IQWiG Reports – Commission No. A21-113

Icosapent ethyl (reduction of cardiovascular risk) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Icosapent-Ethyl (Reduzierung des kardiovaskulären Risikos) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 November 2021). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

No feedback was received in the framework of the present dossier assessment.

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Table of contents

List of tables[2]

Page

[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of figures

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
EAS	European Atherosclerosis Society
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ESC	European Society of Cardiology
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LDL-C	low-density lipoprotein cholesterol
MI	myocardial infarction
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug icosapent ethyl. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 31 August 2021.

Research question

The aim of the present report is to assess the added benefit of icosapent ethyl in comparison with the appropriate comparator therapy (ACT) for reducing the risk of cardiovascular events in statin-treated adult patients at high cardiovascular risk and with elevated triglyceride levels (≥ 150 mg/dL [≥ 1.7 mmol/L]) and either known cardiovascular disease or diabetes mellitus and at least 1 other cardiovascular risk factor.

The G-BA's specification of the ACT results in the research question presented in Table 2.

Table 2: Research question of the benefit assessment of icosapent ethyl

Therapeutic indication	ACT[a]
Reduction of the risk of cardiovascular events in statin-treated adult patients at high cardiovascular risk with elevated triglyceride levels (≥ 150 mg/dL [≥ 1.7 mmol/L]) and: ▪ known cardiovascular disease or ▪ diabetes mellitus and at least 1 other cardiovascular risk factor	Maximum tolerated pharmacological therapy upon the physician's discretion, taking into account statins and cholesterol absorption inhibitors[b, c]
a. Presented is the ACT specified by the G-BA. b. Patients in both study arms are assumed to have received guideline-compliant, individualized treatment of the known cardiovascular disease and the underlying illnesses or risk factors such as hypertension, cardiac arrhythmia, diabetes mellitus, hypercholesterolaemia as well as the accompanying symptoms. c. In both study arms, it should be possible to adjust the primary/concomitant medication to the patient's needs. Unchanged continuation of an inadequate therapy does not correspond to an ACT. In the absence of any optimization options, it must be documented or demonstrated that any potentially remaining treatment options are unsuitable or have been exhausted. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

After receipt of the dossier, the G-BA conducted an assessment procedure in which it changed the ACT for the benefit assessment of icosapent ethyl for reducing the risk of cardiovascular events in statin-treated adult patients at high cardiovascular risk with elevated triglyceride levels (≥ 150 mg/dL [≥ 1.7 mmol/L]) and either known cardiovascular disease or diabetes mellitus and at least 1 other cardiovascular risk factor.

In the original ACT, the G-BA included fibrates as a potential treatment option. The company's dossier questions the relevance of fibrates as a treatment option in the present indication, calling it an unsuitable treatment option. Hence, the G-BA's change in the ACT does not result in any substantial consequences for the present benefit assessment. The latter was carried out in comparison with the ACT specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 52 weeks were used for the derivation of added benefit.

Results

For deriving added benefit, the company used the RCT REDUCE-IT. The REDUCE-IT study is a randomized, double-blind, multicentre study comparing icosapent ethyl with placebo, each in combination with statins ± ezetimib, with the goal of reducing cardiovascular risk in statin-treated patients with elevated triglyceride levels and either known cardiovascular disease or at high risk for developing it.

A total of 8179 patients were randomly allocated in a 1:1 ratio to treatment with icosapent ethyl (4089) or placebo (4090). From the time of randomization, patients received either 2 g icosapent ethyl or mineral oil (as placebo), each twice daily orally in the form of a soft capsule. As concomitant background therapy, patients were to continue stable statin therapy (± ezetimib) for at least 4 weeks. Treatment adjustment (i.e. increased statin dose or addition of ezetimib) was allowed during the study if a low-density lipoprotein cholesterol (LDL-C) level of 130 mg/dL was exceeded at 2 consecutive measurements (at least 1 week apart).

However, the REDUCE-IT study included by the company is unsuitable for assessing the added benefit of icosapent ethyl since it did not implement the ACT as specified by the G-BA.

