Clinical trial results:
A Two-part, Open-label, Randomised, Crossover, Multicentre, Phase II Study to Investigate the Presence of Pancreatic Exocrine Insufficiency (PEI) in Patients with Type 2 Diabetes Mellitus, and to Investigate the Pharmacokinetics of EPANOVA® and OMACOR® Following a Single Oral Dose in Patients with Different Degrees of PEI

Summary

EudraCT number	2014-003511-11
Trial protocol	SK SE DK HU LV PL
Global end of trial date	17 November 2015

Results information

Result version number	v2 (current)
This version publication date	22 December 2016
First version publication date	29 September 2016
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	D5881C00006

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02370537
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	Gärturnavägen 1, Södertälje, Sweden, SE-151 85
Public contact	Stefan Carlsson, AstraZeneca AB, Stefan.C.Carlsson@astrazeneca.com
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 November 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 November 2015
Global end of trial reached?	Yes
Global end of trial date	17 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

In Part A, to describe the distribution of serum triglycerides (TGs) in patients with Type 2 Diabetes Mellitus (T2DM) by degree of PEI as determined by levels of faecal elastase-1 concentrations (FEC). In Part B, to evaluate and compare the plasma exposure of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) from EPANOVA® and OMACOR®, respectively, in patients with T2DM with different levels of FEC.

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation/Good Clinical Practice and applicable regulatory requirements and the AstraZeneca policy on Bioethics.

Background therapy: -

Evidence for comparator:

OMACOR® is an omega-3 fatty acid ethyl esters formulation that is approved treatment for the same indication as EPANOVA®, i.e. as an adjunct to diet to reduce TG levels in adults with severe hypertriglyceridaemia and is used as a comparator in this study. OMACOR® requires hydrolysis in the small intestine by pancreatic lipase for intestinal absorption whereas EPANOVA® does not.

Actual start date of recruitment	07 April 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 25
Country: Number of subjects enrolled	Hungary: 83
Country: Number of subjects enrolled	Latvia: 68
Country: Number of subjects enrolled	Poland: 45
Country: Number of subjects enrolled	Slovakia: 14
Country: Number of subjects enrolled	Sweden: 80
Worldwide total number of subjects	315
EEA total number of subjects	315

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	193
From 65 to 84 years	122
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First patient enrolled: 7 April 2015. Last patient completed Part B: 17 November 2015. This study was performed in 23 centres across 6 countries in Europe.

Pre-assignment

Screening details:

A total of 490 patients were screened and of these, 315 patients met all inclusion and none of the exclusion criteria and completed the first part of the study. 51 patients were randomised to treatment in the second part of the study.

Period 1

Period 1 title	Part A (Open-label recruitment)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Low FEC (EPANOVA® and OMACOR®)

Arm description:

Part A investigated serum lipids, especially TGs and FEC as a measure of pancreatic exocrine function in the study population. Patients in the Low FEC group were determined to have FEC levels <100 microgram per gram (mcg/g). No treatment was administered in Part A which was a recruitment phase for Part B. In Part B, study treatment was administered at Visit 4 and Visit 7 with a randomised crossover design to a treatment sequence: AB (a single dose of EPANOVA® 4 g followed by a single dose of OMACOR® 4 g) or BA (a single dose of OMACOR® 4 g followed by a single dose of EPANOVA® 4 g).

Arm type	Stratum of pancreatic exocrine function
Investigational medicinal product name	EPANOVA®
Investigational medicinal product code	
Other name	Omega-3 carboxylic acids
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

A single dose of EPANOVA® 4 g (administered as 4 x 1 g capsules) was taken orally 30 minutes after the start of a Therapeutic Lifestyle Changes (TLC) diet-based breakfast.

Investigational medicinal product name	OMACOR®
Investigational medicinal product code	
Other name	Omega-3 ethyl ester
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

A single dose of OMACOR® 4 g (administered as 4 x 1 g capsules) was taken orally 30 minutes after the start of a TLC diet-based breakfast.

Arm title	Intermediate FEC (EPANOVA® and OMACOR®)

Arm description:

Part A investigated serum lipids, especially TGs and FEC as a measure of pancreatic exocrine function in the study population. Patients in the Intermediate FEC group were determined to have FEC levels ≥100 mcg/g to <200 mcg/g. No treatment was administered in Part A which was a recruitment phase for Part B. In Part B, study treatment was administered at Visit 4 and Visit 7 with a randomised crossover design to a treatment sequence: AB (a single dose of EPANOVA® 4 g followed by a single dose of OMACOR® 4 g) or BA (a single dose of OMACOR® 4 g followed by a single dose of EPANOVA® 4 g).

Arm type	Stratum of pancreatic exocrine function

Investigational medicinal product name	EPANOVA®
Investigational medicinal product code	
Other name	Omega-3 carboxylic acids
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

A single dose of EPANOVA® 4 g (administered as 4 x 1 g capsules) was taken orally 30 minutes after the start of a TLC diet-based breakfast.

Investigational medicinal product name	OMACOR®
Investigational medicinal product code	
Other name	Omega-3 ethyl ester
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

A single dose of OMACOR® 4 g (administered as 4 x 1 g capsules) was taken orally 30 minutes after the start of a TLC diet-based breakfast.

Arm title	Normal FEC (EPANOVA® and OMACOR®)

Arm description:

Part A investigated serum lipids, especially TGs and FEC as a measure of pancreatic exocrine function in the study population. Patients in the Normal FEC group were determined to have FEC levels ≥200 mcg/g. No treatment was administered in Part A which was a recruitment phase for Part B. In Part B, study treatment was administered at Visit 4 and Visit 7 with a randomised crossover design to a treatment sequence: AB (a single dose of EPANOVA® 4 g followed by a single dose of OMACOR® 4 g) or BA (a single dose of OMACOR® 4 g followed by a single dose of EPANOVA® 4 g).

Arm type	Stratum of pancreatic exocrine function
Investigational medicinal product name	EPANOVA®
Investigational medicinal product code	
Other name	Omega-3 carboxylic acids
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

A single dose of EPANOVA® 4 g (administered as 4 x 1 g capsules) was taken orally 30 minutes after the start of a TLC diet-based breakfast.

