low dose statins. Some of acute mechanisms of action as described in the literature do not necessarily fit with the observation in REDUCE-IT of a lag time of about 1.5 years before efficacy is observed. The applicant has provided post hoc analyses from the REDUCE IT trial indicating a correlation between efficacy on MACE and EPA levels. However, these data are not conclusive due to sparse sampling and the post hoc nature of the analysis with a large impact of imputation rules on the final results.

(3) External validity of the study

Recently EMA (EMEA/H/A-31/1464) has concluded that omega-3 acid ethyl esters – containing medicinal products for oral use are not effective in the secondary prevention after myocardial infarction. This conclusion was based on an analysis of all available data including the GISSI P study (1999), the OMEGA trial, Rauch et al 2008 and meta-analyses. Relevant differences to the data provided within this application are the lower dose used in these studies (1 g daily vs. 4 g Vazkepa) and the composition.

It has been demonstrated within this application that effects on TGs and on some other lipid parameters are dose dependent and considerably more pronounced at the 4 g daily dose as compared to the 2 g daily dose.

Vazkepa contains EPA only, whereas the medicinal products analysed by EMA within EMEA/H/A-31/1464 contained a mixture of EPA and DHA. Different membrane locations and lipid interactions of EPA and DHA may contribute to differences in biological activity (e.g. Sherratt SCR and Mason P Chemistry and Physics of Lipids 2018; 212: 73 – 79).

Wei MY and Jacobson TA (2011 Curr Atheroscler Rep; 13: 474-83) described based on a meta-analytical analysis that both EPA and DHA reduce TG (DHA> than EPA). DHA raised LDL-C and HDL-C whereas EPA non-significantly reduced LDL and had no effect on HDL. The authors speculated that the

greater decrease in triglycerides (and increase in LDL) observed with DHA may result from greater lipoprotein lipase activation by DHA compared with EPA. Based on such considerations it may well be that the clinically relevant effects are different between EPA and DHA.

In addition, two other recent studies failed to show a beneficial effect on CV outcome.

In the VITAL study (N Engl J Med 2019; 380:23-32) no beneficial effect of marine n−3 fatty acids (at a dose of 1 g per day) could be demonstrated in a primary prevention setting (HR for the primary composite MACE endpoint: 0.92 (0.80 – 1.06). Numerically the number of MIs were reduced (145 vs. 200 events, HR 0.72 (0.59 – 0.90)) but no beneficial effect on total stroke or death from CV causes could be demonstrated. Similarly, the ASCEND trial (Wallendszus K et al, N Engl J Med 2018;379:1540-1550.) which tested n−3 supplementation (at a dose of 1 g per day) in adults with diabetes in the United Kingdom, also showed generally null results.

All of these trials investigated lower doses and a different composition of the medicinal product.

Recently the STRENGTH study, a CV outcome trial investigating 4g/day Omega 3-carboxylic acid (containing EPA and DHA) on CV outcome in statin-treated patients with high cardiovascular risk, hypertriglyceridemia, and low levels of high-density lipoprotein cholesterol (HDL-C) has been terminated (JAMA. doi:10.1001/jama.2020.22258 Published online November 15, 2020) based on an interim analysis that indicated a low probability of clinical benefit. With 13078 patients randomized the primary end point occurred in 785 patients (12.0%) treated with omega-3 CA vs 795 (12.2%) treated with corn oil (hazard ratio, 0.99 [95%CI, 0.90-1.09]; P = .84). In this trial corn oil was used as a comparator.

In addition, the recently published OMEMI study (10.1161/CIRCULATIONAHA.120.052209) did not show a benefit of 1.8 g n-3 PUFA (930 mg EPA and 660 mg DHA) versus placebo (corn oil) daily to standard of care in 70-82 years old patients with recent (2-8 weeks) acute myocardial infarction.

It is noted that none of the negative trials used mineral oil as a comparator.

Some external support comes from the JELIS trial (Lancet. 2007 Mar 31;369:1090-8) a study that in a PROBE design investigated efficacy and safety of 1800 g EPA daily on top of statins vs. statins alone in hypercholesteraemic patients in Japan on a broadly defined composite CV endpoint. The primary endpoint showed a statistically significant result although questions arise concerning the definition of the endpoint components and the numerical increase in all-cause mortality, haemorrhagic strokes and a lack of efficacy for ischemic strokes.

Taken together, there are conflicting results reporting in this area and external support is limited. The positive results of the REDUCE-IT study have some external but not quite robust support from the JELIS trial. Most studies in the field used different comparators and failed to show a CV benefit. However, these studies used lower doses of mixtures of EPA/DHA as opposed to high dose of EPA alone used in REDUCE-IT with mineral oil as placebo.

3.4. Unfavourable effects

No major safety concern of Vazkepa was identified. The percentage of patients suffering at least one treatment-emergent adverse event (TEAE) was nearly identical between the treatment groups, Vazkepa and plc. The same was true for serious TEAEs and TEAEs leading to discontinuation.

