IQWiG Reports – Commission No. A22-03

# Icosapent ethyl (cardiovascular risk reduction) –

## Addendum to Commission A21-113[1]

## Addendum

Commission: A22-03
Version: 1.0
Status: 28 January 2022

[1] Translation of addendum A22-03 *Icosapent-Ethyl (Reduzierung des kardiovaskulären Risikos) – Addendum zum Auftrag A21-113* (Version 1.0; Status: 28 January 2022). 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.

# Publishing details

**Publisher**
Institute for Quality and Efficiency in Health Care

**Topic**
Icosapent ethyl (cardiovascular risk reduction) – Addendum to Commission A21-113

**Commissioning agency**
Federal Joint Committee

**Commission awarded on**
11 January 2022

**Internal Commission No.**
A22-03

**Address of publisher**
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

**IQWiG employees involved in the addendum**

- Marc Schulte
- Petra Kohlepp
- Matthias Maiworm
- Regine Potthast
- Volker Vervölgyi

**Keywords:** Eicosapentaenoic Acid Ethyl Ester, Heart Disease Risk Factors, Hypertriglyceridemia, Benefit Assessment, NCT01492361

# Table of contents

**List of tables**

**Page**

**List of figures**

**Page**

**List of abbreviations**

| Abbreviation | Meaning |
|---|---|
| ACT | appropriate comparator therapy |
| AE | adverse event |
| 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 |
| PT | preferred term |
| MACE | major adverse cardiac event |
| MedDRA | Medical Dictionary for Regulatory Activities |
| SMQ | Standardized Medical Dictionary for Regulatory Activities Query |
| SOC | system organ class |

# 1 Background

On 11 January 2022, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A21-113 (Icosapent ethyl – benefit assessment according to § 35a Social Code Book V) [1].

To assess the benefit 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, the pharmaceutical company (hereinafter "company") presented the REDUCE-IT study [2]. For the present therapeutic indication, the G-BA has specified as the appropriate comparator therapy (ACT) maximum tolerated pharmacological therapy upon the physician's discretion, taking into account statins and cholesterol absorption inhibitors. Treatment in the REDUCE-IT study does not meet the specifications of the ACT (limited treatment optimization options, absence of low-density lipoprotein cholesterol (LDL-C)-based therapy, questionable implementation of maximum tolerated therapy). No information was available as to whether the remaining therapy options for REDUCE-T participants were unsuitable or had been exhausted. The REDUCE-IT study was therefore excluded from the benefit assessment.

The G-BA commissioned IQWiG to assess and present the results of the REDUCE-IT study based on the information provided in the dossier [2], taking into account the analyses/information submitted by the company in the commenting procedure [3].

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

## 2 Presentation of the REDUCE-IT study

Below, the REDUCE-IT study is presented and assessed in accordance with the terms of the commission. This study was disregarded in dossier assessment A21-113 [1] because it did not implement the ACT specified by the G-BA [4], particularly by failing to offer LDL-C-based therapy. For instance, rescue therapy in the form of an increased statin dose or addition of ezetimib was allowed only for participants with LDL-C readings > 130 mg/dL in 2 consecutive measurements. It is unclear whether the included patients had received maximum tolerated pharmacological therapy over the course of the study.

The data submitted by the company following the oral hearing [5] further substantiate the idea that the REDUCE-IT study inadequately implemented the LDL-C-based therapy described in guidelines. Said data include information on the percentage of REDUCE-IT study participants who had LDL-C readings below 40 mg/dL, above 100 mg/dL (or 100 to 130 mg/dL), and above 130 mg/dL over the course of the study. These data are each available on the individual Visits 3 through 8, based on the intention-to-treat (ITT) population.

Firstly, it should be noted that the percentages presented by the company are underestimates. Since follow-up periods differed between patients, the number of patients at risk markedly decreased already 1 year after randomization, and even more so in the further course of the study. In the present case, it is therefore appropriate to calculate the percentages based on the patients still being followed up at the time of each visit.

IQWiG-internal estimates, which calculate each of the percentages based on the patients being followed up at the time of the visit, paint the following picture: 1 year after study start (with a specified patient LDL-C reading < 100 mg/dL), 675 patients (19%) in the icosapent ethyl arm and 841 patients (26%) in the comparator arm already had LDL-C > 100 mg/dL. These percentages stayed relatively constant over the further course of the study (after 4 years: 19% versus 27%; after 5 years: 19% versus 24%).

Given that the current guideline published by the European Society of Cardiology and the European Arteriosclerosis Society [6] specifies LDL-C targets of < 55 mg/dL for patients at very high risk of cardiovascular events and < 70 mg/dL for patients at high risk, it is safe to assume that a substantial percentage of patients would have required modifications of the lipid-lowering therapy during the study. In addition to the above-described patients with LDL-C > 100 mg/dL, this might also apply to other patients whose LDL-C readings were below 100 mg/dL.

Overall, the data subsequently submitted by the company substantiate the dossier assessment's conclusion that the ACT specified by the G-BA had been insufficiently implemented.

## 2.1 Study design

A detailed characterization of the REDUCE-IT study can be found in dossier assessment A21-113 [1] and its Appendix B.

**Risk of bias across outcomes (study level)**

Table 1 shows the risk of bias across outcomes (risk of bias at study level).

Table 1: Risk of bias across outcomes (study level) – RCT, direct comparison: icosapent ethyl+ statins ± ezetimib vs. placebo ± ezetimib

| Study | Adequate random sequence generation | Allocation concealment | Blinding | | Nonselective reporting | Absence of other aspects | Risk of bias at study level |
|---|---|---|---|---|---|---|---|
| | | | Patients | Treating staff | | | |
| REDUCE-IT | Yes | Yes | Yes | Yes | Yes | No[a] | High |

a. The placebo (mineral oil) used in the REDUCE-IT study might not be fully inert. This affects all outcomes.
RCT: randomized controlled trial

As discussed in dossier assessment A21-113 [1], a potential bias of the REDUCE-IT results due to the use of mineral oil as the placebo cannot be ruled out entirely.

Therefore, the risk of bias across outcomes was rated as high for the REDUCE-IT study.

## 2.2 Study results

### 2.2.1 Presented outcomes

This addendum presents the following patient-relevant outcomes for the REDUCE-IT study:

- Mortality
  - All-cause mortality
- Morbidity
  - MACE
    - Cardiovascular death
    - Nonfatal myocardial infarction
    - Nonfatal stroke
  - Hospitalization for unstable angina
  - Hospitalization for heart failure

- Health-related quality of life
- Side effects
  - SAEs
  - Discontinuation due to adverse events (AEs)
  - Rhabdomyolysis (preferred term [PT], AE)
  - Haemorrhage (Standardized Medical Dictionary for Regulatory Activities [MedDRA] Query [SMQ], AE, and SAE)
  - Severe hepatotoxicity (SMQ, SAE)
  - Further specific AEs, if any

The choice of patient-relevant outcomes differs from the selection by the company, which used additional outcomes in the dossier (Module 4 A) [2] .

