SYNOPSIS

Name of Sponsor:
Solvay Pharmaceuticals

Individual Study Table:

(For National Authority Use only)

Name of Finished Product:
Omacor®

Name of Active Ingredient:
Eicosapentaenoic acid and Docosahexaenoic acid

Study Title:
A double-blind, placebo-controlled, parallel-group, randomized, multi-center study to investigate the effect of Omacor® (n-3 PUFA) on lipid parameters in HIV-infected subjects treated with HAART (highly active antiretroviral therapy)

Study Protocol Approval Date:
19 APR 2007

Study Protocol Amendment 1 Approval Date:
19 JUN 2007

Study Protocol Amendment 2 Approval Date:
24 JAN 2008

Investigator:
PPD Germany

Study Centers:
PPD Germany PPD

PPD Germany PPD

PPD United Kingdom PPD

PPD United Kingdom PPD

PPD United Kingdom PPD

Publication (Reference):
Not applicable

Study Period:
28 AUG 2007 (first subject first visit) to
18 DEC 2008 (last subject last visit)

Phase of Development:

IV

Objectives:

Primary Objective

The primary objective of this study is to demonstrate that Omacor® is superior to placebo in reducing serum triglycerides in HIV-infected subject with HAART-induced hypertriglyceridemia.

Secondary Objectives

The secondary efficacy objective of this study is to investigate the effect of Omacor® on other fasting lipid parameters from Baseline to Endpoint:

- Fasting serum triglycerides (arithmetic change).
- Fasting total cholesterol (percentage and arithmetic change).
- Fasting high-density lipoprotein (HDL) (percentage and arithmetic change).
- Fasting low-density lipoprotein (LDL) (percentage and arithmetic change).
- Fasting very low-density lipoprotein (VLDL) (percentage and arithmetic change).
- Fasting apolipoprotein A (ApoA) (percentage and arithmetic change).
- Fasting apolipoprotein B (ApoB) (percentage and arithmetic change).

Safety Objectives

The safety objective of this study is to determine the safety and tolerability of Omacor® as compared to placebo by means of the following assessments:

- Adverse events (AEs).
- Laboratory measurements (hematology and biochemistry).
- Virus load.
- Vital signs measurements (weight, body mass index [BMI], systolic blood pressure [SBP], diastolic blood pressure [DBP], and pulse rate).
- Use of concomitant medications.
- Physical examinations.

Methodology:

Human immunodeficiency virus (HIV)-infected male and female subjects treated with highly active antiretroviral therapy (HAART) were to be randomized to one of two treatment groups. Subjects were to receive 2 x 1 g Omacor® capsules or matching placebo capsules twice daily in a double-blinded manner for a duration of 12 weeks. Four visits were scheduled. At Visit 1 (Day -5) subjects were screened for eligibility. At Visit 2 (Day 1) subjects were randomized to treatment and scheduled assessments were performed. At Visit 3 (Day 28) subjects returned for assessments and at Visit 4 (Day 84) the last scheduled assessments were performed. The Baseline value for a variable is defined as the last non-missing fasting value collected before first study medication administration. The Endpoint value for a variable is defined as the last non-missing fasting value in the Treatment Period (Visit 1 [Day 1] to Visit 4 [Day 84]) and was derived using the last observation carried forward (LOCF) post-baseline method.

Number of Subjects (Planned, Consented, Randomized and Analyzed):
Number of Subjects Planned: 60 subjects.

Number of Subjects Consented: 114 subjects.

Number of Subjects Randomized: 51 subjects.

Number of Subjects Analyzed: 50 subjects.

The following subject samples were defined:

All Subjects Consented subject sample: 114 subjects.

All Subjects Allocated to Treatment subject sample:

Total: 51 subjects.

Omacor® treatment group: 25 subjects.

Placebo treatment group: 26 subjects.

Safety subjects sample:

Total: 50 subjects.

Omacor® treatment group: 25 subjects.

Placebo treatment group: 25 subjects.

Full Analysis (FA) subject sample:

Total: 48 subjects.