The ACT defined by the G-BA is maximum tolerated pharmacological therapy upon the physician's discretion, taking into account statins and cholesterol absorption inhibitors; the G-BA specified that both study arms should allow adjusting the primary/concomitant medication based on the individual patient's needs and that the unchanged continuation of an inadequate therapy does not correspond to an ACT.

However, the options for treatment optimization were limited during the REDUCE-IT study. The study's patient population exhibited LDL-C levels between 40 and 100 mg/dL on stable statin therapy (± ezetimib) at baseline. Statin type and dosing were to be continued until the end of the study unless a change was medically necessitated by the occurrence of adverse events (AEs) or lack of effectiveness. As per the guidelines, effectiveness is assessed, in part, on the basis of patients' LDL-C levels. During the course of the study, investigators were blinded to the patients' LDL-C levels. Investigators were unblinded to LDL-C levels only after 2 consecutive measurements of LDL-C levels > 130 mg/dL. Emergency treatment for these patients was either an increased dose of the existing statin or add-on ezetimib therapy.

The absence of LDL-C-based therapy in the REDUCE-IT study is inappropriate. The current guideline from the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) states that in addition to weight loss and lifestyle changes, lowering LDL-C levels is of central importance for risk reduction in patients at high and very high risk of cardiovascular disease. Recommended LDL-C targets are < 70 mg/dL for patients at high risk of cardiovascular events and < 55 g/dL for patients at very high risk. In the REDUCE-IT study, median baseline LDL-C levels were 73.0 mg/dL in the intervention arm and 74.5 mg/dL in the comparator arm (Friedewald formula) or 85.8 mg/dL in the intervention arm and 86.7 mg/dL in the comparator arm (Hopkins formula). Apart from a slight increase in LDL-C levels in the comparator arm shortly after study start, levels remained largely unchanged over the course of the study. Optimization of LDL-C-lowering therapy (via higher statin dose or add-on ezetimib) took place only to a minor extent in the study.

Furthermore, it is unclear whether the patients included in the REDUCE-IT study received maximum tolerated pharmacological therapy. The study's inclusion criteria merely require patients to exhibit baseline LDL-C levels between 40 and 100 mg/dL on stable statin therapy (± ezetimib). Maximum tolerated pharmaceutical therapy was neither an inclusion criterion nor was it documented whether patients had already received the maximum tolerated therapy due to intolerance or contraindications. Only patients who received the maximum approved statin dose plus ezetimib during the study can therefore be assumed to have received maximum tolerated pharmacological therapy. Over the entire course of the study, however, only 38% of patients in the icosapent ethyl arm and 40% of the patients in the placebo arm ever received high-dose statins, and only 8% of patients in both study arms received add-on ezetimib therapy. The available data fail to show to what extent the remaining therapy options were unsuitable or exhausted for the other patients.

All in all, treatment in the REDUCE-IT comparator arm therefore does not reflect the ACT specified by the G-BA, maximum tolerated pharmacological therapy upon the physician's discretion. An adequate comparison of icosapent ethyl versus the ACT of maximum tolerated pharmaceutical therapy requires optimizing lipid-lowering therapy for the individual patient according to the recommended LDL-C target levels over the entire course of the study. However, optimization of LDL-C-lowering therapy (higher statin dose or add-on ezetimib) took place only to a minor extent in the study. It therefore remains questionable whether the effect in favour of icosapent ethyl (hazard ratio: 0.74; 95% CI: [0.65; 0.83]) which was observed in the REDUCE-IT study for the composite cardiovascular outcome of major adverse cardiovascular event (MACE, defined as the composite of cardiovascular death, nonfatal myocardial infarction [MI] and nonfatal stroke) would have still been found if both arms had received guideline-compliant LDL-C-based therapy.

The results of the IMPROVE-IT study comparing ezetimib + simvastatin versus placebo + simvastatin suggest that lowering LDL-C levels by optimizing therapy would be possible in REDUCE-IT as well. In addition, the results show that even small differences in LDL-C levels can lead to a statistically significant difference in cardiovascular risk.