Investigational medicinal product name	OMACOR®
Investigational medicinal product code	
Other name	Omega-3 ethyl ester
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

A single dose of OMACOR® 4 g (administered as 4 x 1 g capsules) was taken orally 30 minutes after the start of a TLC diet-based breakfast.

Number of subjects in period 1	Low FEC (EPANOVA® and OMACOR®)	Intermediate FEC (EPANOVA® and OMACOR®)	Normal FEC (EPANOVA® and OMACOR®)
Started	16	16	283
Completed	16	15	282
Not completed	0	1	1
Consent withdrawn by subject	-	1	-
Adverse event, non-fatal	-	-	1

Period 2

Period 2 title	Part B
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Low FEC (EPANOVA® and OMACOR®)

Arm description:

Part A investigated serum lipids, especially TGs and FEC as a measure of pancreatic exocrine function in the study population. Patients in the Low FEC group were determined to have FEC levels <100 mcg/g. No treatment was administered in Part A which was a recruitment phase for Part B. In Part B, study treatment was administered at Visit 4 and Visit 7 with a randomised crossover design to a treatment sequence: AB (a single dose of EPANOVA® 4 g followed by a single dose of OMACOR® 4 g) or BA (a single dose of OMACOR® 4 g followed by a single dose of EPANOVA® 4 g).

Arm type	Stratum of pancreatic exocrine function
Investigational medicinal product name	EPANOVA®
Investigational medicinal product code	
Other name	Omega-3 carboxylic acids
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

A single dose of EPANOVA® 4 g (administered as 4 x 1 g capsules) was taken orally 30 minutes after the start of a TLC diet-based breakfast.

Investigational medicinal product name	OMACOR®
Investigational medicinal product code	
Other name	Omega-3 ethyl ester
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

A single dose of OMACOR® 4 g (administered as 4 x 1 g capsules) was taken orally 30 minutes after the start of a TLC diet-based breakfast.

Arm title	Intermediate FEC (EPANOVA® and OMACOR®)

Arm description:

Part A investigated serum lipids, especially TGs and FEC as a measure of pancreatic exocrine function in the study population. Patients in the Intermediate FEC group were determined to have FEC levels ≥100 mcg/g to <200 mcg/g. No treatment was administered in Part A which was a recruitment phase for Part B. In Part B, study treatment was administered at Visit 4 and Visit 7 with a randomised crossover design to a treatment sequence: AB (a single dose of EPANOVA® 4 g followed by a single dose of OMACOR® 4 g) or BA (a single dose of OMACOR® 4 g followed by a single dose of EPANOVA® 4 g).

Arm type	Stratum of pancreatic exocrine function
Investigational medicinal product name	OMACOR®
Investigational medicinal product code	
Other name	Omega-3 ethyl ester
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

A single dose of OMACOR® 4 g (administered as 4 x 1 g capsules) was taken orally 30 minutes after the start of a TLC diet-based breakfast.

Investigational medicinal product name	EPANOVA®
Investigational medicinal product code	
Other name	Omega-3 carboxylic acids
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

A single dose of EPANOVA® 4 g (administered as 4 x 1 g capsules) was taken orally 30 minutes after the start of a TLC diet-based breakfast.

Arm title	Normal FEC (EPANOVA® and OMACOR®)

Arm description:

Part A investigated serum lipids, especially TGs and FEC as a measure of pancreatic exocrine function in the study population. Patients in the Normal FEC group were determined to have FEC levels ≥200 mcg/g. No treatment was administered in Part A which was a recruitment phase for Part B. In Part B, study treatment was administered at Visit 4 and Visit 7 with a randomised crossover design to a treatment sequence: AB (a single dose of EPANOVA® 4 g followed by a single dose of OMACOR® 4 g) or BA (a single dose of OMACOR® 4 g followed by a single dose of EPANOVA® 4 g).

Arm type	Stratum of pancreatic exocrine function
Investigational medicinal product name	OMACOR®
Investigational medicinal product code	
Other name	Omega-3 ethyl ester
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

A single dose of OMACOR® 4 g (administered as 4 x 1 g capsules) was taken orally 30 minutes after the start of a TLC diet-based breakfast.

Investigational medicinal product name	EPANOVA®
Investigational medicinal product code	
Other name	Omega-3 carboxylic acids
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

A single dose of EPANOVA® 4 g (administered as 4 x 1 g capsules) was taken orally 30 minutes after the start of a TLC diet-based breakfast.

Number of subjects in period 2	Low FEC (EPANOVA® and OMACOR®)	Intermediate FEC (EPANOVA® and OMACOR®)	Normal FEC (EPANOVA® and OMACOR®)
Started	16	15	282
Randomised in Part B	15	13	23
Period 1 Sequence AB	8 [1]	6 [2]	11 [3]
Period 1 Sequence BA	7 [4]	7 [5]	12 [6]
Period 2 Sequence AB	8 [7]	5 [8]	11 [9]
Period 2 Sequence BA	7 [10]	7 [11]	12 [12]
Completed	15	12	23
Not completed	1	3	259
Consent withdrawn by subject	-	1	-
Not randomised to receive treatment	1	2	259

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects started and completed is presented for Period 2 (Part B) overall; additionally the intermediate milestones represent the numbers of subjects completing each treatment sequence.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects started and completed is presented for Period 2 (Part B) overall; additionally the intermediate milestones represent the numbers of subjects completing each treatment sequence.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects started and completed is presented for Period 2 (Part B) overall; additionally the intermediate milestones represent the numbers of subjects completing each treatment sequence.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects started and completed is presented for Period 2 (Part B) overall; additionally the intermediate milestones represent the numbers of subjects completing each treatment sequence.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects started and completed is presented for Period 2 (Part B) overall; additionally the intermediate milestones represent the numbers of subjects completing each treatment sequence.

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects started and completed is presented for Period 2 (Part B) overall; additionally the intermediate milestones represent the numbers of subjects completing each treatment sequence.

[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects started and completed is presented for Period 2 (Part B) overall; additionally the intermediate milestones represent the numbers of subjects completing each treatment sequence.

[8] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects started and completed is presented for Period 2 (Part B) overall; additionally the intermediate milestones represent the numbers of subjects completing each treatment sequence.