Omacor® treatment group: 23 subjects.

Placebo treatment group: 25 subjects.

Per Protocol (PP) subject sample:

Total: 37 subjects.

Omacor® treatment group: 17 subjects.

Placebo treatment group: 20 subjects.

Diagnosis and Main Criteria for Inclusion:
Subject with a documented HIV infection. Subjects had to be treated with HAART for at least 3 months and had to have serum triglyceride values between 300 mg/100 mL and 1000 mg/100 mL. Subjects who received ongoing fibrate and nicotic acid treatment for at least 3 months before randomization.

Test Product, Dose and Mode of Administration, Batch Number:

Omacor® 1 g oral capsules

Batch number: 1060081-610082 and 70865

Duration of Treatment:

12 weeks

Reference Therapy, Dose and Mode of Administration, Batch Number:

Placebo oral capsules matching the study medication

Batch number: 1060082-610083 and 70866

Criteria for Evaluation

Efficacy:

The primary efficacy variable was the percentage change in fasting serum triglycerides in HIV-infected subject with HAART-induced hypertriglyceridemia treated with Omacor® compared with subjects treated with placebo from Baseline to Endpoint (12 weeks or earlier in case of premature withdrawal).

The secondary efficacy variables were to determine the arithmetic change in fasting serum triglycerides, the arithmetic and percentage change in fasting total cholesterol and cholesterol sub-fractions (HDL, LDL, and VLDL), and the arithmetic and percentage change in fasting ApoA and ApoB.

Safety:

The safety of the subjects was assessed by the recording of AEs, laboratory measurements (hematology and biochemistry), vital signs measurements (SBP, DBP, pulse rate, BMI, and weight), use of concomitant medications, physical examinations, and virus load measurements.

Statistical Methods:

Efficacy Analyses

The primary efficacy variable was to be assessed by an analysis of covariance (ANCOVA) with treatment and center as fixed factors and the Baseline value as covariate. The results are presented as p-values and estimates with 95% confidence intervals (CIs) with an alpha level of 0.05 two-sided.

The treatment per study center interaction was to be examined in a separate analysis with an additional treatment by study center interaction term in the model. An ANCOVA similar to that used for analyzing the primary efficacy variable was to be applied to the secondary efficacy variables.

After treatment unblinding, the distribution of each efficacy laboratory variable were to be tested for normality by means of Shapiro-Wilk's test and a Quantile-Quantile (Q-Q) plot. Depending on the distribution, the data were to be log-transformed if required. Small values from the Shapiro Wilk's test would lead to the rejection of normality and values close to 1 would lead to an indication of normality. The non-linearity of the point on a Q-Q plot indicating a departure from normality was also to be assessed. If the Shaprio-Wilk's value and the Q-Q plot indicated non-normality of any of the efficacy laboratory variables (p-value <0.05), all the efficacy laboratory variables would be log-transformed in addition to the original values.

Safety Analyses

Adverse events were summarized by default summary statistics, for all study centers combined, by treatment group. No treatment-emergent adverse events (TEAEs) of special interest were identified during the Blind Data Review Meeting on 09 FEB 2009.

Laboratory measurements were categorized according to the relevant reference ranges as

abnormal low, normal, or abnormal high. Markedly abnormal values were identified according to pre-defined criteria. The clinical significance of the abnormal values was judged by the Investigator.

Vital signs measurements, including change from Baseline were summarized. Markedly abnormal vital signs values were identified according to pre-defined criteria.

Summary - Conclusions

Efficacy Results:

Primary Efficacy Analysis

For the primary efficacy analysis, fasting serum triglycerides in the FA subject sample, a statistically significant and clinically relevant difference between Omacor® and placebo was observed for the mean percentage change from Baseline to Endpoint (p-value = 0.019; 95% CI [-69.48; -6.53]). In the PP subject sample a similar result was obtained (p-value = 0.008; 95% CI [-94.56; -15.20]). The comparison of the treatment ratio between Omacor® and placebo for the change (based on the log-transformed values) from Baseline showed a statistically significant and clinically relevant difference between Omacor® and placebo in the FA subject sample (p-value = 0.006; 95% CI [0.52; 0.89]) and the PP subject sample (p-value = 0.001; 95% CI [0.43; 0.80]).