Furthermore, patients in the REDUCE-IT comparator arm received mineral oil as placebo in addition to the basic therapy. The European Public Assessment Report (EPAR) by the European Medicines Agency (EMA) discusses the possibility of mineral oil not being completely inert. For instance, substance-specific and indirect effects of mineral oil might lead to reduced uptake of drugs such as statins and affect lipids, lipoproteins, and inflammatory markers. According to the EPAR, the effects of icosapent ethyl in comparison with mineral oil might be overestimated in this case.

The increase in LDL-C levels in the REDUCE-IT comparator arm within the first few months after study start might suggest mineral oil affecting statin uptake. For instance, the comparator arm at visit 3 (Day 120) has a median increase in LDL-C levels (Hopkins formula) by 7.3 mg/dL (relative increase by 8.7%) from baseline; no comparable increase was observed in the intervention arm. Ultimately, however, it remains unclear whether and to what extent the use of mineral oil as placebo leads to an overestimate of the icosapent ethyl effect on the outcome of MACE. Hence, a resulting overestimation of the icosapent ethyl effect in the REDUCE-IT study cannot be fully ruled out.

In summary, the company did not submit any suitable data for assessing the added benefit of icosapent ethyl versus ACT regarding the reduction of the risk of cardiovascular events in statin-treated adult patients at high cardiovascular risk with elevated triglyceride levels (≥ 150 mg/dL [≥ 1.7 mmol/L]) and either known cardiovascular disease or diabetes mellitus and at least 1 other cardiovascular risk factor. Consequently, there is no hint of added benefit of icosapent ethyl in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 presents a summary of the probability and extent of added benefit of icosapent ethyl.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Icosapent ethyl – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Reduction of the risk of cardiovascular events in statin-treated adult patients at high cardiovascular risk with elevated triglyceride levels (≥ 150 mg/dL [≥ 1.7 mmol/L]) as well as: ▪ known cardiovascular disease or ▪ diabetes mellitus and at least 1 other cardiovascular risk factor	Maximum tolerated pharmacological therapy upon the physician's discretion, taking into account statins and cholesterol absorption inhibitors[b, c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Patients in both study arms are assumed to have received guideline-compliant, individualized treatment of the known cardiovascular disease and the corresponding underlying illnesses or risk factors such as hypertension, cardiac arrhythmia, diabetes mellitus, hypercholesterolaemia as well as the accompanying symptoms.
c. Unchanged continuation of an inadequate therapy does not correspond to an ACT. In the absence of any optimization options, it must be documented or demonstrated that any potentially remaining treatment options are unsuitable or have been exhausted.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is to assess the added benefit of icosapent ethyl in comparison with the ACT for reducing the risk of cardiovascular events in statin-treated adult patients at high cardiovascular risk with elevated triglyceride levels (≥ 150 mg/dL [≥ 1.7 mmol/L]) and either known cardiovascular disease or diabetes mellitus and at least 1 other cardiovascular risk factor.

The G-BA's specification of the ACT results in the research question presented in Table 4.

Table 4: Research question of the benefit assessment of icosapent ethyl

Therapeutic indication	**ACT[a]**
Reduction of the risk of cardiovascular events in statin-treated adult patients at high cardiovascular risk with elevated triglyceride levels (≥ 150 mg/dL [≥ 1.7 mmol/L]) and: ▪ known cardiovascular disease or ▪ diabetes mellitus and at least 1 other cardiovascular risk factor	Maximum tolerated pharmacological therapy upon the physician's discretion, taking into account statins and cholesterol absorption inhibitors[b, c]
a. Presented is the ACT specified by the G-BA. b. Patients in both study arms presumably receive guideline-compliant, individualized treatment of the known cardiovascular disease and the corresponding underlying illnesses or risk factors such as hypertension, cardiac arrhythmia, diabetes mellitus, hypercholesterolaemia as well as the accompanying symptoms. c. In both study arms, it should be possible to adjust the primary/concomitant medication to the patient's needs. Unchanged continuation of an inadequate therapy does not correspond to an ACT. In the absence of any optimization options, it must be documented or demonstrated that any potentially remaining treatment options are unsuitable or have been exhausted. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

After receipt of the dossier and in the course of the assessment procedure, the G-BA modified the ACT for the benefit assessment of icosapent ethyl for reducing the risk of cardiovascular events in statin-treated adult patients at high cardiovascular risk and with elevated triglyceride levels (≥ 150 mg/dL [≥ 1.7 mmol/L]) as well as known cardiovascular disease or diabetes mellitus and at least 1 other cardiovascular risk factor [3].