[9] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects started and completed is presented for Period 2 (Part B) overall; additionally the intermediate milestones represent the numbers of subjects completing each treatment sequence.

[10] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects started and

completed is presented for Period 2 (Part B) overall; additionally the intermediate milestones represent the numbers of subjects completing each treatment sequence.

[11] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects started and completed is presented for Period 2 (Part B) overall; additionally the intermediate milestones represent the numbers of subjects completing each treatment sequence.

[12] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects started and completed is presented for Period 2 (Part B) overall; additionally the intermediate milestones represent the numbers of subjects completing each treatment sequence.

Baseline characteristics

Reporting groups	
Reporting group title	Low FEC (EPANOVA® and OMACOR®)

Reporting group description:

Part A investigated serum lipids, especially TGs and FEC as a measure of pancreatic exocrine function in the study population. Patients in the Low FEC group were determined to have FEC levels <100 microgram per gram (mcg/g). No treatment was administered in Part A which was a recruitment phase for Part B. In Part B, study treatment was administered at Visit 4 and Visit 7 with a randomised crossover design to a treatment sequence: AB (a single dose of EPANOVA® 4 g followed by a single dose of OMACOR® 4 g) or BA (a single dose of OMACOR® 4 g followed by a single dose of EPANOVA® 4 g).

Reporting group title	Intermediate FEC (EPANOVA® and OMACOR®)

Reporting group description:

Part A investigated serum lipids, especially TGs and FEC as a measure of pancreatic exocrine function in the study population. Patients in the Intermediate FEC group were determined to have FEC levels ≥100 mcg/g to <200 mcg/g. No treatment was administered in Part A which was a recruitment phase for Part B. In Part B, study treatment was administered at Visit 4 and Visit 7 with a randomised crossover design to a treatment sequence: AB (a single dose of EPANOVA® 4 g followed by a single dose of OMACOR® 4 g) or BA (a single dose of OMACOR® 4 g followed by a single dose of EPANOVA® 4 g).

Reporting group title	Normal FEC (EPANOVA® and OMACOR®)

Reporting group description:

Part A investigated serum lipids, especially TGs and FEC as a measure of pancreatic exocrine function in the study population. Patients in the Normal FEC group were determined to have FEC levels ≥200 mcg/g. No treatment was administered in Part A which was a recruitment phase for Part B. In Part B, study treatment was administered at Visit 4 and Visit 7 with a randomised crossover design to a treatment sequence: AB (a single dose of EPANOVA® 4 g followed by a single dose of OMACOR® 4 g) or BA (a single dose of OMACOR® 4 g followed by a single dose of EPANOVA® 4 g).

Reporting group values	Low FEC (EPANOVA® and OMACOR®)	Intermediate FEC (EPANOVA® and OMACOR®)	Normal FEC (EPANOVA® and OMACOR®)
Number of subjects	16	16	283
Age categorical Units: Subjects			
In Utero	0	0	0
Preterm newborn- gestational age < 37 weeks	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days - 23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
From 18 - 64 years	11	11	171
From 65 - 84 years	5	5	112
Over 85 years	0	0	0
Gender, Male/Female Units: Participants			
Female	5	5	123
Male	11	11	160

Reporting group values	Total		
Number of subjects	315		

Age categorical Units: Subjects			
In Utero	0		
Preterm newborn- gestational age < 37 weeks	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days - 23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
From 18 - 64 years	193		
From 65 - 84 years	122		
Over 85 years	0		
Gender, Male/Female Units: Participants			
Female	133		
Male	182		

End points

End points reporting groups

Reporting group title	Low FEC (EPANOVA® and OMACOR®)

Reporting group description:

Part A investigated serum lipids, especially TGs and FEC as a measure of pancreatic exocrine function in the study population. Patients in the Low FEC group were determined to have FEC levels <100 microgram per gram (mcg/g). No treatment was administered in Part A which was a recruitment phase for Part B. In Part B, study treatment was administered at Visit 4 and Visit 7 with a randomised crossover design to a treatment sequence: AB (a single dose of EPANOVA® 4 g followed by a single dose of OMACOR® 4 g) or BA (a single dose of OMACOR® 4 g followed by a single dose of EPANOVA® 4 g).

Reporting group title	Intermediate FEC (EPANOVA® and OMACOR®)

Reporting group description:

Part A investigated serum lipids, especially TGs and FEC as a measure of pancreatic exocrine function in the study population. Patients in the Intermediate FEC group were determined to have FEC levels ≥100 mcg/g to <200 mcg/g. No treatment was administered in Part A which was a recruitment phase for Part B. In Part B, study treatment was administered at Visit 4 and Visit 7 with a randomised crossover design to a treatment sequence: AB (a single dose of EPANOVA® 4 g followed by a single dose of OMACOR® 4 g) or BA (a single dose of OMACOR® 4 g followed by a single dose of EPANOVA® 4 g).

Reporting group title	Normal FEC (EPANOVA® and OMACOR®)

Reporting group description:

Part A investigated serum lipids, especially TGs and FEC as a measure of pancreatic exocrine function in the study population. Patients in the Normal FEC group were determined to have FEC levels ≥200 mcg/g. No treatment was administered in Part A which was a recruitment phase for Part B. In Part B, study treatment was administered at Visit 4 and Visit 7 with a randomised crossover design to a treatment sequence: AB (a single dose of EPANOVA® 4 g followed by a single dose of OMACOR® 4 g) or BA (a single dose of OMACOR® 4 g followed by a single dose of EPANOVA® 4 g).

Reporting group title	Low FEC (EPANOVA® and OMACOR®)

Reporting group description:

Part A investigated serum lipids, especially TGs and FEC as a measure of pancreatic exocrine function in the study population. Patients in the Low FEC group were determined to have FEC levels <100 mcg/g. No treatment was administered in Part A which was a recruitment phase for Part B. In Part B, study treatment was administered at Visit 4 and Visit 7 with a randomised crossover design to a treatment sequence: AB (a single dose of EPANOVA® 4 g followed by a single dose of OMACOR® 4 g) or BA (a single dose of OMACOR® 4 g followed by a single dose of EPANOVA® 4 g).