In the Omacor® treatment group a negative change was observed in the percentage change of fasting serum triglycerides from Baseline to Endpoint in the FA subject sample (-27.014, [standard deviation {SD}: 29.009]) as well as in the PP subject sample (-33.926 [SD: 24.457]). In the placebo treatment group a positive change was observed in the percentage change in the FA subject sample (12.836 [SD: 62.432]) as well as in the PP subject sample (18.892 [SD: 66.921]).

In both the FA subject sample (0.677 [geometric SD: 1.498]) as well as the PP subject sample (0.616 [geometric SD: 1.482]), a negative change was noted in the concentration of fasting serum triglycerides for the geometric mean of the visit ratio and the comparison of the treatment ratio between Omacor® and placebo for the change from Baseline (based on the log-transformed values) to Endpoint in the Omacor® treatment group. A positive change was observed in the placebo treatment group in the FA subject sample (1.009 [geometric SD: 1.583]) and the PP subject sample (1.061 [geometric SD: 1.590]).

Secondary Efficacy Analysis

The arithmetic change from Baseline to Endpoint showed a negative change in fasting serum triglycerides in the Omacor® treatment group (-1.695 [SD: 2.066]) and a positive change in the placebo treatment group (0.533 [SD: 2.793]) in the FA subject sample. A statistically significant and clinically relevant difference between Omacor® and placebo for the mean arithmetic change in fasting serum triglycerides was noted from Baseline to Endpoint in both the FA subject sample (p-value = 0.021; 95% CI [-3.25; -0.28]) and the PP subject sample (p-value = 0.009; 95% CI [-4.34; -0.67]).

A negative change in the concentration of fasting total cholesterol was observed in the percentage change (-2.719 [SD: 14.796]), the arithmetic change (-0.226 [SD: 0.970]) and the geometric mean of the visit ratio (0.961 [geometric SD: 1.182]) from Baseline to Endpoint in the Omacor® treatment group for the FA subject sample. A negative change in fasting total

cholesterol was also observed for the placebo treatment group in the FA subject sample for the percentage change (-2.152 [SD: 13.107]), the arithmetic change (-0.196 [SD: 0.861]) and the geometric mean of the visit ratio (0.970 [geometric SD: 1.142]) from Baseline to Endpoint. No statistically significant difference was observed in the comparison of the treatment ratio between Omacor® and placebo in fasting total cholesterol for the change (based on the log-transformed values) (p-value = 0.658; 95% CI [0.90; 1.07]) from Baseline to Endpoint, the percentage change (p-value = 0.710; 95% CI [-9.18; 6.32]) from Baseline to Endpoint, or the arithmetic change (p-value = 0.645; 95% CI [-0.61; 0.38]) from Baseline to Endpoint in the FA subject sample. The results obtained for subjects in the PP subject sample confirm the results of the FA subject sample.

A positive change in the concentration of fasting HDL was observed for the percentage change from Baseline to Endpoint in the Omacor® treatment group (0.555 [SD: 17.973]) and a negative change was observed in the placebo treatment group (-5.000 [SD: 17.404]) in the FA subject sample. A negative change was noted in the concentration of fasting HDL for the arithmetic change in the Omacor® treatment group (-0.001 [SD: 0.174]) and the placebo treatment group (-0.064 [SD: 0.190]) and the geometric mean of the visit ratio from Baseline to Endpoint in the Omacor® treatment group (0.988 [geometric SD: 1.218]) and the placebo treatment group (0.932 [geometric SD: 1.230]) in the FA subject sample. No statistically significant difference between Omacor® and placebo in fasting HDL was observed in the comparison of the treatment ratio between Omacor® and placebo for the change (based on log-transformed values) (p-value = 0.300; 95% CI [0.94; 1.21]) from Baseline to Endpoint, the percentage change (p-value = 0.229; 95% CI [-4.23; 17.15]) from Baseline to Endpoint, or the arithmetic change (p-value = 0.207; 95% CI [-0.04; 0.18]) from Baseline to Endpoint in the FA subject sample. The results obtained for subjects in the FA subject sample were supported by the results of the PP subject sample.