Table 2 shows the outcomes for which data were available in the REDUCE-IT study.

Table 2: Matrix of outcomes – RCT, direct comparison: icosapent ethyl+ statins ± ezetimib vs. placebo + statins ± ezetimib

| Study | Outcomes | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | **All-cause mortality** | **MACE[a]** | **Hospitalization for unstable angina** | **Hospitalization for heart failure** | **Health-related quality of life** | **SAEs** | **Discontinuation due to AEs** | **Rhabdomyolysis (PT, AEs)** | **Haemorrhage (SMQ, AEs, and SAEs)[b]** | **Severe hepatotoxicity (SMQ, SAE)[c]** | **Further specific AEs** |
| REDUCE-IT | Yes | Yes | Yes | Yes | No[d] | Yes | Yes | Yes | Yes | Yes | No[e] |

a: Composite outcome, consisting of the components of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.
b. Operationalized as the following SMQs (MedDRA coded): “gastrointestinal haemorrhage (SMQ)”, “central nervous system haemorrhages and cerebrovascular conditions (SMQ)”, and “haemorrhage terms (excluding laboratory terms (SMQ)”.
c. Operationalized as SMQ “hepatic disorders” (MedDRA coded).
d. Outcome not recorded.
e. No further specific AEs were identified.

AE: adverse event; MACE: major adverse cardiac event; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query

### 2.2.2 Risk of bias

Table 3 shows the risk of bias for the results of the relevant outcomes.

Table 3: Study-level and outcome-specific risk of bias – RCT, direct comparison: icosapent ethyl+ statins ± ezetimib vs. placebo + statins ± ezetimib

| Study | Study level | Outcomes | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | All-cause mortality | MACE[a] | Hospitalization for unstable angina | Hospitalization for heart failure | Health-related quality of life | SAEs | Discontinuation due to AEs | Rhabdomyolysis (PT, AEs) | Haemorrhage (SMQ, AEs, and SAEs)[b] | Severe hepatotoxicity (SMQ, SAE)[c] | Further specific AEs |
| REDUCE-IT | H | H[d] | H[d] | H[d] | H[d] | –[e] | H[d] | H[d] | H[d] | H[d] | H[d] | – |

a: Composite outcome, consisting of the components of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.
b. Operationalized as the following SMQs (MedDRA coded): "gastrointestinal haemorrhage (SMQ)", "central nervous system haemorrhages and cerebrovascular conditions (SMQ)" and "haemorrhage terms (excluding laboratory terms" (SMQ)"
c. Operationalized as SMQ "hepatic disorders" (MedDRA coded).
d. Due to the high risk of bias on the study level.
e. Outcome not recorded.

AE: adverse event; H: high; L: low; MACE: major adverse cardiac event; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query

### 2.2.3 Results

Table 4 and Table 5 summarize the results of the comparison of icosapent ethyl versus placebo for reducing the risk of cardiovascular events in adult statin-treated patients at high cardiovascular risk with elevated triglycerides (≥ 150 mg/dL [≥ 1.7 mmol/L]) and either established cardiovascular disease or diabetes mellitus and at least 1 further cardiovascular risk factor. Where necessary, IQWiG calculations are provided in addition to the data from the company's dossier.

Results on common AEs, SAEs, and discontinuation due to AEs are presented in Appendix A. Kaplan-Meier curves on the event time analyses can be found in Appendix B.

Table 4: Results (mortality, morbidity, and health-related quality of life, time to event) – RCT, direct comparison: icosapent ethyl + statins ± ezetimib vs. placebo + statins ± ezetimib

| **Study**<br>**Outcome category**<br>**Outcome** | **Icosapent ethyl + statins ± ezetimib** | | **Placebo + statins ± ezetimib** | | **Icosapent ethyl + statins ± ezetimib vs. placebo + statins ± ezetimib** |
|---|---|---|---|---|---|
| | **N** | **Median time to event in months [95% CI]**<br>**Patients with event n (%)** | **N** | **Median time to event in months [95% CI]**<br>**Patients with event n (%)** | **HR[a] [95% CI]; p-value[b]** |
| **REDUCE-IT** | | | | | |
| **Mortality** | | | | | |
| All-cause mortality | 4089 | ND<br>274 (6.7) | 4090 | ND<br>310 (7.6) | 0.87 [0.74; 1.02]; 0.092 |
| **Morbidity** | | | | | |
| MACE[c] | 4089 | ND<br>459 (11.2) | 4090 | ND<br>606 (14.8) | 0.74 [0.65; 0.83]; < 0.001 |
| Cardiovascular death[d] | 4089 | ND<br>174 (4.3) | 4090 | ND<br>213 (5.2) | 0.80 [0.66; 0.98]; 0.032 |
| Nonfatal myocardial infarction[d] | 4089 | ND<br>237 (5.8) | 4090 | ND<br>332 (8.1) | 0.70 [0.59; 0.82]; < 0.001 |
| Nonfatal stroke[d] | 4089 | ND<br>85 (2.1) | 4090 | ND<br>118 (2.9) | 0.71 [0.54; 0.94]; 0.015 |
| Hospitalization for unstable angina | 4089 | ND<br>108 (2.6) | 4090 | ND<br>157 (3.8) | 0.68 [0.53; 0.87]; 0.002 |
| Hospitalization for heart failure | 4089 | ND<br>141 (3.4) | 4090 | ND<br>144 (3.5) | 0.97 [0.77; 1.22]; 0.781 |
| **Health-related quality of life** | No outcomes of the "quality of life" category were recorded. | | | | |

a. HR and CI: Cox proportional hazards model, stratified by stratification factors at randomization (cardiovascular risk category [secondary prevention; primary prevention], geographic region, use of ezetimib).
b. p-value: log-rank test stratified by stratification factors at randomization.
c. Composite cardiovascular outcome with the components of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.
d. Presented are all events over the entire course of the study, rather than the events entered into the composite outcome.