Reporting group title	Intermediate FEC (EPANOVA® and OMACOR®)

Reporting group description:

Part A investigated serum lipids, especially TGs and FEC as a measure of pancreatic exocrine function in the study population. Patients in the Intermediate FEC group were determined to have FEC levels ≥100 mcg/g to <200 mcg/g. No treatment was administered in Part A which was a recruitment phase for Part B. In Part B, study treatment was administered at Visit 4 and Visit 7 with a randomised crossover design to a treatment sequence: AB (a single dose of EPANOVA® 4 g followed by a single dose of OMACOR® 4 g) or BA (a single dose of OMACOR® 4 g followed by a single dose of EPANOVA® 4 g).

Reporting group title	Normal FEC (EPANOVA® and OMACOR®)

Reporting group description:

Part A investigated serum lipids, especially TGs and FEC as a measure of pancreatic exocrine function in the study population. Patients in the Normal FEC group were determined to have FEC levels ≥200 mcg/g. No treatment was administered in Part A which was a recruitment phase for Part B. In Part B, study treatment was administered at Visit 4 and Visit 7 with a randomised crossover design to a treatment sequence: AB (a single dose of EPANOVA® 4 g followed by a single dose of OMACOR® 4 g) or BA (a single dose of OMACOR® 4 g followed by a single dose of EPANOVA® 4 g).

Subject analysis set title	Low FEC (EPANOVA® and OMACOR®)
Subject analysis set type	Full analysis

Subject analysis set description:

Patients had low levels (<100 mcg/g) of FEC, as determined by the average of the FEC from 2 stool samples collected between Visit 2 and Visit 3 as a measure of pancreatic exocrine function.

Subject analysis set title	Intermediate FEC (EPANOVA® and OMACOR®)
Subject analysis set type	Full analysis

Subject analysis set description:

Patients had intermediate levels (≥100 to <200 mcg/g) of FEC, as determined by the average of the FEC from 2 stool samples collected between Visit 2 and Visit 3 as a measure of pancreatic exocrine function.

Subject analysis set title	Normal FEC (EPANOVA® and OMACOR®)
Subject analysis set type	Full analysis

Subject analysis set description:

Patients had normal levels (≥200 mcg/g) of FEC, as determined by the average of the FEC from 2 stool samples collected between Visit 2 and Visit 3 as a measure of pancreatic exocrine function.

Subject analysis set title	Low FEC (EPANOVA® and OMACOR®)
Subject analysis set type	Per protocol

Subject analysis set description:

Part A investigated serum lipids, especially TGs and FEC to assess the relationship between serum TGs and degree of pancreatic exocrine function (as measured by FEC) in the study population. Patients in the Low FEC group were determined to have FEC levels <100 mcg/g. No treatment was administered in Part A which was a recruitment phase for Part B.

Subject analysis set title	Intermediate FEC (EPANOVA® and OMACOR®)
Subject analysis set type	Per protocol

Subject analysis set description:

Part A investigated serum lipids, especially TGs and FEC to assess the relationship between serum TGs and degree of pancreatic exocrine function (as measured by FEC) in the study population. Patients in the Intermediate FEC group were determined to have FEC levels ≥100 mcg/g to <200 mcg/g. No treatment was administered in Part A which was a recruitment phase for Part B.

Subject analysis set title	Normal FEC (EPANOVA® and OMACOR®)
Subject analysis set type	Per protocol

Subject analysis set description:

Part A investigated serum lipids, especially TGs and FEC to assess the relationship between serum TGs and degree of pancreatic exocrine function (as measured by FEC) in the study population. Patients in the Normal FEC group were determined to have FEC levels ≥200 mcg/g. No treatment was administered in Part A which was a recruitment phase for Part B.

Subject analysis set title	Low FEC (EPANOVA®)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

In Part B, study treatment was administered at Visit 4 (Day 21+5) and Visit 7 (10 to 14 days after Visit 4) with a randomised crossover design. Patients with low FEC, <100 mcg/g were randomised in Part B to a treatment sequence: AB (a single dose of EPANOVA® 4 g followed by a single dose of OMACOR® 4 g) or BA (a single dose of OMACOR® 4 g followed by a single dose of EPANOVA® 4 g).

Subject analysis set title	Low FEC (OMACOR®)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

In Part B, study treatment was administered at Visit 4 (Day 21+5) and Visit 7 (10 to 14 days after Visit 4) with a randomised crossover design. Patients with low FEC, <100 mcg/g were randomised in Part B to a treatment sequence: AB (a single dose of EPANOVA® 4 g followed by a single dose of OMACOR® 4 g) or BA (a single dose of OMACOR® 4 g followed by a single dose of EPANOVA® 4 g).

Subject analysis set title	Intermediate FEC (EPANOVA®)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

In Part B, study treatment was administered at Visit 4 (Day 21+5) and Visit 7 (10 to 14 days after Visit 4) with a randomised crossover design. Patients with intermediate FEC, ≥ 100 to <200 mcg/g, were randomised in Part B to a treatment sequence: AB (a single dose of EPANOVA® 4 g followed by a single dose of OMACOR® 4 g) or BA (a single dose of OMACOR® 4 g followed by a single dose of EPANOVA® 4 g).

Subject analysis set title	Intermediate FEC (OMACOR®)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

In Part B, study treatment was administered at Visit 4 (Day 21+5) and Visit 7 (10 to 14 days after Visit 4) with a randomised crossover design. Patients with intermediate FEC, ≥ 100 to <200 mcg/g, were randomised in Part B to a treatment sequence: AB (a single dose of EPANOVA® 4 g followed by a single dose of OMACOR® 4 g) or BA (a single dose of OMACOR® 4 g followed by a single dose of EPANOVA® 4

g).

Subject analysis set title	Normal FEC (EPANOVA®)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

In Part B, study treatment was administered at Visit 4 (Day 21+5) and Visit 7 (10 to 14 days after Visit 4) with a randomised crossover design. Patients with normal FEC, ≥ 200 mcg/g, were randomised in Part B to a treatment sequence: AB (a single dose of EPANOVA® 4 g followed by a single dose of OMACOR® 4 g) or BA (a single dose of OMACOR® 4 g followed by a single dose of EPANOVA® 4 g).