In the original ACT, the G-BA included fibrates as a potential treatment option. The company's dossier questions the relevance of fibrates as a treatment option in the present indication, calling it an unsuitable treatment option. Hence, the G-BA's change in the ACT does not result in any substantial consequences for the present benefit assessment. The latter was carried out in comparison with the ACT specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier. RCTs with a minimum duration of 52 weeks were used for the derivation of added benefit. This concurs with the company's inclusion criteria.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources cited by the company in the dossier:

- Study list on icosapent ethyl (as of 1 June 2021)
- Bibliographic literature search on icosapent ethyl (most recent search on 1 June 2021)
- Search in trial registries / study results databases on icosapent ethyl (most recent search on 1 June 2021)
- Search on the G-BA website on icosapent ethyl (most recent search on 2 June 2021)

To check the completeness of the study pool:

- Search in trial registries for icosapent ethyl (most recent search on 9 September 2021); see Appendix A of the full dossier assessment for search strategies.

The check did not identify any additional relevant studies.

2.3.1 Study pool of the company

The study listed in the table below was included by the company.

Table 5: Study pool of the company – RCT, direct comparison: icosapent ethyl + statins ± ezetimib vs. placebo + statins ± ezetimib

Study	Study category			Available sources		
	Approval study for the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (yes/no [reference])	Registry entries[b] (yes/no [reference])	Publication and other sources[c] (yes/no [reference])
REDUCE-IT	Yes	Yes	No	Yes [4]	Yes [5-7]	Yes [8,9]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
G-BA: Federal Joint Committee; RCT: randomized controlled trial

For deriving added benefit, the company used the RCT REDUCE-IT. However, the REDUCE-IT study included by the company is unsuitable for assessing the added benefit of icosapent ethyl versus the ACT. The reasons are explained below.

2.3.2 Study design

The REDUCE-IT study is a randomized, double-blind, multicentre study comparing icosapent ethyl with placebo, each in combination with statins ± ezetimib, with the goal of reducing

cardiovascular risk in statin-treated patients with elevated triglyceride levels and either known cardiovascular disease or at high risk for developing it.

It included patients who had an LDL-C level between 40 and 100 mg/dL and fasting triglyceride level of 135 to 500 mg/dL on stable statin ± ezetimib therapy. Stable therapy was defined as a consistent daily dose of the same statin and (if applicable) a consistent daily ezetimib dose, each at 28 days before the lipid testing conducted to qualify for randomization. In the course of the study, the lower limit for the triglyceride level was increased from 135 to 200 mg/dL in an effort to include more patients with levels ≥ 200 mg/dL.

According to the study's inclusion criteria, 2 patient groups were to be included:

- Patients at high risk of cardiovascular disease (primary prevention)

  Patients at high cardiovascular risk were defined as men and women ≥ 50 years of age with diabetes mellitus (type 1 or type 2) requiring pharmacological treatment and at least 1 of the following additional cardiovascular risk factors: advanced age (men ≥ 55 years; women ≥ 65 years), smoking, hypertension, low high-density lipoprotein cholesterol (HDL-C) level (men ≤ 40 mg/dL, women ≤ 50 mg/dL), increased high-sensitivity C-reactive protein, kidney failure, retinopathy, microalbuminuria or macroalbuminuria, or ankle-brachial index (ABI) < 0.9.

- Patients aged ≥ 45 years at very high risk of cardiovascular disease, i.e. with known cardiovascular disease (secondary prevention).

  Known cardiovascular disease was defined as the presence of at least 1 of the following: (a) coronary artery disease; (b) cerebrovascular disease or carotid disease; (c) peripheral arterial occlusive disease.

A total of 8179 patients were randomly allocated in a 1:1 ratio to treatment with icosapent ethyl (N = 4089) or placebo (N = 4090). Randomization was stratified by the factors of primary/secondary prevention, geographic region, and ezetimib administration.