CI: confidence interval; CNS: central nervous system; HR: hazard ratio; MACE: major adverse cardiac event; n: number of patients with event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial

Table 5: Results (side effects, dichotomous) – RCT, direct comparison: icosapent ethyl + statins ± ezetimib vs. placebo + statins ± ezetimib

| Study<br>Outcome category<br>Outcome | Icosapent ethyl + statins ± ezetimib | | Placebo + statins ± ezetimib | | Icosapent ethyl + statins ± ezetimib vs. placebo + statins ± ezetimib |
|---|---|---|---|---|---|
| | N | Patients with event<br>n (%) | N | Patients with event<br>n (%) | RR [95% CI];<br>p-value[a] |
| **REDUCE-IT** | | | | | |
| **Side effects** | | | | | |
| AEs (supplementary information) | 4089 | 3343 (81.8) | 4090 | 3326 (81.3) | – |
| SAEs | 4089 | 1252 (30.6) | 4090 | 1254 (30.7) | 1.00 [0.94; 1.07]; 0.982 |
| Discontinuation due to AEs | 4089 | 321 (7.9) | 4090 | 335 (8.2) | 0.96 [0.83; 1.11]; 0.682 |
| Rhabdomyolysis (PT, AEs) | 4089 | 3 (0.1) | 4090 | 6 (0.1) | 0.50 [0.13; 2.00][b]; 0.352 |
| Haemorrhage (SMQ, AEs)[c] | 4089 | 482 (11.8) | 4090 | 404 (9.9) | 1.19 [1.05; 1.35]; 0.006 |
| Haemorrhage (SMQ, SAE)[c] | 4089 | 111 (2.7) | 4090 | 85 (2.1) | 1.31 [0.99; 1.73]; 0.071 |
| Severe hepatotoxicity (SMQ, SAE)[d] | 4089 | 16 (0.4) | 4090 | 12 (0.3) | 1.33 [0.63; 2.82]; 0.532 |

a. Institute's calculation, unconditional exact test (CSZ method according to [7]).
b: IQWiG calculation of RR and CI (asymptotic).
c. Operationalized as the following SMQs (MedDRA coded): "gastrointestinal haemorrhage (SMQ)", "central nervous system haemorrhages and cerebrovascular conditions (SMQ)" and "haemorrhage terms (excluding laboratory terms) (SMQ)".
d. Operationalized as SMQ "hepatic disorders" (MedDRA coded).

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; PT: preferred term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SMQ: Standardized MedDRA Query

Overall, the certainty of conclusions for all outcomes is limited due to the high risk of bias of results on the study level.

## Mortality

### *All-cause mortality*

For the outcome of overall survival, no statistically significant difference between treatment groups was found.

**Morbidity**

***MACE***

For the outcome of MACE, consisting of the components of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke, there is a statistically significant difference in favour or icosapent ethyl versus placebo, each in combination with statins ± ezetimib.

***Hospitalization for unstable angina***

For the outcome of hospitalization for unstable angina, there is no statistically significant difference in favour or icosapent ethyl versus placebo, each in combination with statins ± ezetimib.

***Hospitalization for heart failure***

No statistically significant difference between treatment groups was found for the outcome of hospitalization for heart failure.

**Health-related quality of life**

Outcomes in this category were not surveyed in the REDUCE-IT study.

**Side effects**

***SAEs, discontinuation due to AEs***

There were no statistically significant differences between treatment groups for the outcomes of SAEs and discontinuation due to AEs.

***Specific AEs***

*Rhabdomyolysis (PT, AEs) and severe hepatotoxicity (SMQ, SAE)*

For the specific AEs of rhabdomyolysis (PT, AE) and severe hepatotoxicity (SMQ, SAE), there are no statistically significant differences between treatment groups.

*Haemorrhage (SMQ, AE, and SAE)*

For the specific AE of haemorrhage (SMQ, AE), there is a statistically significant difference to the disadvantage of icosapent ethyl + statins ± ezetimib versus placebo + statins ± ezetimib.

For the specific AE of haemorrhage (SMQ, SAE), there are no statistically significant differences between treatment groups.

### 2.2.4 Subgroups and other effect modifiers

The following potential effect modifiers were taken into account for the present addendum:

- Sex (female/male)
- Age (≤ 65 years / > 65 years)
- Cardiovascular risk category (secondary/primary prevention)

For the outcomes in question, the available subgroup results do not show any statistically significant interactions for any of the 3 attributes. Hence, there are no relevant effect modifications or subgroup effects.

### 2.3 Summary

Overall, the results of the REDUCE-IT study show the following for icosapent ethyl + statins ± ezetimib versus placebo + statins ± ezetimib:

- Advantage for icosapent ethyl + statins ± ezetimib:
  - MACEs
  - Hospitalization for unstable angina
- No advantage or disadvantage for icosapent ethyl + statins ± ezetimib:
  - All-cause mortality
  - Hospitalization for heart failure
  - SAEs
  - Discontinuation due to AEs
  - Various specific AEs (rhabdomyolysis, haemorrhage [SAE], severe hepatotoxicity)
- Disadvantage for icosapent ethyl + statins ± ezetimib:
  - Specific AE (haemorrhage [AE])

No outcomes were surveyed in the category of health-related quality of life.

The G-BA decides on the added benefit.

## 3 References

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

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Icosapent-Ethyl (Reduzierung des kardiovaskulären Risikos) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2021 [Accessed: 01.12.2021]. URL: https://www.iqwig.de/download/a21-113_icosapent-ethyl_nutzenbewertung-35a-sgb-v_v1-0.pdf.

2. Amarin Pharmaceuticals Ireland. Icosapent-Ethyl (Vazkepa); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2021 [Accessed: 07.01.2022]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/730/#dossier.

3. Amarin Pharmaceuticals Ireland. Stellungnahme zum IQWiG-Bericht Nr. 1244: Icosapent-Ethyl (Reduzierung des kardiovaskulären Risikos) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung. [Soon available under https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/730/#beschluesse].

4. Gemeinsamer Bundesausschuss. Nutzenbewertungsverfahren zum Wirkstoff Icosapent-Ethyl (Bekannter Wirkstoff mit neuem Unterlagenschutz: Dyslipidämie, vorbehandelte Patienten); Änderung der zweckmäßigen Vergleichstherapie. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/730/ in the document "Zusammenfassende Dokumentation"].

5. Gemeinsamer Bundesausschuss. Icosapent-Ethyl (D-726); mündliche Anhörung gemäß § 35 a Abs. 2 Satz 2 SGB V; stenografisches Wortprotokoll [online]. 2022 [Accessed: 20.01.2021]. URL: https://www.g-ba.de/downloads/91-1031-730/2022-01-10_Wortprotokoll_Icosapent-Ethyl_D-726.pdf.

6. Mach F, Baigent C, Catapano AL et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020; 41(1): 111-188. https://dx.doi.org/10.1093/eurheartj/ehz455.

7. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574. https://dx.doi.org/10.1016/0167-9473(94)90148-1.

## Appendix A Results on side effects

For the total rates of AEs and SAEs, the following tables present events for the System Organ Classes (SOCs) and PTs in accordance with MedDRA on the basis of the following criteria:

- total rate of AEs (irrespective of severity grade): events which occurred in at least 1% of the patients in 1 study arm
- total rates of SAEs: events which occurred in at least 1% of the patients in 1 study arm
- in addition, for all events irrespective of the severity grade: events which occurred in at least 10 patients and in at least 1% of the patients in 1 study arm

For the outcome "discontinuation due to AEs", all events (SOCs/PTs) which occurred in at least 10 patients in at least 1 study arm.