Subject analysis set title	Normal FEC (OMACOR®)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

In Part B, study treatment was administered at Visit 4 (Day 21+5) and Visit 7 (10 to 14 days after Visit 4) with a randomised crossover design. Patients with normal FEC, ≥ 200 mcg/g, were randomised in Part B to a treatment sequence: AB (a single dose of EPANOVA® 4 g followed by a single dose of OMACOR® 4 g) or BA (a single dose of OMACOR® 4 g followed by a single dose of EPANOVA® 4 g).

Subject analysis set title	Low FEC (OMACOR®)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

In Part B, study treatment was administered at Visit 4 (Day 21+5) and Visit 7 (10 to 14 days after Visit 4) with a randomised crossover design. Patients with low FEC, <100 mcg/g were randomised in Part B to a treatment sequence: AB (a single dose of EPANOVA® 4 g followed by a single dose of OMACOR® 4 g) or BA (a single dose of OMACOR® 4 g followed by a single dose of EPANOVA® 4 g).

Subject analysis set title	Normal FEC (EPANOVA®)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

In Part B, study treatment was administered at Visit 4 (Day 21+5) and Visit 7 (10 to 14 days after Visit 4) with a randomised crossover design. Patients with normal FEC, ≥ 200 mcg/g, were randomised in Part B to a treatment sequence: AB (a single dose of EPANOVA® 4 g followed by a single dose of OMACOR® 4 g) or BA (a single dose of OMACOR® 4 g followed by a single dose of EPANOVA® 4 g).

Subject analysis set title	Normal FEC (OMACOR®)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

In Part B, study treatment was administered at Visit 4 (Day 21+5) and Visit 7 (10 to 14 days after Visit 4) with a randomised crossover design. Patients with normal FEC, ≥ 200 mcg/g, were randomised in Part B to a treatment sequence: AB (a single dose of EPANOVA® 4 g followed by a single dose of OMACOR® 4 g) or BA (a single dose of OMACOR® 4 g followed by a single dose of EPANOVA® 4 g).

Primary: Part A: Serum TG level.

End point title	Part A: Serum TG level.[1]

End point description:

For Part A, the distribution of serum TG levels by the degree of PEI was assessed in patients with T2DM. Data is presented for the Per Protocol Analysis Set which included all enrolled patients without an important protocol deviation.

End point type	Primary

End point timeframe:

7 days after enrollment.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analysis was planned and performed for the variables in Part A.

End point values	Low FEC (EPANOVA® and OMACOR®)	Intermediate FEC (EPANOVA® and OMACOR®)	Normal FEC (EPANOVA® and OMACOR®)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	15	16	278	
Units: millimole per litre (mmol/L)				
arithmetic mean (standard deviation)	2.07 (± 0.63)	1.68 (± 0.57)	2 (± 1.16)	

Statistical analyses

No statistical analyses for this end point

Primary: Part B: Baseline corrected area under the plasma concentration time curve from time zero to last measurable concentration (AUC[0-last]) for total EPA following administration of EPANOVA® and OMACOR®.

End point title	Part B: Baseline corrected area under the plasma concentration time curve from time zero to last measurable concentration (AUC[0-last]) for total EPA following administration of EPANOVA® and OMACOR®.

End point description:

Baseline corrected AUC(0-last) was measured for total EPA following administration of single oral doses of EPANOVA® 4 g (A) and OMACOR® 4 g (B) (2-way crossover design) to patients with T2DM and different degrees of PEI. Data is presented for the Pharmacokinetic (PK) Analysis Set which included all randomised patients who received at least one dose of study treatment in Part B and had at least one post-dose PK measurement without any important protocol deviations.

End point type	Primary

End point timeframe:

Blood samples for analysis were taken at 1, 0.5, and 0.05 hours pre-dose, to be used as baseline, and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 24 and 48 hours post-dose.

End point values	Low FEC (EPANOVA®)	Low FEC (OMACOR®)	Intermediate FEC (EPANOVA®)	Intermediate FEC (OMACOR®)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	14	13	12
Units: hours*mcg per millilitre (h*mcg/mL)				
geometric mean (geometric coefficient of variation)	2170 (± 65.2)	1650 (± 31.3)	2000 (± 82.8)	946 (± 96)

End point values	Normal FEC (EPANOVA®)	Normal FEC (OMACOR®)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	22		
Units: hours*mcg per millilitre (h*mcg/mL)				
geometric mean (geometric coefficient of variation)	2070 (± 36.1)	1260 (± 126)		

Statistical analyses

Statistical analysis title	OMACOR® v EPANOVA® for low FEC group
Statistical analysis description:	
Back transformed results are based on the analysis of natural log-transformed data with a Linear Mixed Model containing the terms of FEC classification, treatment, FEC x treatment, sequence, and period as fixed effects and patient nested within sequence as random effect.	
Comparison groups	Low FEC (EPANOVA®) v Low FEC (OMACOR®)
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Geometric least-squares (GLS) Mean Ratio
Point estimate	0.75
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.52
upper limit	1.1

Statistical analysis title	OMACOR® v EPANOVA® for intermediate FEC group
Statistical analysis description:	
Back transformed results are based on the analysis of natural log-transformed data with a Linear Mixed Model containing the terms of FEC classification, treatment, FEC x treatment, sequence, and period as fixed effects and patient nested within sequence as random effect.	
Comparison groups	Intermediate FEC (EPANOVA®) v Intermediate FEC (OMACOR®)
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	GLS Mean ratio
Point estimate	0.48
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.32
upper limit	0.72

Statistical analysis title	OMACOR® v EPANOVA® for normal FEC group
Statistical analysis description:	
Back transformed results are based on the analysis of natural log-transformed data with a Linear Mixed Model containing the terms of FEC classification, treatment, FEC x treatment, sequence, and period as fixed effects and patient nested within sequence as random effect.	

Comparison groups	Normal FEC (EPANOVA®) v Normal FEC (OMACOR®)
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	GLS Mean Ratio
Point estimate	0.6
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.44
upper limit	0.82

Primary: Part B: Baseline corrected AUC(0-last) for total DHA following administration of EPANOVA® and OMACOR®.

End point title	Part B: Baseline corrected AUC(0-last) for total DHA following administration of EPANOVA® and OMACOR®.