Regarding specific AEs by organ class, a numerically higher frequency in the Vazkepa group was observed for the following terms:

- oedema peripheral

- atrial fibrillation
- musculoskeletal pain
- hyperuricaemia/Gout
- cardiac conduction disorders
- dermatitis/Eczema/Rash
- allergic conditions
- fatigue, asthenia
- dysgeusia
- bleeding

The latter was evaluated as AE of special interest since previous studies with ω3-fatty acid containing marine oil gave hints for increased bleeding risk.

Vice versa, the AE of anaemia was more frequent in the plc than in the Vazkepa group.

For all the mentioned terms, the numerical imbalance in frequency between the Vazkepa and the plc group was small so that they could at least in part be chance findings. The pharmacodynamic effects of EPA are complex so that it is difficult to predict on a mechanistic basis which AEs could be biologically plausible.

However, further analysis by the applicant revealed that bleeding risk was particularly increased in subjects concomitantly taking anti-coagulant or anti-platelet medication. AEs of gout were predominantly increased in patients taking Vazkepa and having a history of gout. Accordingly, atrial fibrillation was also more frequent with Vazkepa compared to plc predominantly in the subpopulation of subjects with history of AE. These findings indicate that bleeding, gout and atrial fibrillation are true side effects of Vazkepa. This information was included in the agreed SmPC along with the most susceptible subpopulations as mentioned above.

In addition, diarrhoea was frequently reported in the Vazkepa group (9% of patients). This condition was slightly more frequent in the plc group (11%), but this can be expected since the plc substance was mineral oil which can be used as laxative. Probably for this reason, constipation was more frequently reported in the Vazkepa than in the plc group.

There were also findings in serum chemistry and haematology parameters.

Mean haemoglobin (Hb) levels were virtually identical at baseline in the plc and Vazkepa group but increase in the latter and remained higher than plc throughout the study. Erythrocyte count remained constant so that obviously the Hb content per erythrocyte increased, although this was not measured in the study.

There were consistent changes in some serum chemistry parameters, identified by mean increase or decrease from baseline and a higher incidence of values above upper or below lower limit of normal.

- Total bilirubin slightly increased over time with Vazkepa and more pronounced decreased with plc (mineral oil)
- Alkaline phosphatase slightly decreased with Vazkepa and markedly increased with mineral oil
- Creatine kinase slightly increase with Vazkepa and markedly decreased with mineral oil

The underlying mechanism of these findings are unclear, but the magnitude of these changes was small so that they are unlikely to be of clinical relevance.

3.5. Uncertainties and limitations about unfavourable effects

In respect to AE incidence, there were some numerical imbalances between the Vazkepa and the plc group. It cannot be decided whether the difference was due to an effect of Vazkepa or an effect of the plc substance mineral oil. Evaluation of laboratory findings revealed that there were consistent changes from baseline also in the case of mineral oil treatment so that the latter appears to have effects of its own; the underlying mechanism is unclear.

The observed effects of Vazkepa and mineral oil were small, and each individual effect cannot be regarded as adverse. However, the desired effect of Vazkepa on CV outcome has also to be regarded as a sum of (in part unknown) small effects, each of which alone would be regarded minor or virtually negligible. Vice versa this means that it is difficult to predict to which extent these small effects add up to relevant adverse effects.

Increased bleeding risk could be associated with lower risk of thrombosis which in turn may contribute to the beneficial CV outcome.

The reason for the cardiac effects (atrial fibrillation, conduction disorders) is not known. A potential mechanism could be related to the fact that EPA can inhibit several cardiac ion channels in micromolar concentrations. However, it is not clear whether the circulating EPA concentrations are sufficient for relevant channel inhibition because EPA is highly bound to plasma proteins.

3.6. Effects Table

Table. Effects Table for Vazkepa indicated to reduce the risk of cardiovascular events in adult statin-treated patients at high cardiovascular risk with elevated triglycerides (≥150 mg/dL) and established cardiovascular disease, or diabetes, and at least one other cardiovascular risk factor.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Primary endpoint (5-fold MACE)	CV death, nonfatal myocardial infarction (MI), nonfatal stroke, coronary revascularization, unstable angina	Events (% of patients)	705 (17.2%)	901 (22.0%)	HR (95% CI) 0.752 (0.682 -0.830) P-value 0.00000001 The potentially negative impact of the comparator (mineral oil) on CV events.	REDUCE-IT study
Key secondary endpoint (3-fold MACE)	CV death, nonfatal myocardial infarction (MI), nonfatal stroke		459 (11.2%)	606 (14.8%)	0.735 (0.651 -0.830) P-value 0.0000006 The potentially negative impact of the comparator (mineral oil) on CV events.	

