## 2. SYNOPSIS

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**TITLE OF STUDY:**

A Phase 4 Randomised, Double-Blind, Placebo-Controlled, Parallel-Group, Multicentre Study of Colesevelam as Add-On Therapy in Patients with Familial Hypercholesterolaemia

**INVESTIGATORS / STUDY CENTRES:**

Patients were enrolled at 8 centres in 5 countries of the European Union (EU): 4 centres in The Netherlands and 1 centre each in the United Kingdom (UK), Germany, France and Sweden.

**PUBLICATION (REFERENCE):**

Not applicable for this report.

**STUDIED PERIOD:**

First Patient Screened: 22 August 2007

Last Patient Completed Double-Blind Phase: 09 December 2008

**PHASE OF DEVELOPMENT:**

Phase 4

**OBJECTIVES:**

This study has been conducted in patients with familial hypercholesterolaemia (FH) to:

1. Assess the efficacy of colesevelam added to a maximal tolerated and stable regimen of statin and ezetimibe in further decreasing the low-density lipoprotein (LDL) cholesterol level in terms of additional percentage decrease and in terms of reaching below target level of LDL cholesterol.
2. Evaluate the safety and tolerability of colesevelam added to a maximal tolerated and stable regimen of statin and ezetimibe.

**METHODOLOGY:**

This report describes the double-blind period of a phase 4 prospective, randomised, placebo-controlled, parallel-group, multicentre study. Colesevelam was administered to patients with FH as add-on therapy to a maximally-tolerated and stable regimen of a statin and ezetimibe, on which their LDL cholesterol level was still above their target (for either primary or secondary prevention).

After providing signed informed consent, eligible patients who met screening entry criteria entered a 4-week Screening run-in period to assess the stability of the lipid-lowering effect of the statin and ezetimibe combination treatment the patient had been on for at least 3 months. Following the 4-week run-in period, patients returned for a Baseline Visit for assessment of the Baseline Inclusion Criterion which mandated that patients have a stable LDL cholesterol level defined as ≤ 10% variability between the Screening and Baseline LDL cholesterol levels. If the first Baseline LDL cholesterol level was not within the required 10% variability, a second Baseline level was taken 2 weeks later, if appropriate, for comparison with the Screening LDL cholesterol level. Patients who did not meet the Baseline Inclusion Criterion were considered screen failures and excluded from the study. If the Baseline Inclusion Criterion was met, patients were randomised to study treatment, marking the start of the double-blind phase of the study. Patients were planned to be randomised in a 1:1 ratio (40 patients per group) using a central

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randomisation algorithm, with stratification per centre.

Double-blind phase study treatment consisted of a 12-week period of 6 tablets daily, either with colesevelam (625 mg per tablet) or matching placebo. Patients took the study treatment either as 6 tablets once daily or as 3 tablets twice daily. In addition to the study treatment, each patient was instructed to continue to take their existing stable and maximal tolerated dose of statin and ezetimibe as normal. The start of daily treatment with colesevelam or placebo was defined as the Day 1 Visit.

During the 12-week double-blind treatment period, patients had study visits at Weeks 6 and 12 (± 1 week) at which time efficacy and safety assessments were conducted. Adverse events (AEs) and concomitant medications were collected from the time of obtaining informed consent throughout the entire study.

Following completion of the 12-week double-blind phase of treatment, patients began the open-label phase of the study which entailed 40 weeks of open-label colesevelam treatment (6 tablets per day, 625 mg per tablet). The current clinical study report describes the results up to the end of the double-blind study phase. The results for the open-label study phase will be presented in a separate clinical study report.

**NUMBER OF PATIENTS (PLANNED AND ANALYSED):**

Statistical assumptions for detecting a difference in decrease of LDL cholesterol on colesevelam compared to placebo as add-on to stable statin and ezetimibe therapy were based on an estimated treatment difference of 9% with an anticipated standard deviation of 12%.

Based on the above assumptions, 40 patients were required for randomisation per treatment group to have a sufficient number of patients per group for the Intent to Treat (ITT) analysis with 90% power, 2-sided tests at the 5% significance level. Patients that dropped out before Week 6 were allowed to be replaced to a maximum of approximately 90 patients randomised.

A total of 138 patients were screened for study participation of which 52 were screen failures. There were 86 patients randomised and 80 of these patients completed the Week 12 Visit.