From the time of randomization, patients received either 2 g icosapent ethyl or mineral oil (the latter as placebo), each twice daily orally in the form of a soft capsule (see Table 14 in Appendix B of the full dossier assessment). Icosapent ethyl dosing in the studies was administered in line with approval and the SPC [8,10]. As concomitant background therapy, patients were to continue stable statin therapy (± ezetimib) for at least 4 weeks. Treatment adjustment (i.e. increased statin dose or addition of ezetimib) was allowed during the study if an LDL-C level of 130 mg/dL was exceeded at 2 consecutive measurements (at least 1 week apart).

Treatment was administered from randomization to study end (or treatment or study discontinuation [see Table 15 in Appendix B of the full dossier assessment]); study end was planned to occur after about 1612 events in the primary outcome. Since individual patients were

included in the study at different points of the recruitment phase (which lasted about 4.7 years) but completed it at approximately the same time (study end), treatment and follow-up durations vary between patients. The median follow-up duration in both REDUCE-IT treatment arms was 4.9 years.

The primary outcome of the REDUCE-IT study was a composite outcome consisting of cardiovascular death, nonfatal myocardial infarction [MI, including silent MI], nonfatal stroke, coronary revascularization, and unstable angina which, according to a (non)invasive examination, was due to myocardial ischaemia and required emergency hospitalization. Further patient-relevant outcomes were surveyed in the categories of mortality, morbidity, and side effects.

Appendix B of the full dossier assessment provides additional information on the characterization of the study, interventions, and included patients.

2.3.3 Limited possibility to optimize concomitant therapy in the REDUCE-IT study

The ACT defined by the G-BA is maximum tolerated pharmacological therapy upon the physician's discretion taking into account statins and cholesterol absorption inhibitors; the G-BA also specified that both study arms should allow adjusting the basic/concomitant medication to the individual patient's needs and that unchanged continuation of an inadequate therapy does not correspond to an ACT.

However, the options for treatment optimization were limited during the REDUCE-IT study. As described above, the study included a patient population which exhibited LDL-C levels of 40 to 100 mg/dL on stable statin therapy (± ezetimib) at baseline. Statin type and dosing were to be continued until the end of the study unless a change was medically necessitated due to the occurrence of AEs or lack of effectiveness. In accordance with guidelines, effectiveness is assessed, in part, on the basis of patients' LDL-C levels [11]. However, the study blinded investigators to patients' LDL-C levels. Investigators were unblinded with regard to LDL-C levels only after 2 consecutive measurements of LDL-C levels > 130 mg/dL. Emergency treatment for these patients was either an increased dose of the existing statin or add-on ezetimib therapy.

This made it impossible to administer outcome-oriented individualized therapy in the study. This is reflected in the patients' LDL-C level profiles, which mostly show sustained LDL-C levels over the course of the study (see Figure 1).

