



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 | v1 |
| This version publication date | 29 September 2016 |
| First version publication date | 29 September 2016 |

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 | Gärtnavägen 1, Södertälje, Sweden, SE-151 85 |
| Public contact | Stefan Carlsson, AstraZeneca AB, Stefan.C.Carlsson@astrazeneca.com |
| Scientific contact | Stefan Carlsson, AstraZeneca AB, Stefan.C.Carlsson@astrazeneca.com |

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:

315 patients were enrolled (signed consent form) and started Part A of the study. Patients who met all inclusion and none of the exclusion criteria were included in the study. 51 patients were randomised to treatment in Part B.

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 | 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 Therapeutic Lifestyle Changes (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 | 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 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 | 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 | 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 | 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 |

[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).

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 (OMACOR®) v Low FEC (EPANOVA®) |
| 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 (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 | 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 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 |

| | |
|-----------------------------------|---|
| 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 |

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 occurrences (all) | 0 / 15 (0.00%) 0 | 0 / 15 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 15 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Abdominal Pain subjects affected / exposed occurrences (all) | 0 / 15 (0.00%) 0 | 0 / 15 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Dry Mouth subjects affected / exposed occurrences (all) | 0 / 15 (0.00%) 0 | 0 / 15 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Flatulence subjects affected / exposed occurrences (all) | 0 / 15 (0.00%) 0 | 0 / 15 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 15 (0.00%) 0 | 0 / 13 (0.00%) 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 occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 23 (0.00%) 0 | 0 / 23 (0.00%) 0 |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 2 / 23 (8.70%) 2 | 0 / 23 (0.00%) 0 |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 23 (4.35%) 1 | 0 / 23 (0.00%) 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