The Safety Population comprised the 85 patients who received at least 1 dose of randomised, double-blind study treatment administration and had at least 1 post-Baseline clinical safety assessment. The ITT Population included the 82 patients from the Safety Population who had evaluable Baseline lipid assessment data as well as post-Baseline data for at least 1 lipid assessment. The Per Protocol (PP) Population consisted of the 74 patients from the ITT Population who had sufficient primary efficacy data, a treatment compliance of ≥ 75% during the double-blind phase, and no major protocol deviations deemed to possibly influence the efficacy analyses.

**DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:**

Patients who met all of the following inclusion criteria were eligible to participate in this study:

**SCREENING INCLUSION:**

1. Patients must be males or females between 18 and 75 years of age, inclusive
2. Patients must have a clinical diagnosis of FH defined as EITHER
   a. Presence of a documented LDL-receptor mutation OR
   b. History of untreated LDL cholesterol level above the 95$^{th}$ percentile for sex and age in combination with documentation of at least 1 of the following:
      i. Presence of typical tendon xanthomas in the patient or first degree relative
      ii. An LDL cholesterol level above the 95$^{th}$ percentile for age and sex in a first degree relative

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iii. Proven coronary artery disease in the patient or in a first degree relative under the age of 60

3. Patients must have been provided and undergone lifestyle changes for more than 6 months at time of Screening
4. Patients must have been treated for at least 3 consecutive months preceding the Screening Visit with a stable lipid-lowering treatment regimen consisting of a maximal tolerated combination of a statin with ezetimibe and are still above their target for LDL cholesterol being 2.5 mmol/L (100 mg/dL)
5. Patients must be committed to following the protocol requirements as evidenced by written informed consent
6. Patients should be comfortable with swallowing at least 3 placebo tablets

**BASELINE INCLUSION:**

At the Baseline Visit, patients were required to have stable LDL cholesterol defined as a variability of 10% or less between the Screening LDL cholesterol level and the Baseline LDL cholesterol level assessed at least 4 weeks after Screening. If the first Baseline level was not within the required 10% variability, a second Baseline level was taken within 2 weeks, if appropriate, for comparison to the Screening LDL cholesterol level. In order to prevent a substantial screen failure rate due to the Baseline Inclusion Criterion, specific conditions were set in the study protocol to allow a higher variability level. However, it was not necessary to change the Baseline Inclusion Criterion variability level in this study.

Patients who met any of the following exclusion criteria were not eligible for participation in this study:

**SCREENING EXCLUSION:**

1. Patients with a known allergy to any of the components used in colesevelam or placebo or any other medications like statin or ezetimibe required for participation in this study
2. Patients with a bowel or biliary obstruction
3. Patients with secondary causes of hypercholesterolaemia, eg, hypothyroidism, nephrotic syndrome (defined as proteinuria >2 g/L), dysproteinaemias, obstructive liver disease, other pharmacological therapies, alcoholism
4. Patients with triglyceride level of > 3.4 mmol/L
5. Patients with dysphagia, swallowing disorders, severe gastrointestinal motility disorders, inflammatory bowel disease, or major gastrointestinal tract surgery
6. Patients have undergone LDL-apheresis within 1 year prior to the Screening Visit and/or need to undergo LDL-apheresis
7. Patients with active liver disease or unexplained persistent elevations in transaminases
8. Patients on fenofibrates or on concomitant cholestyramine as this will affect the area under the curve of ezetimibe
9. Patients with poorly-controlled diabetes (ie, glycosylated haemoglobin (HbA1c) > 9% at Screening)
10. Patients with clinically significant (CS) abnormal haematology, renal, or other laboratory parameters that could be the result of an underlying malignancy or systemic infection as judged by the Investigator
11. Patients with a heart transplant, concurrent congestive heart failure (New York Heart Association [NYHA] Class 3 or 4), life-threatening ventricular arrhythmias, unstable angina, recent myocardial infarction within the past 6 months prior to Screening, or patients undergoing haemodialysis, or with active disease who may not be healthy enough to successfully complete all protocol requirements
12. Fertile women who are pregnant, nursing or using either no or an inadequate form of contraception taking into account the recommendations for adequate intake of oral contraceptives as outlined in the concomitant medication section
13. Patients with a recent history of alcoholism or drug abuse, or severe emotional, behavioural, or psychiatric

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problems who may not be able to adequately comply with the requirements of the study or who may be unable to consent

14. Patients receiving experimental medications or participating in another study using an experimental drug or procedure within 30 days prior to signing informed consent

**TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION; BATCH NUMBER:**

Colesevelam hydrochloride, 625 mg tablets taken orally with liquid (eg, water), either 6 tablets once daily or 3 tablets twice daily, for a total dose per day of 3,750 mg.

**REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION; BATCH NUMBER:**

Placebo tablets taken orally with liquid (eg, water), either 6 tablets once daily or 3 tablets twice daily. The placebo tablets were identical in appearance to the Investigational Product.

**DURATION OF TREATMENT:**

Double-Blind Phase: Randomised treatment for 12 weeks with either colesevelam or placebo as add-on therapy to a maximally-tolerated and stable regimen of a statin and ezetimibe.

**CRITERIA FOR EVALUATION:**

**EFFICACY:**

The study's primary efficacy evaluation involved a comparison between the treatment groups for percent change in LDL cholesterol level from Baseline (defined as the measurement taken closest in time prior to the Day 1 Visit) to Week 6.

Secondary efficacy evaluations were:

- The percent change from Baseline at Weeks 6 and 12 for high-density lipoprotein (HDL) cholesterol, total cholesterol, apolipoprotein A1(ApoA1), apolipoprotein B (ApoB), ApoB/ApoA1 ratio and triglycerides, as well as LDL cholesterol at Week 12 only
- The absolute change from Baseline at Weeks 6 and 12 for HbA1c, highly sensitive C-reactive protein (hsCRP) and fasting glucose
- Achievement rates at Weeks 6 and 12 for:
  - LDL cholesterol < 2.5 mmol/L (goal rate)
  - ≥ 15% decrease in LDL cholesterol level (responder rate)

**SAFETY:**

Safety was evaluated on the basis of incidence of AEs and serious adverse events (SAEs), and changes in clinical laboratory evaluations (eg, liver and renal function, haematology and blood chemistry), vital signs and concomitant medications.

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**STATISTICAL METHODS:**

**EFFICACY:**

The primary efficacy hypothesis of superiority of colesevelam to placebo was evaluated by considering the percent change from Baseline in LDL cholesterol levels at Week 6. For this analysis, an analysis of covariance (ANCOVA) at $\alpha = 0.05$ was conducted with treatment group and centre as main effects. LDL cholesterol measurement at Baseline and age were tested for inclusion in the model as covariates, but neither was included as they were both found to be nonsignificant. The least-squares (LS) means and differences of the LS means (including the 95% confidence interval of the difference and *P*-value) were provided.

The ITT Population was used as the primary efficacy analysis population with the PP Population as a confirmative measure.

Secondary efficacy analyses were conducted to assess:

The percent change from Baseline at Weeks 6 and 12 for HDL cholesterol, total cholesterol, ApoA1, ApoB, ApoB/ApoA1 ratio and triglycerides as well as LDL cholesterol at Week 12 only.

The absolute change from Baseline at Weeks 6 and 12 for HbA1c, hsCRP and fasting glucose.

For these analyses, ANCOVAs were conducted at $\alpha = 0.05$ with treatment group and centre as main effects. For each parameter, the LS means and differences of LS means (including the 95% confidence interval of the difference and *P*-value) were provided. Due to skewness of change from Baseline data for triglycerides, secondary endpoints related to triglycerides were also analysed non-parametrically, as a confirmative measure, using the Wilcoxon Rank Sum Test with the corresponding Hodges-Lehmann estimate of the shift parameter.

Secondary efficacy analyses were also conducted to compare the frequencies of targets 'achieved' and 'not achieved' between treatment groups at Weeks 6 and 12 for the following:

LDL cholesterol level < 2.5 mmol/L.

LDL responder (≥ 15% decrease in LDL cholesterol level).

These analyses were performed using Fisher's Exact Test at $\alpha = 0.05$ to compare the treatment groups.

**SAFETY:**

No inferential analyses were performed on safety data.

AEs were summarised by treatment assignment per preferred term (PT) and system organ class (SOC), for death, treatment-emergent death, SAE, treatment-emergent SAE (TESAE), treatment-emergent AE (TEAE), premature discontinuation due to a TEAE, severe TEAE, and related TEAE.

Safety laboratory data (blood chemistry and haematology) at Screening and at Weeks 6 and 12 were summarised by treatment assignment. At Weeks 6 and 12, change from Baseline was also tabulated.

Physical examination findings at Screening and at Weeks 6 and 12 were tabulated by body system, both overall and by treatment assignment. At Weeks 6 and 12, change from Baseline was also tabulated.