Table 6: Common AEs[a] – RCT, direct comparison: icosapent ethyl + statins ± ezetimib vs. placebo + statins ± ezetimib (multipage table)

| Study | Patients with event n (%) | |
|---|---|---|
| SOC[b] PT[b] | Icosapent ethyl + statins ± ezetimib N = 4089 | Placebo + statins ± ezetimib N = 4090 |
| **REDUCE-IT** | | |
| **Total AE rate** | 3343 (81.8) | 3326 (81.3) |
| Infections and infestations | 1822 (44.6) | 1774 (43.4) |
| Nasopharyngitis | 314 (7.7) | 300 (7.3) |
| Upper respiratory tract infection | 312 (7.6) | 320 (7.8) |
| Bronchitis | 306 (7.5) | 300 (7.3) |
| Pneumonia | 263 (6.4) | 277 (6.8) |
| Influenza | 263 (6.4) | 271 (6.6) |
| Urinary tract infection | 253 (6.2) | 261 (6.4) |
| Sinusitis | 169 (4.1) | 166 (4.1) |
| Cellulitis | 117 (2.9) | 104 (2.5) |
| Gastroenteritis | 81 (2.0) | 86 (2.1) |
| Cystitis | 76 (1.9) | 75 (1.8) |
| Herpes zoster | 71 (1.7) | 74 (1.8) |
| Lower respiratory tract infection | 57 (1.4) | 41 (1.0) |
| Acute sinusitis | 55 (1.3) | 49 (1.2) |
| Respiratory tract infection | 46 (1.1) | 49 (1.2) |
| Onychomycosis | 44 (1.1) | 43 (1.1) |
| Diverticulitis | 43 (1.1) | 45 (1.1) |
| Gastroenteritis viral | 41 (1.0) | 52 (1.3) |
| Sepsis | 33 (0.8) | 42 (1.0) |
| Musculoskeletal and connective tissue disorders | 1466 (35.9) | 1406 (34.4) |
| Back pain | 335 (8.2) | 309 (7.6) |
| Arthralgia | 313 (7.7) | 310 (7.6) |
| Osteoarthritis | 241 (5.9) | 218 (5.3) |
| Pain in an extremity | 235 (5.7) | 241 (5.9) |
| Musculoskeletal pain | 176 (4.3) | 130 (3.2) |
| Myalgia | 135 (3.3) | 147 (3.6) |
| Muscle spasms | 101 (2.5) | 136 (3.3) |
| Bursitis | 72 (1.8) | 75 (1.8) |
| Arthritis | 71 (1.7) | 66 (1.6) |
| Rotator cuff syndrome of the shoulder | 62 (1.5) | 68 (1.7) |
| Neck pain | 62 (1.5) | 51 (1.2) |
| Intervertebral disc displacement | 57 (1.4) | 36 (0.9) |
| Osteoarthritis of the spine | 51 (1.2) | 50 (1.2) |
| Musculoskeletal chest pain | 45 (1.1) | 48 (1.2) |

Table 6: Common AEs[a] – RCT, direct comparison: icosapent ethyl + statins ± ezetimib vs. placebo + statins ± ezetimib (multipage table)

| Study | Patients with event n (%) | |
|---|---|---|
| SOC[b] PT[b] | Icosapent ethyl + statins ± ezetimib N = 4089 | Placebo + statins ± ezetimib N = 4090 |
| Tendonitis | 42 (1.0) | 36 (0.9) |
| Gastrointestinal disorders | 1350 (33.0) | 1437 (35.1) |
| Diarrhoea | 367 (9.0) | 453 (11.1) |
| Constipation | 221 (5.4) | 149 (3.6) |
| Nausea | 190 (4.6) | 197 (4.8) |
| Gastro-oesophageal reflux disease | 124 (3.0) | 118 (2.9) |
| Abdominal pain | 119 (2.9) | 118 (2.9) |
| Abdominal pain upper | 103 (2.5) | 102 (2.5) |
| Colon polyp | 90 (2.2) | 118 (2.9) |
| Dyspepsia | 84 (2.1) | 81 (2.0) |
| Vomiting | 83 (2.0) | 100 (2.4) |
| Haemorrhoids | 67 (1.6) | 66 (1.6) |
| Gastritis | 53 (1.3) | 55 (1.3) |
| Flatulence | 47 (1.1) | 49 (1.2) |
| Diverticula | 45 (1.1) | 50 (1.2) |
| Abdominal discomfort | 45 (1.1) | 31 (0.8) |
| Dysphagia | 43 (1.1) | 29 (0.7) |
| Eructation | 43 (1.1) | 20 (0.5) |
| General disorders and administration site conditions | 1030 (25.2) | 979 (23.9) |
| Chest pain | 273 (6.7) | 290 (7.1) |
| Oedema peripheral | 267 (6.5) | 203 (5.0) |
| Fatigue | 228 (5.6) | 196 (4.8) |
| Non-cardiac chest pain | 161 (3.9) | 173 (4.2) |
| Peripheral swelling | 60 (1.5) | 47 (1.1) |
| Asthenia | 56 (1.4) | 50 (1.2) |
| Pyrexia | 54 (1.3) | 45 (1.1) |
| Chest discomfort | 49 (1.2) | 56 (1.4) |
| Oedema | 42 (1.0) | 26 (0.6) |
| Nervous system disorders | 1004 (24.6) | 972 (23.8) |
| Dizziness | 235 (5.7) | 246 (6.0) |
| Headache | 171 (4.2) | 180 (4.4) |
| Syncope | 82 (2.0) | 82 (2.0) |
| Peripheral neuropathy | 64 (1.6) | 66 (1.6) |
| Paraesthesia | 64 (1.6) | 44 (1.1) |
| Carpal tunnel syndrome | 60 (1.5) | 63 (1.5) |
| Hypoaesthesia | 57 (1.4) | 57 (1.4) |

Table 6: Common AEs[a] – RCT, direct comparison: icosapent ethyl + statins ± ezetimib vs. placebo + statins ± ezetimib (multipage table)