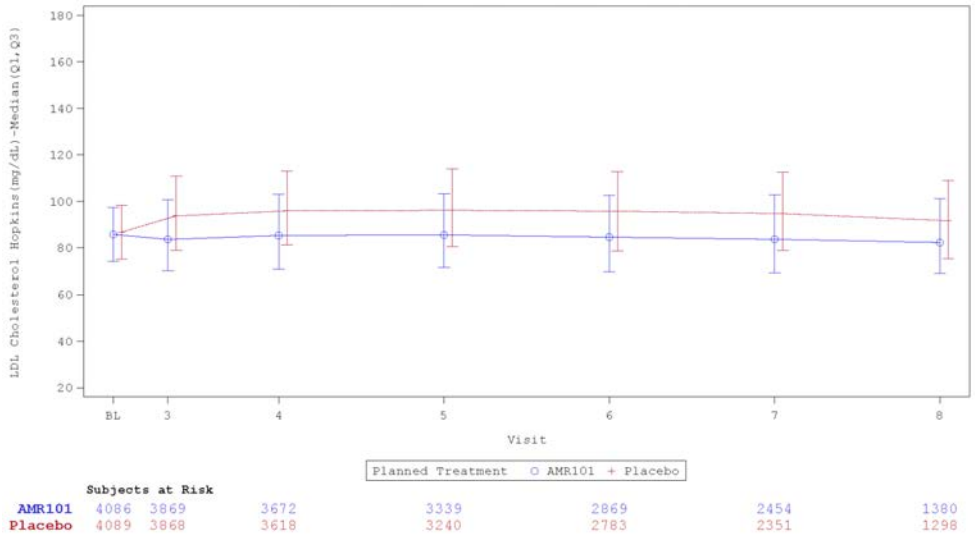

Figure 1: LDL-C level profiles over time in mg/dL (median [interquartile range]) as per Hopkins formula in the REDUCE-IT study

The absence of LDL-C-based therapy in the REDUCE-IT study is inappropriate. The current ESC and EAS guideline [11] specifies that, in addition to weight loss and lifestyle changes, reducing LDL-C levels as essential for lowering risk in patients at high and very high risk of cardiovascular disease. Recommended LDL-C targets are < 70 mg/dL for patients at high risk of cardiovascular events and < 55 g/dL for patients at very high risk.

In the REDUCE-IT study, about 70% of patients were at very high risk (due to a history of cardiovascular diseases), and the remaining 30% of patients were at high risk of cardiovascular events (see Table 15 in Appendix B of the full dossier assessment). Median baseline LDL-C levels were 73.0 mg/dL in the intervention arm and 74.5 mg/dL in the comparator arm (Friedewald formula) or 85.8 mg/dL in the intervention arm and 86.7 mg/dL in the comparator arm (Hopkins formula). Apart from a slight increase in LDL-C levels in the comparator arm shortly after study start, levels remained largely constant over the course of the study (Figure 1). Optimization of LDL-C-lowering therapy (via higher statin dose or add-on ezetimib) took place only to a minor extent in the study. Regarding concomitant medication, further study documents show that, in both study arms, only about 25% of patients with a low statin dose at baseline received an increase to a moderate or high dose over the course of the study (see Table 17 in Appendix B of the full dossier assessment for definitions of low, moderate, and high dose).

Furthermore, it is unclear whether the patients included in the REDUCE-IT study received maximum tolerated pharmacological therapy. The study's inclusion criteria merely require patients to exhibit baseline LDL-C levels between 40 and 100 mg/dL on stable statin therapy (± ezetimib). Maximum tolerated pharmacological therapy was not an inclusion criterion, and it was not documented whether patients had already received the maximum tolerated therapy due to intolerance or contraindications. Only patients who received the maximum approved statin dose plus ezetimib during the study can therefore be assumed to have received maximum

tolerated pharmacological therapy. However, over the entire course of the study, only 38% of patients in the icosapent ethyl arm and 40% of patients in the placebo arm ever received high-dose statins (see Table 17 in Appendix B of the full dossier assessment), and only 8% of patients in both study arms received add-on ezetimib therapy (see Table 16 in Appendix B). The available data fail to show the extent to which the remaining therapy options were unsuitable or had been exhausted for the other patients.

All in all, treatment in the REDUCE-IT comparator arm therefore does not reflect the ACT specified by the G-BA, maximum tolerated pharmacological therapy upon the physician's discretion.

It must be noted that, in the REDUCE-IT study, an effect in favour of icosapent ethyl was found, for instance for the outcome of major adverse cardiac event (MACE, consisting of the components cardiovascular death, nonfatal MI, and nonfatal stroke) (hazard ratio: 0.74; 95% CI: [0.65; 0.83]). Notably, treatment escalation took place only in the intervention arm through the administration of icosapent ethyl, while patients in the comparator arm continued their inadequate background lipid-lowering therapy. Overall, it remains questionable whether the effect would have been found if both arms had received guideline-compliant LDL-C-based therapy.