Vital signs, including temperature, systolic and diastolic blood pressure, heart rate, height (only at Screening), weight and body mass index (BMI), at Screening and at Weeks 6 and 12 were summarised by treatment assignment. At Weeks 6 and 12, change from Baseline was also tabulated.

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**SUMMARY – CONCLUSIONS**

**EFFICACY:**

Colesevelam, as add-on therapy to a maximally-tolerated and stable regimen of a statin and ezetimibe, significantly reduced LDL cholesterol levels compared to placebo at Week 6 (-18.7%, $P < 0.0001$). At Week 12 of treatment, colesevelam continued to indicate a significant difference compared with placebo (-11.8%, $P = 0.0001$). Patients who received colesevelam treatment had a sustained reduction of more than 11% in LDL cholesterol levels from Baseline to Weeks 6 and 12. The treatment groups were comparable at Baseline in terms of demographics and baseline characteristics including age, BMI and lipid levels. The mean Baseline LDL cholesterol level for both treatment groups was approximately 3.8 mmol/L, which is still above the recommended target level despite maximally-tolerated and stable combination lipid-lowering therapy. Furthermore, although only available for 27 patients (12 in the colesevelam group and 15 in the placebo group), the untreated level for LDL cholesterol was found to be quite high (LDL cholesterol: 8.0 mmol/L [SD = 1.75]).

There was no significant difference between treatment groups in terms of the number of patients able to reach the published target LDL cholesterol level for patients at high risk for cardiovascular disease, that being less than 2.5 mmol/L. There was however a significant difference ($P < 0.0001$) in the number of patients able to achieve a target treatment response of at least a 15% decrease in LDL cholesterol level by Week 6, as none of placebo-treated patients and 33% of colesevelam-treated patients reached this target response. This significant difference was maintained at Week 12 ($P = 0.0123$).

Total cholesterol comprises LDL cholesterol and correspondingly, total cholesterol levels were significantly reduced with colesevelam treatment at Weeks 6 (LS mean treatment difference = -11.5%, $P < 0.0001$) and 12 (LS mean treatment difference = -7.3%, $P = 0.0036$). Treatment differences from Baseline to Weeks 6 and 12 also presented a pattern of significant improvement with colesevelam treatment over placebo for ApoB/ApoA1 ratio (Week 6: LS mean treatment difference = -13.0%, $P = 0.0002$; Week 12: LS mean treatment difference = -11.2%, $P = 0.0073$).

Patients treated with colesevelam in this study showed increases in mean triglyceride levels at both Weeks 6 and 12 compared to Baseline. Although the increase in triglyceride levels for colesevelam- compared to placebo-treated patients was significant at Week 6 (LS treatment difference = 13.0%, $P = 0.0403$), the results at Week 12 were not statistically significantly different due to an increase over time in triglyceride levels with placebo (LS treatment difference = 3.4%, $P = 0.6129$). The results of the non-parametric analyses using the Wilcoxon Rank Sum Test with the corresponding Hodges-Lehmann estimate of the shift parameter confirmed the results of the parametric analyses.

Although not significant at Week 6, colesevelam-treated patients had significantly reduced levels of HbA1c from Baseline to Week 12 as compared with placebo-treated patients (LS mean treatment difference = -0.1%, $P = 0.0272$). There were no significant differences between treatment groups for HDL cholesterol or hsCRP at Weeks 6 or 12.

**SAFETY:**

The safety results of this study indicate that treatment with colesevelam as add-on therapy to a maximally-tolerated and stable regimen of a statin and ezetimibe was safe and well tolerated by patients. A similar proportion of patients with TEAEs was observed with colesevelam as with placebo treatment. Gastrointestinal Disorders were the most frequently occurring related TEAEs in both treatment groups. The majority of TEAEs were of mild or moderate severity in both treatment groups. Each treatment group had 1 patient that experienced a severe TEAE in

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the Gastrointestinal Disorders SOC. The treatment groups were similar in terms of number of patients that discontinued study participation prematurely due to an AE (colesevelam: 3 patients, placebo: 2 patients). During the 12-week double-blind phase of this study only 2 TESAEs were reported, which were considered by the investigator to be not related, and were for one patient treated with placebo. No clinically meaningful changes in safety laboratory parameters, vital signs or physical examination findings were observed. No new safety concerns were identified during this study.

**CONCLUSION:** [redacted]