| Study | Patients with event n (%) | |
|---|---|---|
| SOC[b] PT[b] | Icosapent ethyl + statins ± ezetimib N = 4089 | Placebo + statins ± ezetimib N = 4090 |
| Sciatica | 57 (1.4) | 54 (1.3) |
| Diabetic neuropathy | 55 (1.3) | 37 (0.9) |
| Respiratory, thoracic and mediastinal disorders | 989 (24.2) | 946 (23.1) |
| Dyspnoea | 254 (6.2) | 240 (5.9) |
| Cough | 241 (5.9) | 241 (5.9) |
| Chronic obstructive pulmonary disease | 116 (2.8) | 107 (2.6) |
| Dyspnoea on exertion | 95 (2.3) | 90 (2.2) |
| Sleep apnoea syndrome | 88 (2.2) | 91 (2.2) |
| Epistaxis | 61 (1.5) | 48 (1.2) |
| Oropharyngeal pain | 58 (1.4) | 58 (1.4) |
| Asthma | 57 (1.4) | 53 (1.3) |
| Allergic rhinitis | 46 (1.1) | 36 (0.9) |
| Pleural effusion | 29 (0.7) | 44 (1.1) |
| Metabolic and nutritional disorders | 953 (23.3) | 877 (21.4) |
| Gout | 171 (4.2) | 127 (3.1) |
| Diabetes mellitus | 169 (4.1) | 173 (4.2) |
| Diabetes mellitus type 2 | 147 (3.6) | 133 (3.3) |
| Vitamin D deficiency | 94 (2.3) | 67 (1.6) |
| Hypokalaemia | 83 (2.0) | 78 (1.9) |
| Hyperglycaemia | 71 (1.7) | 93 (2.3) |
| Diabetes mellitus inadequate control | 61 (1.5) | 31 (0.8) |
| Hypoglycaemia | 60 (1.5) | 58 (1.4) |
| Dehydration | 51 (1.2) | 43 (1.1) |
| Hyperkalaemia | 32 (0.8) | 55 (1.3) |
| Hypomagnesaemia | 29 (0.7) | 43 (1.1) |
| Cardiac disorders | 910 (22.3) | 855 (20.9) |
| Atrial fibrillation | 215 (5.3) | 159 (3.9) |
| Angina | 200 (4.9) | 205 (5.0) |
| Palpitations | 78 (1.9) | 75 (1.8) |
| Angina, unstable | 64 (1.6) | 88 (2.2) |
| Cardiac failure congestive | 56 (1.4) | 60 (1.5) |
| Ventricular extrasystoles | 27 (0.7) | 48 (1.2) |
| Investigations | 869 (21.3) | 931 (22.8) |
| Blood glucose increased | 105 (2.6) | 120 (2.9) |
| Blood pressure increased | 76 (1.9) | 71 (1.7) |
| Glycosylated haemoglobin increased | 64 (1.6) | 72 (1.8) |

Table 6: Common AEs[a] – RCT, direct comparison: icosapent ethyl + statins ± ezetimib vs. placebo + statins ± ezetimib (multipage table)

| Study | Patients with event n (%) | |
|---|---|---|
| SOC[b] PT[b] | Icosapent ethyl + statins ± ezetimib N = 4089 | Placebo + statins ± ezetimib N = 4090 |
| Troponin increased | 63 (1.5) | 69 (1.7) |
| Low-density lipoprotein increased | 59 (1.4) | 89 (2.2) |
| Blood creatine phosphokinase increased | 54 (1.3) | 79 (1.9) |
| Weight decreased | 50 (1.2) | 52 (1.3) |
| Troponin T increased | 46 (1.1) | 51 (1.2) |
| Blood uric acid increased | 45 (1.1) | 39 (1.0) |
| Cardiac murmur | 42 (1.0) | 45 (1.1) |
| Blood creatinine increased | 36 (0.9) | 45 (1.1) |
| Injury, poisoning and procedural complications | 748 (18.3) | 697 (17.0) |
| Fall | 149 (3.6) | 138 (3.4) |
| Contusion | 102 (2.5) | 85 (2.1) |
| Pulled muscle | 62 (1.5) | 39 (1.0) |
| Laceration | 59 (1.4) | 65 (1.6) |
| Skin abrasion | 44 (1.1) | 26 (0.6) |
| Ligament strain | 41 (1.0) | 41 (1.0) |
| Intraprocedural pain | 36 (0.9) | 50 (1.2) |
| Vascular disorders | 709 (17.3) | 717 (17.5) |
| Hypertension | 320 (7.8) | 344 (8.4) |
| Hypotension | 99 (2.4) | 95 (2.3) |
| Intermittent claudication | 44 (1.1) | 39 (1.0) |
| Hypertensive crisis | 30 (0.7) | 43 (1.1) |
| Skin and subcutaneous tissue disorders | 619 (15.1) | 557 (13.6) |
| Rash | 116 (2.8) | 83 (2.0) |
| Skin lesion | 50 (1.2) | 38 (0.9) |
| Eczema | 44 (1.1) | 37 (0.9) |
| Skin ulceration | 44 (1.1) | 32 (0.8) |
| Actinic keratosis | 42 (1.0) | 40 (1.0) |
| Dermatitis | 42 (1.0) | 25 (0.6) |
| Pruritus | 41 (1.0) | 39 (1.0) |
| Renal and urinary disorders | 607 (14.8) | 561 (13.7) |
| Acute kidney injury | 103 (2.5) | 89 (2.2) |
| Nephrolithiasis | 85 (2.1) | 79 (1.9) |
| Haematuria | 77 (1.9) | 60 (1.5) |
| Chronic kidney disease | 55 (1.3) | 49 (1.2) |
| Renal failure | 54 (1.3) | 51 (1.2) |
| Renal insufficiency | 45 (1.1) | 40 (1.0) |

Table 6: Common AEs[a] – RCT, direct comparison: icosapent ethyl + statins ± ezetimib vs. placebo + statins ± ezetimib (multipage table)

| Study | Patients with event n (%) | |
|---|---|---|
| SOC[b] PT[b] | Icosapent ethyl + statins ± ezetimib N = 4089 | Placebo + statins ± ezetimib N = 4090 |
| Renal cyst | 45 (1.1) | 37 (0.9) |
| Urinary retention | 43 (1.1) | 35 (0.9) |
| Neoplasms benign, malignant and unspecified (incl. cysts and polyps) | 510 (12.5) | 513 (12.5) |
| Basal cell carcinoma | 87 (2.1) | 82 (2.0) |
| Prostate cancer | 45 (1.1) | 47 (1.1) |
| Eye disorders | 478 (11.7) | 429 (10.5) |
| Cataract | 233 (5.7) | 208 (5.1) |
| Psychiatric disorders | 372 (9.1) | 362 (8.9) |
| Insomnia | 124 (3.0) | 111 (2.7) |
| Depression | 113 (2.8) | 103 (2.5) |
| Anxiety | 86 (2.1) | 86 (2.1) |
| Blood and lymphatic system disorders | 321 (7.9) | 372 (9.1) |
| Anaemia | 191 (4.7) | 236 (5.8) |
| Reproductive system and breast disorders | 275 (6.7) | 268 (6.6) |
| Benign prostatatic hyperplasia | 93 (2.3) | 80 (2.0) |
| Erectile dysfunction | 46 (1.1) | 58 (1.4) |
| Ear and labyrinth disorders | 227 (5.6) | 208 (5.1) |
| Vertigo | 73 (1.8) | 80 (2.0) |
| Hepatobiliary disorders | 181 (4.4) | 176 (4.3) |
| Cholelithiasis | 61 (1.5) | 61 (1.5) |
| Hepatic steatosis | 47 (1.1) | 48 (1.2) |
| Endocrine disorders | 122 (3.0) | 139 (3.4) |
| Hypothyroidism | 59 (1.4) | 74 (1.8) |
| Immune system disorders | 100 (2.4) | 74 (1.8) |
| Seasonal allergy | 42 (1.0) | 34 (0.8) |

a. Events which occurred in ≥ 1% of patients in at least 1 study arm.
b. MedDRA version 20.1; SOCs and PTs used unmodified from Module 4 A.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: preferred term; RCT: randomized controlled trial; SOC: System Organ Class