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Other secondary endpoints	Any MI		392 (9.6%)	507 (12.4%)	0.753 (0.660, 0.859 P <.0001	
	Emergent/Urgent Revascularization		250 (6.1%)	355 (8.7%)	0.688 (0.585, 0.808) p <.0001	
	CV Death		174 (4.3%)	213 (5.2%)	0.803 (0.657, 0.981) p = 0.0315	
	Unstable Angina		108 (2.6%)	157 (3.8%)	0.679 (0.531, 0.868) P = 0.0018	
	Any Stroke		98 (2.4%)	134 (3.3%)	0.720 (0.555, 0.934) P = 0.0129	
	Total Mortality/Nonfatal MI/Nonfatal Stroke		549 (13.4%)	690 (16.9%)	0.772 (0.690, 0.864) p<.0001	
	Total mortality		274 (6.7%)	310 (7.6%)	0.870 (0.739 – 0.864) P = 0.0915 Not significant but consistent	
Unfavourable Effects						
						REDUCE-IT study
Oedema peripheral		n (%)	267 (6.5)	203 (5.0)		
Atrial fibrillation			215 (5.3)	159 (3.9)	Unclear whether the circulating EPA concentrations are sufficient for relevant channel inhibition because EPA is highly bound to plasma proteins.	
Musculo-skeletal pain			176 (4.3)	130 (3.2)		
Gout			171 (4.2)	127 (3.1)		
Bleeding			482 (11.8)	404 (9.9)	Increased bleeding risk could be associated with lower risk of thrombosis which in turn may contribute to the beneficial CV outcome.	
CNS bleeding			20 (0.5)	12 (0.3)		

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Constipation			5.4%	3.6%	The relative incidence of constipation in this study may have been confounded by a residual laxative effect for placebo (mineral oil 4 mL).	

Abbreviations: MACE – major adverse cardiovascular events, CV – cardiovascular, MI – myocardial infarction

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The benefit as demonstrated for primary 5-fold MACE endpoint (CV death, nonfatal MI, nonfatal stroke, coronary revascularisation, unstable angina caused by myocardial ischemia and associated with emergent hospitalisation) and the key secondary 3-fold MACE endpoint (CV death, nonfatal MI, nonfatal stroke), which is considered even more important, is clinically relevant. The result was consistent over a wide variety of predefined subgroups, was seen in patients in two risk categories (primary and secondary prevention) and was supported by secondary endpoints (all MIs, all strokes, CV mortality, unstable angina, composite of all-cause mortality, nonfatal MIs, nonfatal strokes). Numerically, the effect on CV mortality was preserved for all-cause mortality. A benefit was also seen when recurrent events were evaluated, although the respective analysis was difficult to interpret. Irrespective of the uncertainties as discussed above, these results indicate a meaningful clinical benefit to the patients.

The wording of the proposed indication sufficiently represents the patient population with a demonstrated positive benefit/risk balance.

Overall, the safety profile can be considered rather benign. There appears to be a slightly increased risk of bleeding, particularly in subjects concomitantly taking anticoagulant or anti-platelet medication; this is considered important because it can seriously affect the use of Vazkepa (e.g. in case of intracranial bleeding). However, it should be noted that Vazkepa numerically decreased total mortality so that the overall effect of Vazkepa on mortality remains positive.

Vazkepa appears to increase the incidence of gout and atrial fibrillation, particularly in subjects with a history of the respective condition. It is assumed that these unfavourable effects are manageable with appropriate therapy and would not preclude use of Vazkepa for preventing CV events.

There were some minor changes in laboratory values in patients taking Vazkepa compared to the placebo group which most likely are not clinically relevant.

3.7.2. Balance of benefits and risks

The benefits of Vazkepa have been established in terms of important clinical outcomes although the evidence was established in a single pivotal study. The effect size is moderate but clinically meaningful.

After amending the wording of the indication and specifying age as a CV risk factor in the study description, the proposed target population appropriately reflects the study population with respect to baseline cardiovascular (CV) risk (patients at "high cardiovascular risk") and triglyceride (TG) levels (≥150 mg/dL), for which a positive benefit-risk balance has been demonstrated. The applicant stated that reference to "statin-treated patients" in the wording of indication would better reflect the inclusion criteria in pivotal study than reference to "maximally tolerated" statin therapy which was initially requested in line with the recommendations of clinical guidelines. This was considered acceptable.

The safety profile of Vazkepa was considered relatively benign. The risks are potentially important in adherence to treatment in real life conditions (e.g. GI effects) and for the safe use of the product (e.g. atrial fibrillation and bleeding) but seem relatively infrequent and potentially manageable.

3.8. Conclusions

The overall B/R of Vazkepa is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Vazkepa is favourable in the following indication:

Vazkepa is indicated to reduce the risk of cardiovascular events in adult statin-treated patients at high cardiovascular risk with elevated triglycerides (≥150 mg/dL) and

- *established cardiovascular disease, or*
- *diabetes, and at least one other cardiovascular risk factor.*

For study details including cardiovascular risk factors and results with respect to effects on cardiovascular events see section 5.1.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive

2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that icosapent ethyl is considered to be a new active substance as it differs significantly in properties with regard to efficacy from known mixture of "omega-3-acid ethyl esters 90" contained in medicinal product(s) previously authorised within the European Union.