End point description:

Baseline corrected AUC(0-last) was measured for total DHA following administration of single oral doses of EPANOVA® 4 g (A) and OMACOR® 4 g (B) (2-way crossover design) to patients with T2DM and different degrees of PEI. Data is presented for the PK Analysis Set which included all randomised patients who received at least one dose of study treatment in Part B and had at least one post-dose PK measurement without any important protocol deviations.

End point type	Primary

End point timeframe:

Blood samples for analysis were taken at 1, 0.5, and 0.05 hours pre-dose, to be used as baseline, and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 24 and 48 hours post-dose.

End point values	Low FEC (EPANOVA®)	Low FEC (OMACOR®)	Intermediate FEC (EPANOVA®)	Intermediate FEC (OMACOR®)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	14	13	12
Units: h*mcg/mL				
geometric mean (geometric coefficient of variation)	801 (± 55.7)	1040 (± 47.1)	719 (± 85)	567 (± 70.7)

End point values	Normal FEC (EPANOVA®)	Normal FEC (OMACOR®)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	22		
Units: h*mcg/mL				
geometric mean (geometric coefficient of variation)	625 (± 90.2)	810 (± 105)		

Statistical analyses

Statistical analysis title	OMACOR® v EPANOVA® for low FEC group

Statistical analysis description:

Back transformed results are based on the analysis of natural log-transformed data with a Linear Mixed Model containing the terms of FEC classification, treatment, FEC x treatment, sequence, and period as fixed effects and patient nested within sequence as random effect.

Comparison groups	Low FEC (EPANOVA®) v Low FEC (OMACOR®)
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	GLS Mean Ratio
Point estimate	1.28
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.84
upper limit	1.93

Statistical analysis title	OMACOR® v EPANOVA® for intermediate FEC group

Statistical analysis description:

Back transformed results are based on the analysis of natural log-transformed data with a Linear Mixed Model containing the terms of FEC classification, treatment, FEC x treatment, sequence, and period as fixed effects and patient nested within sequence as random effect.

Comparison groups	Intermediate FEC (EPANOVA®) v Intermediate FEC (OMACOR®)
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	GLS Mean Ratio
Point estimate	0.8
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.51
upper limit	1.25

Statistical analysis title	OMACOR® v EPANOVA® for normal FEC group

Statistical analysis description:

Back transformed results are based on the analysis of natural log-transformed data with a Linear Mixed Model containing the terms of FEC classification, treatment, FEC x treatment, sequence, and period as fixed effects and patient nested within sequence as random effect.

Comparison groups	Normal FEC (EPANOVA®) v Normal FEC (OMACOR®)

Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	GLS Mean Ratio
Point estimate	1.29
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.92
upper limit	1.82

Primary: Part B: Baseline corrected AUC(0-last) for total EPA+DHA following administration of EPANOVA® and OMACOR®.

End point title	Part B: Baseline corrected AUC(0-last) for total EPA+DHA following administration of EPANOVA® and OMACOR®.

End point description:

Baseline corrected AUC(0-last) was measured for the sum of EPA and DHA (total EPA+DHA) following administration of single oral doses of EPANOVA® 4 g (A) and OMACOR® 4 g (B) (2-way crossover design) to patients with T2DM and different degrees of PEI. Data is presented for the PK Analysis Set which included all randomised patients who received at least one dose of study treatment in Part B and had at least one post-dose PK measurement without any important protocol deviations.

End point type	Primary

End point timeframe:

Blood samples for analysis were taken at 1, 0.5, and 0.05 hours pre-dose, to be used as baseline, and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 24 and 48 hours post-dose.

End point values	Low FEC (EPANOVA®)	Low FEC (OMACOR®)	Intermediate FEC (EPANOVA®)	Intermediate FEC (OMACOR®)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	14	13	12
Units: h*nanomole/mL (h*nmol/mL)				
geometric mean (geometric coefficient of variation)	9700 (± 57.7)	8780 (± 32.9)	8990 (± 72.4)	5130 (± 80.6)

End point values	Normal FEC (EPANOVA®)	Normal FEC (OMACOR®)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	22		
Units: h*nanomole/mL (h*nmol/mL)				
geometric mean (geometric coefficient of variation)	8890 (± 43.8)	6690 (± 112)		

Statistical analyses

Statistical analysis title	OMACOR® v EPANOVA® for low FEC group
Statistical analysis description:	
Back transformed results are based on the analysis of natural log-transformed data with a Linear Mixed Model containing the terms of FEC classification, treatment, FEC x treatment, sequence, and period as fixed effects and patient nested within sequence as random effect.	
Comparison groups	Low FEC (EPANOVA®) v Low FEC (OMACOR®)
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	GLS Mean Ratio
Point estimate	0.9
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.63
upper limit	1.28

Statistical analysis title	OMACOR® v EPANOVA® for intermediate FEC group
Statistical analysis description:	
Back transformed results are based on the analysis of natural log-transformed data with a Linear Mixed Model containing the terms of FEC classification, treatment, FEC x treatment, sequence, and period as fixed effects and patient nested within sequence as random effect.	
Comparison groups	Intermediate FEC (EPANOVA®) v Intermediate FEC (OMACOR®)
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	GLS Mean Ratio
Point estimate	0.58
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.39
upper limit	0.85

Statistical analysis title	OMACOR® v EPANOVA® for normal FEC group
Statistical analysis description:	
Back transformed results are based on the analysis of natural log-transformed data with a Linear Mixed Model containing the terms of FEC classification, treatment, FEC x treatment, sequence, and period as fixed effects and patient nested within sequence as random effect.	
Comparison groups	Normal FEC (EPANOVA®) v Normal FEC (OMACOR®)
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	GLS Mean Ratio
Point estimate	0.75

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.55
upper limit	1

Primary: Part B: Baseline corrected maximum plasma drug concentration (Cmax) for total EPA following administration of EPANOVA® and OMACOR®.

End point title	Part B: Baseline corrected maximum plasma drug concentration (Cmax) for total EPA following administration of EPANOVA® and OMACOR®.

End point description:

Baseline corrected Cmax was measured for total EPA following administration of single oral doses of EPANOVA® 4 g (A) and OMACOR® 4 g (B) (2-way crossover design) to patients with T2DM and different degrees of PEI. Data is presented for the PK Analysis Set which included all randomised patients who received at least one dose of study treatment in Part B and had at least one post-dose PK measurement without any important protocol deviations.