Table 7: Common AEs[a] – RCT, direct comparison: icosapent ethyl + statins ± ezetimib vs. placebo + statins ± ezetimib

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[b]**<br>**PT[b]** | **Icosapent ethyl + statins ± ezetimib N = 4089** | **Placebo + statins ± ezetimib N = 4090** |
| **REDUCE-IT** | | |
| **Total SAE rate** | 1252 (30.6) | 1254 (30.7) |
| Infections and infestations | 332 (8.1) | 309 (7.6) |
| Pneumonia | 105 (2.6) | 118 (2.9) |
| Cardiac disorders | 192 (4.7) | 224 (5.5) |
| Angina | 48 (1.2) | 48 (1.2) |
| Angina unstable | 41 (1.0) | 53 (1.3) |
| Musculoskeletal and connective tissue disorders | 188 (4.6) | 165 (4.0) |
| Osteoarthritis | 81 (2.0) | 73 (1.8) |
| General disorders and administration site conditions | 139 (3.4) | 153 (3.7) |
| Chest pain | 66 (1.6) | 66 (1.6) |
| Non-cardiac chest pain | 49 (1.2) | 52 (1.3) |
| Renal and urinary disorders | 120 (2.9) | 100 (2.4) |
| Acute kidney injury | 47 (1.1) | 34 (0.8) |

a. Events which occurred in ≥ 1% patients in at least 1 study arm.
b. MedDRA version 20.1; SOCs and PTs taken from Module 4 A .

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse events; SOC: System Organ Class

Table 8: Discontinuation due to AEs[a] – RCT, direct comparison: icosapent ethyl + statins ± ezetimib vs. placebo + statins ± ezetimib

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[b]**<br>**PT[b]** | **Icosapent ethyl + statins ± ezetimib N = 4089** | **Placebo + statins ± ezetimib N = 4090** |
| **REDUCE-IT** | | |
| **Overall rate of discontinuations due to AEs** | 321 (7.9) | 335 (8.2) |
| Gastrointestinal disorders | 146 (3.6) | 160 (3.9) |
| Diarrhoea | 47 (1.1) | 76 (1.9) |
| Nausea | 23 (0.6) | 18 (0.4) |
| Neoplasms benign, malignant and unspecified (incl. cysts and polyps) | 41 (1.0) | 39 (1.0) |
| Skin and subcutaneous tissue disorders | 24 (0.6) | 20 (0.5) |
| Rash | 7 (0.2) | 10 (0.2) |
| Musculoskeletal and connective tissue disorders | 21 (0.5) | 22 (0.5) |
| Investigations | 20 (0.5) | 21 (0.5) |
| Nervous system disorders | 18 (0.4) | 20 (0.5) |
| Respiratory, thoracic and mediastinal disorders | 16 (0.4) | 12 (0.3) |
| General disorders and administration site conditions | 15 (0.4) | 11 (0.3) |
| Renal and urinary disorders | 15 (0.4) | 3 (0.1) |
| Infections and infestations | 12 (0.3) | 16 (0.4) |
| Cardiac disorders | 12 (0.3) | 10 (0.2) |
| Blood and lymphatic system disorders | 5 (0.1) | 14 (0.3) |

a. Events which occurred in ≥ 10 patients in at least 1 study arm.
b. MedDRA version 20.1; SOCs and PTs used unmodified from Module 4 A.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: preferred term; RCT: randomized controlled trial; SOC: System Organ Class

## Appendix B Kaplan-Meier curves

### B.1 Mortality

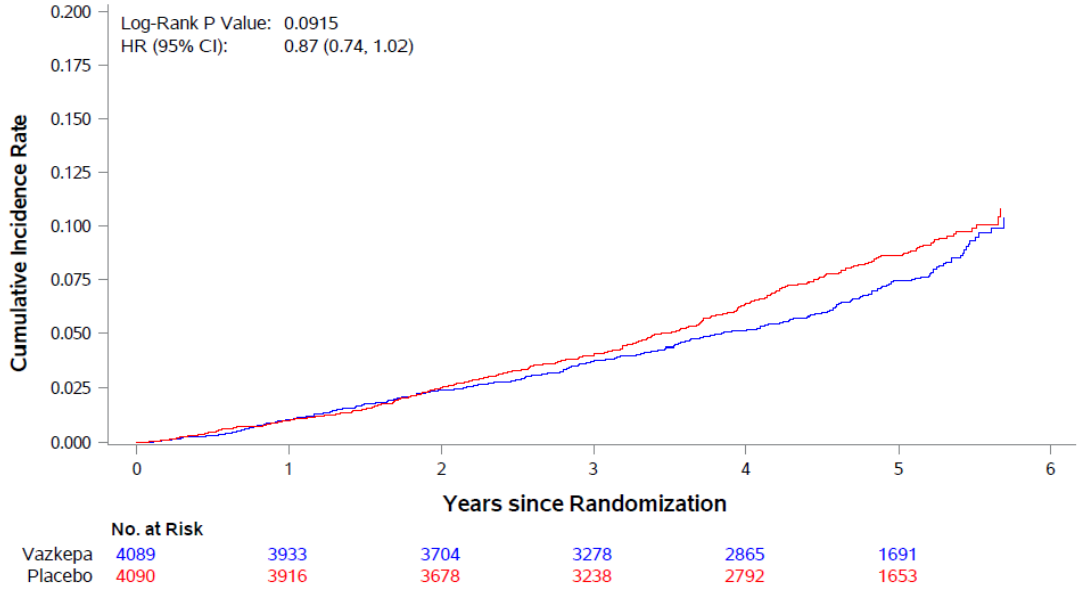


Figure 1: Kaplan-Meier curves for the outcome of all-cause mortality in the REDUCE-IT study – RCT, direct comparison: icosapent ethyl + statins ± ezetimib vs. placebo + statins ± ezetimibe