The percentage change (25.016 [SD: 28.586]), the arithmetic change (0.632 [SD: 0.671]) and the geometric mean of the visit ratio (1.223 [geometric SD: 1.241]) showed a positive change from Baseline to Endpoint in the concentration of fasting LDL in the Omacor® treatment group for the FA subject sample. A negative change was observed for the placebo treatment group in the percentage change (-27.913 [SD: 24.095]), the arithmetic change (-0.802 [SD: 0.616]) and the geometric mean of the visit ratio (0.688 [geometric SD: 1.402]) in the FA subject sample. In fasting LDL a statistically significant difference between Omacor® and placebo in the comparison of treatment ratio between Omacor® and placebo for the change (based on log-transformed values) (p-value = 0.002; 95% CI [1.33; 2.62]) from Baseline to Endpoint, the percentage change (p-value = 0.005; 95% CI [21.53; 91.48]) from Baseline to Endpoint, and the arithmetic change (p-value = 0.002; 95% CI [0.73; 2.36]) from Baseline to Endpoint was noted for the FA subject sample. The results obtained for the subjects in the PP subject sample confirm the results of the FA subject sample.

In the Omacor® treatment group a negative change in the concentration of fasting VLDL was observed in the percentage change (-31.949 [SD: 19.082]), the arithmetic change (-0.546 [SD: 0.397]) and the geometric mean of the visit ratio (0.651 [geometric SD: 1.393]) from Baseline to Endpoint in the FA subject sample. In the placebo treatment group a negative change was also observed in the percentage change (-2.431 [SD: 23.783]), the arithmetic change (-0.059 [SD: 0.388]) and the geometric mean of the visit ratio (0.945 [geometric

SD: 1.311]) from Baseline to Endpoint for the FA subject sample. The comparison of the treatment ratio between Omacor® and placebo for the change (based on log-transformed values) (p-value = 0.004; 95% CI [0.48; 0.85]) from Baseline to Endpoint, the percentage change (p-value = 0.002; 95% CI [-55.45; -14.06]) from Baseline to Endpoint, and the arithmetic change (p-value = 0.002; 95% CI [-0.94; -0.26]) from Baseline to Endpoint showed a statistically significant difference between Omacor® and placebo in fasting VLDL for the FA subject sample. The results obtained for subjects in the PP subject sample support the results of the FA subject sample.

In the FA subject sample a negative change in the concentration of fasting ApoA from Baseline to Endpoint was observed for the percentage change (-3.160 [SD: 20.073]), the arithmetic change (-0.053 [SD: 0.244]) and the geometric mean of the visit ratio (0.948 [geometric SD: 1.243]) in the Omacor® treatment group. In the FA subject sample a negative change was also observed for the placebo treatment group in the percentage change (-2.463 [SD: 15.002]), the arithmetic change (-0.051 [SD: 0.199]) and the geometric mean of the visit ratio (0.964 [geometric SD: 1.172]) from Baseline to Endpoint. No statistically significant difference between Omacor® and placebo was observed in fasting ApoA for the comparison of the treatment ratio between Omacor® and placebo for the change (based on log-transformed values) (p-value = 0.423; 95% CI [0.86; 1.07]) from Baseline to Endpoint, the percentage change (p-value = 0.493; 95% CI [-13.41; 6.58]) from Baseline to Endpoint, and the arithmetic change (p-value = 0.569; 95% CI [-0.16; 0.09]) from Baseline to Endpoint in the FA subject sample. The results obtained for subjects in the PP subject sample confirm the results of the FA subject sample.