This has been substantiated by the results of the IMPROVE-IT study comparing ezetimib + simvastatin versus placebo + simvastatin, which show, firstly, that it is possible to lower LDL-C levels by optimizing the therapy. Secondly, they show that even small differences in LDL-C levels can produce statistically significant differences in cardiovascular risk. The IMPROVE-IT study included patients hospitalized due to acute coronary syndrome within 10 days before randomization (ezetimib + simvastatin arm: 9067 patients; placebo + simvastatin arm: 9077 patients). As per protocol, the simvastatin dose was to be increased to 80 mg/day if the LDL-C level was > 79 mg/dL at 2 consecutive measurements[4]. From a mean baseline LDL-C of 93.8 mg/dL in both study arms, patients in the ezetimib + simvastatin arm achieved a mean reduction by 34.9 mg/dL. In the simvastatin + placebo arm, the mean reduction over the course of the study was 20.8 mg/dL. The resulting between-group difference in LDL-C change (mean difference: -14.2; 95% CI: [-14.8; -13.5]) was associated with a statistically significant effect in favour of ezetimib for the outcome of MACE, which consisted of cardiovascular death, nonfatal MI, and nonfatal stroke (hazard ratio: 0.90; 95% CI: [0.84; 0.97] [12].

Overall, an adequate comparison of icosapent ethyl versus the ACT of maximum tolerated pharmacological therapy requires individualized optimization of lipid-lowering therapy as per the recommended LDL-C target levels throughout the course of the study. It is doubtful whether

[4] In an amendment of the study protocol, the simvastatin dose for patients who had taken 80 mg/day simvastatin for less than 1 year was limited to 40 mg/day. However, this affected only a small percentage of patients (total: 5.6%; ezetimib/simvastatin arm: 2.5%, simvastatin arm: 8.7%).

the effect observed in the REDUCE-IT study would have remained in place if patients had received optimal LDL-C-based therapy.

2.3.4 Mineral oil as placebo may lead to overestimation of icosapent ethyl effect

Patients in the REDUCE-IT comparator arm received mineral oil as placebo in addition to the primary therapy. The EPAR of the EMA discusses the possibility of mineral oil not being completely inert [8]. For instance, substance-specific and indirect effects of mineral oil might lead to reduced uptake of drugs such as statins and affect lipids, lipoproteins, and inflammatory markers. According to the EPAR, the effects of icosapent ethyl in comparison with mineral oil might be overestimated in this case.

The increase in LDL-C levels in the REDUCE-IT comparator arm within the first few months after study start might suggest mineral oil affecting statin uptake. For instance, at visit 3 (Day 120), the comparator arm shows a median increase in LDL-C levels (Hopkins formula) by 7.3 mg/dL from baseline (relative increase by 8.7%, see Figure 1 in Section 2.3.3), while no comparable difference can be observed in the intervention arm. According to the EPAR, analyses taking into account physical and chemical characteristics of pharmaceuticals, effectiveness, and bleeding patterns did not show any substantial influence of mineral oil on the absorption of statins, platelet aggregation inhibitors, or anticoagulants. Therefore, the EMA expects the adverse effect exerted on the outcome of MACE due to the use of mineral oil as a placebo to remain below 10% [8].

Ultimately, it remains unclear whether and to what extent the use of mineral oil as placebo leads to an overestimation of the icosapent ethyl effect on the outcome of MACE. Hence, a resulting overestimation of the icosapent ethyl effect in the REDUCE-IT study cannot be fully ruled out.

2.4 Results on added benefit

The company did not submit any suitable data for assessing the added benefit of icosapent ethyl versus ACT regarding the reduction of the risk of cardiovascular events in statin-treated adult patients at high cardiovascular risk and with elevated triglyceride levels (≥ 150 mg/dL [≥ 1.7 mmol/L]) as well as known cardiovascular disease or diabetes mellitus and at least 1 other cardiovascular risk factor. Consequently, there is no hint of added benefit of icosapent ethyl in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

The company did not submit any suitable data for assessing the added benefit of icosapent ethyl in comparison with the ACT for reducing the risk of cardiovascular events in statin-treated adult patients at high cardiovascular risk and with elevated triglyceride levels (≥ 150 mg/dL [≥ 1.7 mmol/L]) as well as known cardiovascular disease or diabetes mellitus and at least 1 other cardiovascular risk factor. An added benefit is therefore not proven.

The assessment described above differs from that by the company, which derived an indication of major added benefit in consideration of the results of the REDUCE-IT study.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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