## B.2 Morbidity

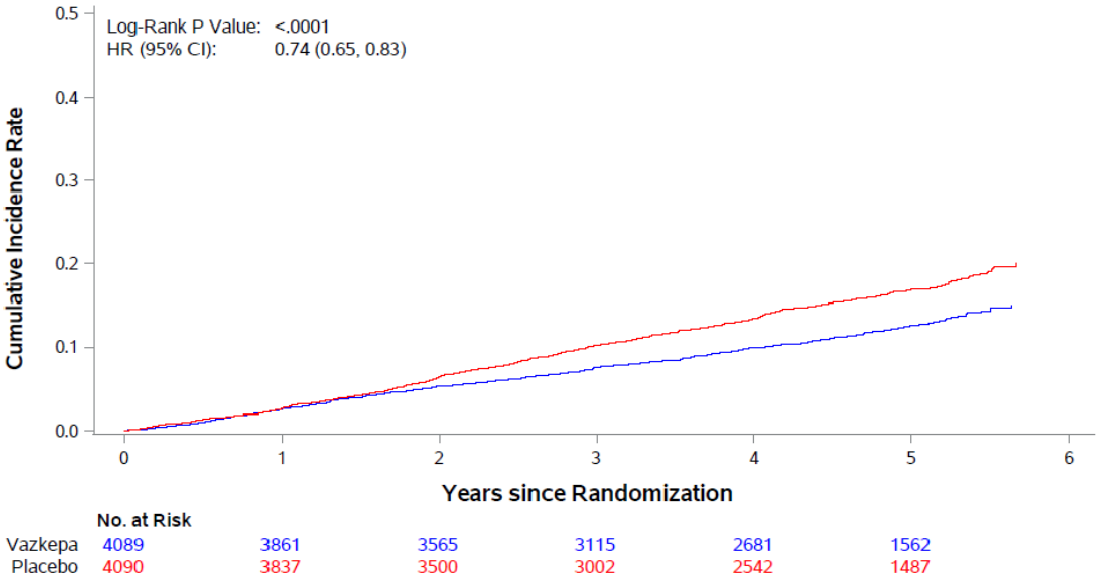


Figure 2: Kaplan-Meier curves for the outcome of MACE, consisting of the components cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke, in the REDUCE-IT study – RCT, direct comparison: icosapent ethyl + statins ± ezetimib vs. placebo + statins ± ezetimibe

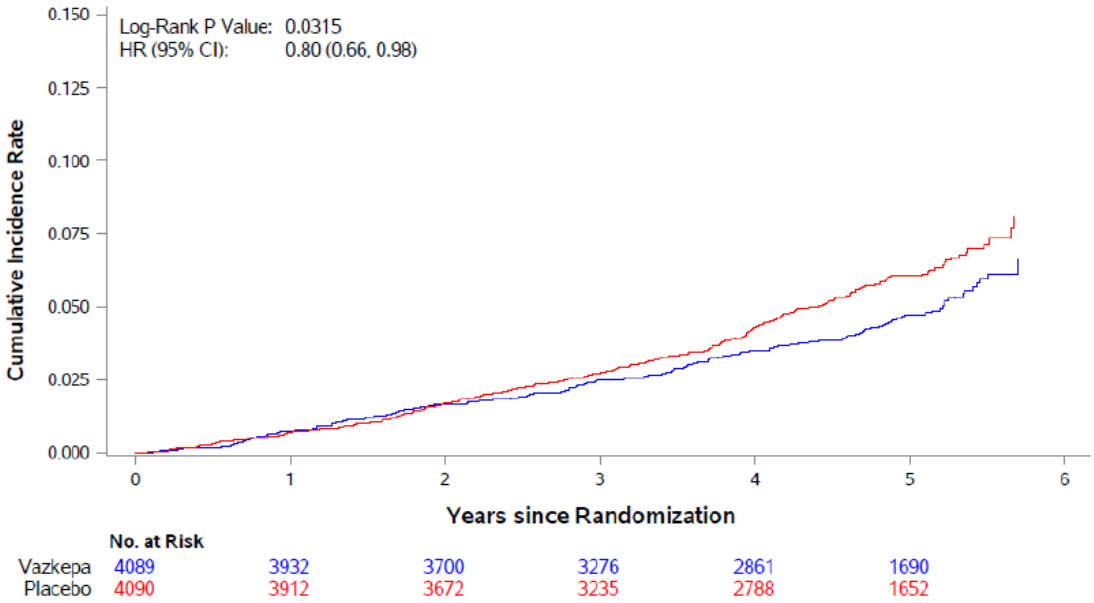


Figure 3: Kaplan-Meier curves for the outcome of cardiovascular death in the REDUCE-IT study – RCT, direct comparison: icosapent ethyl + statins ± ezetimib vs. placebo + statins ± ezetimib

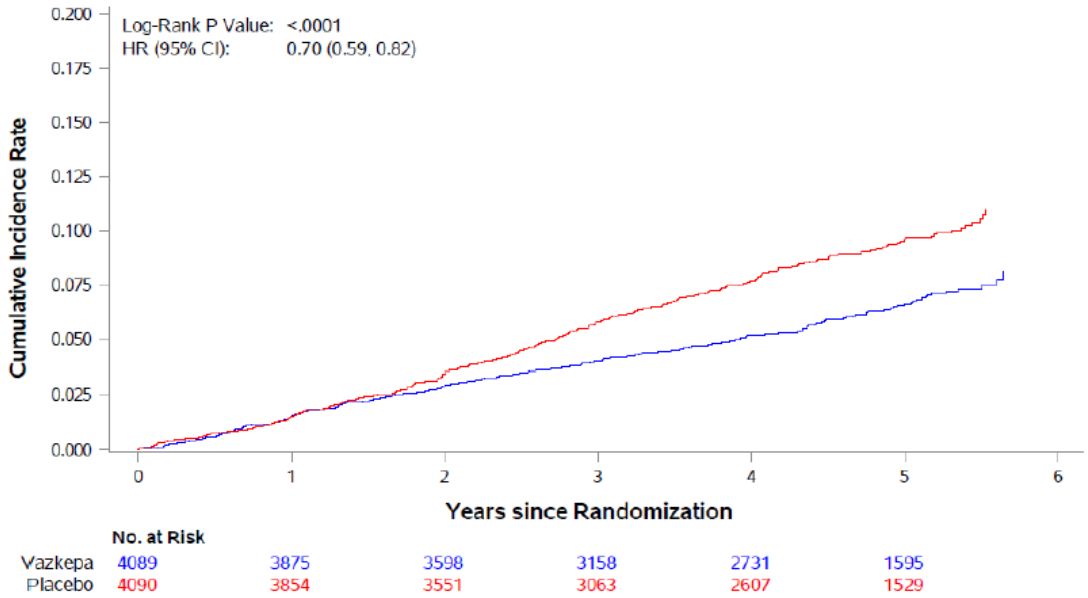


Figure 4: Kaplan-Meier curves for the outcome of nonfatal myocardial infarction in the REDUCE-IT study – RCT, direct comparison: icosapent ethyl + statins ± ezetimib vs. placebo + statins ± ezetimibe