In fasting ApoB a positive change in the Omacor® treatment group was observed from Baseline to Endpoint for the percentage change (9.991 [SD: 24.839]), the arithmetic change (0.074 [SD: 0.238]) and the geometric mean of the visit ratio (1.070 [geometric SD: 1.283]) for the FA subject sample. A negative change was noted in the placebo treatment group for the percentage change (-7.155 [SD: 18.880]), the arithmetic change (-0.100 [SD: 0.214]) and the geometric mean of the visit ratio (0.906 [geometric SD: 1.269]) from Baseline to Endpoint for the FA subject sample.

A statistically significant difference between Omacor® and placebo in fasting ApoB was noted for the mean percentage change (p-value = 0.023; 95% CI [2.11; 27.02]) and the mean arithmetic change (p-value = 0.027; 95% CI [0.02; 0.27]) from Baseline to Endpoint in the FA subject sample. No statistically significant difference was noted between Omacor® and placebo in fasting ApoB for the comparison of the treatment ratio between Omacor® and placebo for the change (based on the log-transformed values) (p-value = 0.053; 95% CI [1.00; 1.33]) from Baseline to Endpoint in the FA subject sample. In the PP subject sample the comparison of the treatment ratio between Omacor® and placebo for the change (based on log-transformed values) (p-value = 0.235; 95% CI [0.92; 1.36]) from Baseline to Endpoint, the percentage change (p-value = 0.167; 95% CI [-5.19; 28.59]) from Baseline to Endpoint, and the arithmetic change (p-value = 0.206; 95% CI [-0.06; 0.27]) from Baseline to Endpoint showed no statistically significant difference between Omacor® and placebo for fasting ApoB.

Safety Results:

No deaths or severe AEs were reported.

One subject in the placebo treatment group reported a treatment-emergent serious adverse event (TESAE) (diabetes mellitus) considered moderate in severity and unrelated to the study medication. The event resolved without concomitant therapy.

Two subjects in the Omacor® treatment group prematurely withdrew from the study due to AEs. Subject PPD withdrew due to dizziness, headache and sleep disorder (all three events were considered moderate in severity and probably related to the study mediation). Subject PPD withdrew due to cholelithiasis (considered moderate in severity and probably related to the study medication).

The majority of TEAEs reported were considered unrelated to the study medication by the Investigator.

The TEAEs considered related to the study medication by the Investigator were categorized in the System Organ Class Gastrointestinal disorders, Hepatobiliary disorders, Nervous system disorders and Skin and subcutaneous tissue disorders. All drug-related TEAEs were considered moderate or mild in severity and no concomitant therapy was introduced.

Values for some of the hematology laboratory variables lower/higher than the reference ranges were noted. No trends were noted over time and between the treatment groups. Values for some of the biochemistry laboratory variables higher than the upper limit of the reference ranges were noted. An increase in the mean alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, serum lipase and uric acid values from Baseline were noted in the Omacor® treatment group. An increase in the mean ALT and serum lipase values from Baseline were noted in the placebo treatment group.

Minimum values that were lower than the limit of the reference range was noted for the T-cell cluster of differentiation subset (CD4) count in the placebo treatment group. An increase in the mean CD4 count was noted in both the Omacor® treatment group and the placebo treatment group.

Markedly abnormal and clinically significant laboratory values were noted but none were recorded as AEs.

Markedly abnormal vital signs were noted but no significant changes in vital signs were observed.

Conclusion:

- Omacor®, which has been shown to be a reliable source of long chain n-3 PUFAs, has been shown to reduce triglyceride levels in HIV-infected subjects using HAART.
- In HIV-infected subjects with HAART-induced hypertriglyceridemia, Omacor® administered as 2 x 1 g capsules twice daily for 12 weeks was effective treatment in reducing fasting serum triglycerides.
- In this study, HIV-infected subjects using HAART who received 2 x 1 g Omacor® capsules twice daily did not report any severe TEAEs. The AEs that were reported were as expected for HIV-infected subjects with HAART-induced hypertriglyceridemia.

Date of Report:

29 JAN 2010