End point type	Primary

End point timeframe:

Blood samples for analysis were taken at 1, 0.5, and 0.05 hours pre-dose, to be used as baseline, and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 24 and 48 hours post-dose.

End point values	Low FEC (EPANOVA®)	Intermediate FEC (EPANOVA®)	Intermediate FEC (OMACOR®)	Low FEC (OMACOR®)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	13	12	15
Units: mcg/mL				
geometric mean (geometric coefficient of variation)	137 (± 70.5)	116 (± 53.3)	53.9 (± 70.1)	71.5 (± 64)

End point values	Normal FEC (EPANOVA®)	Normal FEC (OMACOR®)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	23		
Units: mcg/mL				
geometric mean (geometric coefficient of variation)	131 (± 36.2)	69.3 (± 76.2)		

Statistical analyses

Statistical analysis title	OMACOR® v EPANOVA® for low FEC group

Statistical analysis description:

Back transformed results are based on the analysis of natural log-transformed data with a Linear Mixed Model containing the terms of FEC classification, treatment, FEC x treatment, sequence, and period as fixed effects and patient nested within sequence as random effect.

Comparison groups	Low FEC (OMACOR®) v Low FEC (EPANOVA®)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	GLS Mean Ratio
Point estimate	0.52
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.37
upper limit	0.73

Statistical analysis title	OMACOR® v EPANOVA® for intermediate FEC group

Statistical analysis description:

Back transformed results are based on the analysis of natural log-transformed data with a Linear Mixed Model containing the terms of FEC classification, treatment, FEC x treatment, sequence, and period as fixed effects and patient nested within sequence as random effect.

Comparison groups	Intermediate FEC (EPANOVA®) v Intermediate FEC (OMACOR®)
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	GLS Mean Ratio
Point estimate	0.46
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.32
upper limit	0.67

Statistical analysis title	OMACOR® v EPANOVA® for normal FEC group

Statistical analysis description:

Back transformed results are based on the analysis of natural log-transformed data with a Linear Mixed Model containing the terms of FEC classification, treatment, FEC x treatment, sequence, and period as fixed effects and patient nested within sequence as random effect.

Comparison groups	Normal FEC (EPANOVA®) v Normal FEC (OMACOR®)
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	GLS Mean Ratio
Point estimate	0.53
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.4
upper limit	0.7

Primary: Part B: Baseline corrected Cmax for total DHA following administration of EPANOVA® and OMACOR®.

End point title	Part B: Baseline corrected Cmax for total DHA following administration of EPANOVA® and OMACOR®.

End point description:

Baseline corrected Cmax was measured for total DHA following administration of single oral doses of EPANOVA® 4 g (A) and OMACOR® 4 g (B) (2-way crossover design) to patients with T2DM and different degrees of PEI. Data is presented for the PK Analysis Set which included all randomised patients who received at least one dose of study treatment in Part B and had at least one post-dose PK measurement without any important protocol deviations.

End point type	Primary

End point timeframe:

Blood samples for analysis were taken at 1, 0.5, and 0.05 hours pre-dose, to be used as baseline, and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 24 and 48 hours post-dose.

End point values	Low FEC (EPANOVA®)	Intermediate FEC (EPANOVA®)	Intermediate FEC (OMACOR®)	Low FEC (OMACOR®)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	13	12	15
Units: mcg/mL				
geometric mean (geometric coefficient of variation)	59 (± 58.6)	56 (± 40.6)	51 (± 52)	60.5 (± 47.3)

End point values	Normal FEC (EPANOVA®)	Normal FEC (OMACOR®)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	23		
Units: mcg/mL				
geometric mean (geometric coefficient of variation)	53.8 (± 41.8)	59.7 (± 53.9)		

Statistical analyses

Statistical analysis title	OMACOR® v EPANOVA® for low FEC group

Statistical analysis description:

Back transformed results are based on the analysis of natural log-transformed data with a Linear Mixed Model containing the terms of FEC classification, treatment, FEC x treatment, sequence, and period as fixed effects and patient nested within sequence as random effect.

Comparison groups	Low FEC (EPANOVA®) v Low FEC (OMACOR®)

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	GLS Mean Ratio
Point estimate	1.02
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.77
upper limit	1.36

Statistical analysis title	OMACOR® v EPANOVA® for normal FEC group

Statistical analysis description:

Back transformed results are based on the analysis of natural log-transformed data with a Linear Mixed Model containing the terms of FEC classification, treatment, FEC x treatment, sequence, and period as fixed effects and patient nested within sequence as random effect.

Comparison groups	Normal FEC (EPANOVA®) v Normal FEC (OMACOR®)
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	GLS Mean Ratio
Point estimate	1.11
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.88
upper limit	1.4

Statistical analysis title	OMACOR® v EPANOVA® for intermediate FEC

Statistical analysis description:

Back transformed results are based on the analysis of natural log-transformed data with a Linear Mixed Model containing the terms of FEC classification, treatment, FEC x treatment, sequence, and period as fixed effects and patient nested within sequence as random effect.

Comparison groups	Intermediate FEC (EPANOVA®) v Intermediate FEC (OMACOR®)
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	GLS mean Ratio
Point estimate	0.92
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.67
upper limit	1.25

Primary: Part B: Baseline corrected Cmax for total EPA+DHA following administration of EPANOVA® and OMACOR®.

End point title	Part B: Baseline corrected Cmax for total EPA+DHA following administration of EPANOVA® and OMACOR®.

End point description:

Baseline corrected Cmax was measured for the sum of EPA and DHA (total EPA+DHA) following administration of single oral doses of EPANOVA® 4 g (A) and OMACOR® 4 g (B) (2-way crossover design) to patients with T2DM and different degrees of PEI. Data is presented for the PK Analysis Set which included all randomised patients who received at least one dose of study treatment in Part B and had at least one post-dose PK measurement without any important protocol deviations.

End point type	Primary

End point timeframe:

Blood samples for analysis were taken at 1, 0.5, and 0.05 hours pre-dose, to be used as baseline, and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 24 and 48 hours post-dose.