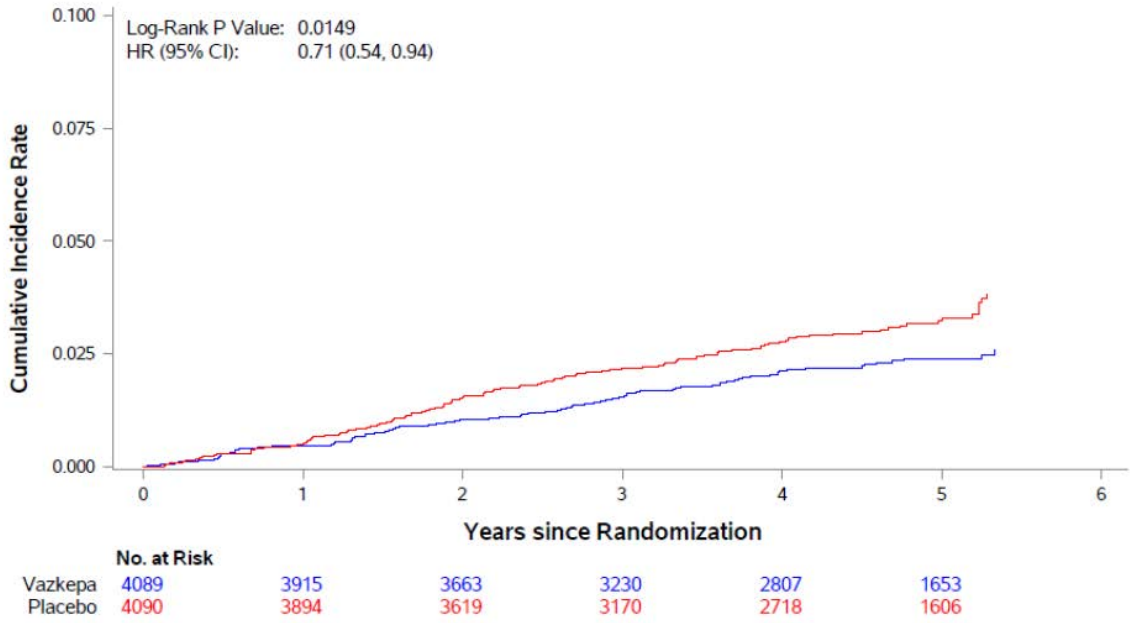


Figure 5: Kaplan-Meier curves for the outcome of nonfatal stroke in the REDUCE-IT study – RCT, direct comparison: icosapent ethyl + statins ± ezetimib vs. placebo + statins ± ezetimibe

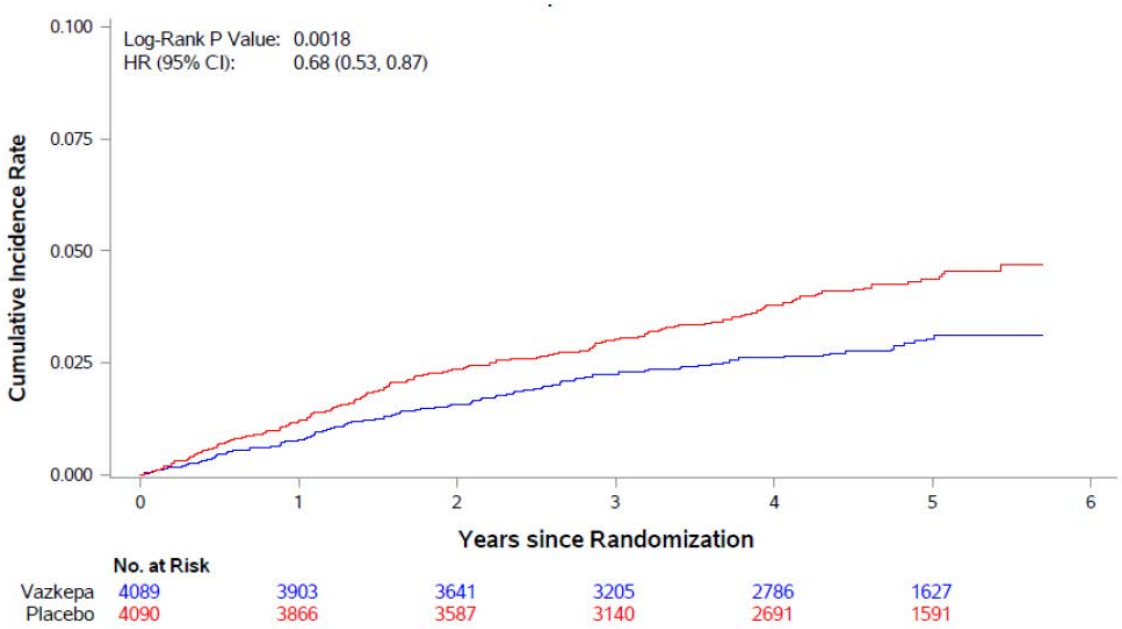


Figure 6: Kaplan-Meier curves for the outcome of hospitalization for unstable angina in the REDUCE-IT study – RCT, direct comparison: icosapent ethyl + statins ± ezetimib vs. placebo + statins ± ezetimibe

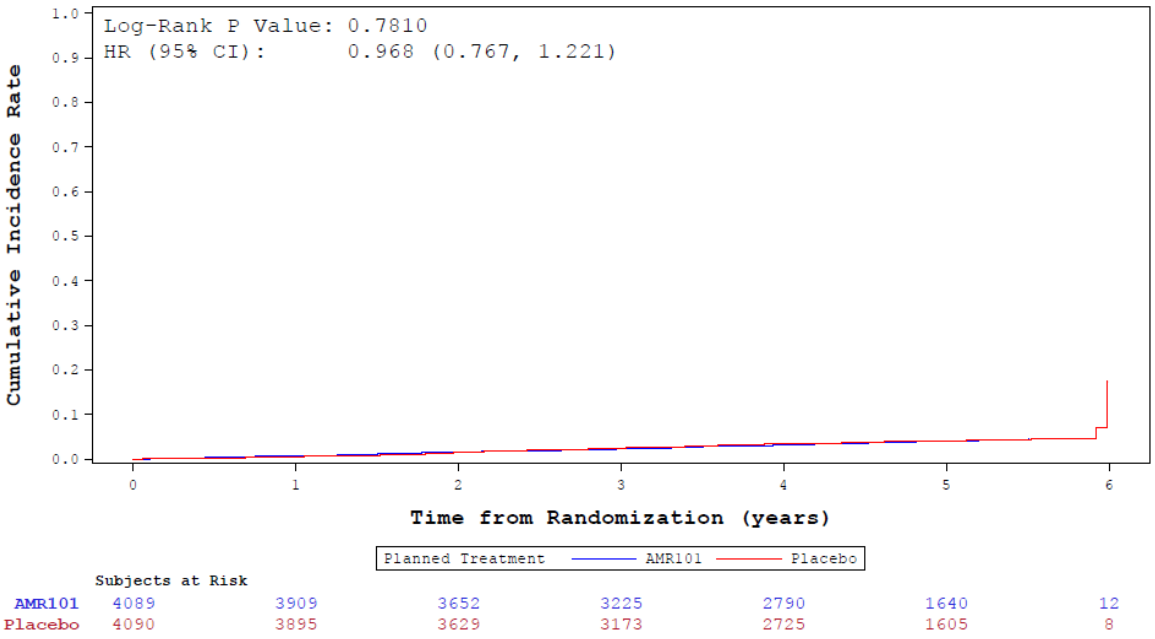


Figure 7: Kaplan-Meier curves for the outcome of hospitalization for heart failure in the REDUCE-IT study – RCT, direct comparison: icosapent ethyl + statins ± ezetimib vs. placebo + statins ± ezetimib