End point values	Low FEC (EPANOVA®)	Intermediate FEC (EPANOVA®)	Intermediate FEC (OMACOR®)	Low FEC (OMACOR®)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	13	12	15
Units: nmol/mL				
geometric mean (geometric coefficient of variation)	622 (± 69.7)	553 (± 47)	328 (± 57.2)	421 (± 54)

End point values	Normal FEC (EPANOVA®)	Normal FEC (OMACOR®)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	23		
Units: nmol/mL				
geometric mean (geometric coefficient of variation)	592 (± 36.6)	413 (± 61.7)		

Statistical analyses

Statistical analysis title	OMACOR® v EPANOVA® for low FEC group

Statistical analysis description:

Back transformed results are based on the analysis of natural log-transformed data with a Linear Mixed Model containing the terms of FEC classification, treatment, FEC x treatment, sequence, and period as fixed effects and patient nested within sequence as random effect.

Comparison groups	Low FEC (EPANOVA®) v Low FEC (OMACOR®)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	GLS Mean
Point estimate	0.68

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.49
upper limit	0.92

Statistical analysis title	OMACOR® v EPANOVA® for intermediate FEC group

Statistical analysis description:

Back transformed results are based on the analysis of natural log-transformed data with a Linear Mixed Model containing the terms of FEC classification, treatment, FEC x treatment, sequence, and period as fixed effects and patient nested within sequence as random effect.

Comparison groups	Intermediate FEC (EPANOVA®) v Intermediate FEC (OMACOR®)
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	GLS Mean Ratio
Point estimate	0.6
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.42
upper limit	0.84

Statistical analysis title	OMACOR® v EPANOVA® for normal FEC group

Statistical analysis description:

Back transformed results are based on the analysis of natural log-transformed data with a Linear Mixed Model containing the terms of FEC classification, treatment, FEC x treatment, sequence, and period as fixed effects and patient nested within sequence as random effect.

Comparison groups	Normal FEC (EPANOVA®) v Normal FEC (OMACOR®)
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	GLS Mean Ratio
Point estimate	0.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.54
upper limit	0.9

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events (AEs) were collected until the safety follow-up contact (Visit 10). Serious AEs were collected from Visit 1 (screening) onwards over a period of up to 13 weeks. Other AEs were recorded from Visit 2 over a period of 7 weeks.

Adverse event reporting additional description:

Regular investigator assessment at study sites. Population used was the Safety Analysis Set which included all patients who received at least 1 dose of study treatment in Part B.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Low FEC (EPANOVA®)

Reporting group description:

Patients had low levels (<100 mcg/g) of FEC, as determined by the average of the FEC from 2 stool samples collected between Visit 2 and Visit 3 as a measure of pancreatic exocrine function. AEs with an onset date on or after the date of administration of EPANOVA® 4 g at Visit 4 were reported for this group.

Reporting group title	Low FEC (OMACOR®)

Reporting group description:

Patients had low levels (<100 mcg/g) of FEC, as determined by the average of the FEC from 2 stool samples collected between Visit 2 and Visit 3 as a measure of pancreatic exocrine function. AEs with an onset date on or after the date of administration of OMACOR® 4 g at Visit 4 were reported for this group.

Reporting group title	Intermediate FEC (EPANOVA®)

Reporting group description:

Patients had intermediate levels (≥100 to <200 mcg/g) of FEC, as determined by the average of the FEC from 2 stool samples collected between Visit 2 and Visit 3 as a measure of pancreatic exocrine function. AEs with an onset date on or after the date of administration of EPANOVA® 4 g at Visit 4 were reported for this group.

Reporting group title	Intermediate FEC (OMACOR®)

Reporting group description:

Patients had intermediate levels (≥100 to <200 mcg/g) of FEC, as determined by the average of the FEC from 2 stool samples collected between Visit 2 and Visit 3 as a measure of pancreatic exocrine function. AEs with an onset date on or after the date of administration of OMACOR® 4 g at Visit 4 were reported for this group.

Reporting group title	Normal FEC (EPANOVA®)

Reporting group description:

Patients had normal levels (≥200 mcg/g) of FEC, as determined by the average of the FEC from 2 stool samples collected between Visit 2 and Visit 3 as a measure of pancreatic exocrine function. AEs with an onset date on or after the date of administration of EPANOVA® 4 g at Visit 4 were reported for this group.

Reporting group title	Normal FEC (OMACOR®)

Reporting group description:

Patients had normal levels (≥200 mcg/g) of FEC, as determined by the average of the FEC from 2 stool samples collected between Visit 2 and Visit 3 as a measure of pancreatic exocrine function. AEs with an onset date on or after the date of administration of OMACOR® 4 g at Visit 4 were reported for this group.

Serious adverse events	Low FEC (EPANOVA®)	Low FEC (OMACOR®)	Intermediate FEC (EPANOVA®)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 13 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Musculoskeletal and connective tissue disorders			
Rotator cuff syndrome			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Intermediate FEC (OMACOR®)	Normal FEC (EPANOVA®)	Normal FEC (OMACOR®)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 23 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Musculoskeletal and connective tissue disorders			
Rotator cuff syndrome			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Low FEC (EPANOVA®)	Low FEC (OMACOR®)	Intermediate FEC (EPANOVA®)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	0 / 13 (0.00%)
Injury, poisoning and procedural complications			
Traumatic Ulcer			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0

Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Abdominal Pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Dry Mouth			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Intermediate FEC (OMACOR®)	Normal FEC (EPANOVA®)	Normal FEC (OMACOR®)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	5 / 23 (21.74%)	1 / 23 (4.35%)
Injury, poisoning and procedural complications			
Traumatic Ulcer			
subjects affected / exposed	0 / 12 (0.00%)	0 / 23 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 12 (0.00%)	2 / 23 (8.70%)	0 / 23 (0.00%)
occurrences (all)	0	2	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 12 (0.00%)	1 / 23 (4.35%)	0 / 23 (0.00%)
occurrences (all)	0	1	0

Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 12 (0.00%)	1 / 23 (4.35%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Abdominal Pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 23 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Dry Mouth			
subjects affected / exposed	0 / 12 (0.00%)	1 / 23 (4.35%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Flatulence			
subjects affected / exposed	0 / 12 (0.00%)	1 / 23 (4.35%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 23 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported