SUMMARY

ASTRAZENECA

FINISHED PRODUCT:

ACTIVE INGREDIENT: Rosuvastatin

Trial title (number): A 30-Week, Forced-titration and Randomised, Crossover, Multicentre, Multinational Trial to Evaluate the Efficacy and Safety of rosuvastatin and Atorvastatin in Subjects with Homozygous Familial Hypercholesterolaemia (4522IL/0054): Full Report of the First 18 Weeks (forced-titration) and Last 12 Weeks of Treatment (crossover period) for Efficacy and for Safety

Clinical phase: III

First subject recruited: 19 April 2000
Last subject completed the forced-titration period: 04 December 2000
First subject entered the crossover period: 23 September 2000
Last subject completed: 22 February 2001
AstraZeneca approval date: 02 October 2001

Principal investigator(s) and location (centre number):
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Publications: None at the time of writing this report.
Note: A report has been issued (20 March 2001) covering efficacy and safety results from the forced-titration period of this trial. Since issue, there have been additions / updates to some of forced-titration period data; however, the key conclusions have not altered. The current report presents full, updated efficacy and safety results from the forced-titration period and efficacy and safety results from the crossover period. Forced-titration and crossover results are presented separately, as the different design of the 2 treatment periods does not allow a fully integrated set of results over the 30-week trial period.

OBJECTIVES OF THE TRIAL
The primary objective was to assess the efficacy of rosvastatin in the reduction of low-density lipoprotein cholesterol (LDL-C) levels in subjects with homozygous familial hypercholesterolaemia after 18 weeks of open label treatment.

The secondary objectives of the trial were as follows:

- to assess the efficacy of rosvastatin in the reduction of LDL-C levels in subjects with homozygous familial hypercholesterolaemia at Weeks 6 and 12;
- to compare the efficacy of rosvastatin with that of atorvastatin in modifying LDL-C, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG), and lipoprotein fractions after 6 weeks of each randomised treatment (ie, at the Week 24 and 30 time points);
- to assess the efficacy of rosvastatin in reducing cholesterol synthesis via measurement of serum and urinary mevalonic acid at Weeks 0, 6, 12, 18, 24 and 30;
- to compare the effects of treatment with rosvastatin and atorvastatin on the following inflammatory markers: C-reactive protein (CRP), E-Selectin, and interleukin-6 (IL-6) after 6 weeks of each randomised treatment;
- to examine the relationship between LDL-C receptor status and response to statins;
- to determine the safety and tolerability of rosvastatin by evaluating the incidence and severity of adverse events and abnormal laboratory values.

Also of interest was to assess the effects of rosvastatin on other lipids and lipid ratios at Weeks 6, 12 and 18, and lipoprotein fractions and lipoprotein ratio, and inflammatory markers at Week 18.

METHODS
Design: This was a multinational, multicentre trial with an open label dose titration period and a double blind, 2-group, crossover, comparative period during which subjects received randomised treatment. After a 4-week dietary lead-in period, subjects entered the first treatment phase of the trial: the open label dose titration period, in which subjects received a forced-titration of rosvastatin from 20 mg to 40 mg to 80 mg at 6-week intervals over 18 weeks. After 18 weeks
of treatment, subjects were assigned to 1 of 2 randomised treatment (randomisation was allocated at the start of the forced-titration period) groups for the crossover period of the trial: Group I received rosuvastatin 80 mg for 6 weeks and then atorvastatin 80 mg for the next 6 weeks, and Group II received atorvastatin 80 mg for 6 weeks and then rosuvastatin 80 mg for the next 6 weeks. No washout period was scheduled during the crossover part of the trial because each period of treatment in this phase was considered long enough to eliminate the possibility of carry over of the effects of treatment.

Population: The primary endpoint is non-comparative in the forced-titration period of the trial. Forced-titration period: the sample size of the subject population was determined by the availability of subjects through the participating centres; 40 to 60 recruited subjects with homozygous familial hypercholesterolaemia were expected. Crossover period: approximately 36 evaluable subjects with homozygous familial hypercholesterolaemia, derived from the 44 subjects entering the forced-titration period, will give 90% power to detect a 6% difference in LDL-C lowering from baseline between rosuvastatin and atorvastatin comparator during the crossover period of the trial.

Key inclusion criteria:
For entry to dietary lead-in and forced-titration period: Men or women aged ≥10 years with homozygous familial hypercholesterolaemia (based on genetic, clinical or functional criteria); discontinuation of all cholesterol-lowering drugs and dietary supplements; and fasting TG levels <6.77 mmol/L (600 mg/dL).

For entry into crossover period: Any subject who had completed the forced-titration period of the trial.

Key exclusion criteria:
Assessed at the dietary lead-in period: Known heterozygous familial hypercholesterolaemia; history of malignancy (unless basal or squamous cell skin carcinoma); and various concomitant illnesses, including active liver disease or hepatic dysfunction (defined by an alanine aminotransferase [ALT], aspartate aminotransferase [AST], or bilirubin concentration >1.5 x the upper limit of normal [ULN]); active arterial disease, uncontrolled hypertension, uncontrolled hypothyroidism; serum creatine kinase (CK) concentration >3 x ULN.

Assessed throughout the trial: Usage of concomitant medications known to affect the lipid profile or present a potential safety concern (eg, through drug interaction).

Dosage: Subjects took oral doses of encapsulated trial treatment once daily, approximately 3 hours after the evening meal. During the forced-titration period of the trial, subjects took each titrated rosuvastatin dose increment as a single encapsulated tablet (ie, 20 mg, 40 mg, and 80 mg) for 6 weeks. During the crossover period of the trial, subjects received treatment according to their randomised treatment group: Group I received rosuvastatin 80 mg for 6 weeks and then atorvastatin 80 mg for 6 weeks. Group II received the atorvastatin 80 mg for 6 weeks followed by rosuvastatin 80 mg for 6 weeks. Note: atorvastatin 80 mg was supplied as 2 x 40 mg encapsulated tablets (2 capsules); to maintain the blind in the crossover period of the trial, rosuvastatin 80 mg was also supplied as 2 x 40 mg encapsulated tablets.

Formulation and batch numbers are as follows:

**Forced-titration and crossover periods:** rosuvastatin 40 mg (F12566, 99-3159)

**Forced-titration period only:** rosuvastatin 20 mg (F12522, 00-0045) and 80 mg (F12568, 99-3135)
**Crossover period only:** atorvastatin 40 mg (F12560, 99-0513).

**Key assessments:**

**Efficacy:**

*Forced-titration period:* Fasting LDL-C, HDL-C, TG, TC, lipid ratios, and serum and urinary mevalonic acid were assessed at Weeks 0 (baseline), 6, 12 and 18; fasting apolipoprotein B (ApoB), apolipoprotein A-I (ApoA-I), apolipoprotein E (ApoE) and lipoprotein (a) (Lp(a)) and inflammatory markers, CRP, IL-6 and E-selectin at Weeks 0 and 18. The percentage change from baseline (Week 0) to Week 18 in LDL-C levels was the primary endpoint of this trial, and analyses were performed on LOCF value from the ITT population. These analyses were repeated for the following secondary endpoints: LDL-C at Weeks 6 and 12, and TC, HDL-C, TG, LDL-C/HDL-C, TC/HDL-C, non HDL-C/HDL-C at Weeks 6, 12 and 18. Summaries of the changes from baseline to Week 18 in ApoB, ApoA-I, ApoE and Lp(a) levels, and the ratio ApoB/ApoA-I; these analyses were performed on the LOCF values in the ITT population.

Descriptive statistics of percentage change from baseline were presented for the inflammatory markers (CRP, IL-6, E-selectin) at Week 18 and for serum and urinary mevalonic acid at Weeks 6, 12 and 18.

Subgroup and exploratory analyses were performed on LDL-C data, based on certain demographic groupings.

*Crossover period:* The following were assessed during the crossover period at Weeks 24 and 30: fasting LDL-C, HDL-C, TG, TC and lipid ratios; fasting ApoB, ApoA-I, ApoE and Lp(a); inflammatory markers CRP, E-Selectin, and IL-6; and mevalonic acid (serum and urinary). Endpoints for the crossover period of this trial included the % changes from baseline at the beginning of the forced-titration period (Week 0) and the last post-baseline value obtained either at Week 24 or Week 30 in the following variables: LDL-C, TC, HDL-C, TG, LDL-C/HDL-C, TC/HDL-C, non HDL-C/HDL-C, ApoB, ApoA-I, ApoE, and Lp(a). Lipid data from Weeks 24 and 30 were used in the calculations for the secondary endpoints during the crossover period. In the crossover period the per-protocol (PP) population was the primary population of interest for analyses of changes from baseline in lipids and lipoprotein fractions (note: during the crossover period the PP population excluded major protocol violators at Week 0 and all major protocol deviators during either the forced-titration or crossover periods). These analyses were performed on the observed (by-visit) data in the PP population using Analysis of Variance (ANOVA); the initial ANOVA model included terms for subject, period, treatment, centre and centre-by-treatment interaction.

Descriptive statistics of percentage change from baseline were presented from the intention-to-treat (ITT) population for the inflammatory markers at Weeks 24 and 30, and for serum and urinary mevalonic acid at Weeks 24 and 30. No inferential statistics were performed on the inflammatory marker or mevalonic acid findings, as these were exploratory data.

Subgroup and exploratory analyses were performed on LDL-C data, based on certain demographic groupings.

Dietary compliance was assessed and evaluated throughout the 30-week trial period (Weeks -4, 0, 6, 12 and 18, and Weeks 24 and 30).
Data for very-low density lipoprotein subfraction 1 and 2 (VLDL-1, VLDL-2), intermediate-density lipoprotein (IDL) and low-density lipoprotein (LDL) though collected throughout the trial but were not available for this report.

Safety: For both forced-titration and crossover periods the standard safety assessments included adverse event reports, clinical laboratory data (hepatic biochemistry, CK, renal biochemistry, haematology, urinalysis), vital signs, electrocardiograms (ECGs), and physical examination. All data were summarised.

RESULTS

Demography: Forced-titration period
A total of 46 subjects were recruited from 4 centres, of which 44 were eligible to enter the forced-titration treatment period following the dietary lead-in period. All 44 subjects received treatment. There were 44 subjects in the safety population, 2 of whom had no baseline or post-baseline assessments; the remaining 42 subjects comprised the ITT population. A total of 6 subjects withdrew (5 due to protocol non-compliance) during the forced-titration period, including the 2 subjects with no baseline or post-baseline measurements. There were 4 subjects with major protocol violations at baseline and 7 with major protocol deviations (1 of whom was withdrawn) during the forced-titration period. Thus at Week 18, 31 subjects were included in the PP population. Thirty-eight subjects completed the forced-titration period and entered the comparative, double blind, crossover period. The first subject entered the trial (screened) on April 19, 2000 and the last subject completed the Week 18 visit on December 4, 2000. The mean body weight and mean body mass index of the 44 subjects entering the forced-titration period was 71.13 kg and 24.72 kg/m², respectively. The majority of subjects were Caucasians aged between 18 and 63 years (there were 8 subjects < 18 years of age). Homozygous familial hypercholesterolaemia was genetically, clinically or functionally confirmed in 43 subjects. Receptor status was negative in 6 subjects, defective in 30 subjects and unknown in 8 subjects; 11 subjects received apheresis and 4 subjects had a portacaval shunt. The 2 subjects without baseline or post-baseline measurements (both withdrawn) received apheresis and were of defective receptor status. One subject (receptor negative status, receiving apheresis) had blood samples taken <7 days after apheresis at Weeks 0, 6 and 12, making the data invalid for ITT analysis at these time points and for group mean percentage change from baseline calculations.

Demography: crossover period
The ITT population comprised 38 subjects who completed the forced-titration period; the same 38 subjects were in the safety population. During the crossover period there were 6 major protocol violators (non-compliance with randomised trial medication), who were excluded from the PP population. Also excluded from the PP population were the 4 major protocol violators and 6 major protocol deviators from the forced-titration period. Thus in the crossover period, there were 22 subjects in the PP population. The first subject began randomised treatment on September 23, 2000 and the last subject completed the last crossover visit (Week 30) on February 22, 2001. All 38 subjects who entered the crossover period at Week 18 were assigned to 1 of 2 randomised treatment groups with 19 subjects in each group: Group I (assigned to the treatment sequence: rosuvastatin/atorvastatin) or Group II (assigned to the treatment sequence: atorvastatin/rosuvastatin). The majority of the subjects were Caucasians between 18 and
63 years of age (there were 7 subjects < 18 years of age), with a mean body weight of 67.57 kg (rosuvastatin/atorvastatin) and 76.13 kg (atorvastatin/rosuvastatin). Receptor status was negative in 6 subjects (including the subject with blood samples taken < 7 days after apheresis at Weeks 0, 6 and 12), defective in 28 subjects and unknown in 4 subjects; 6 subjects were receiving regular apheresis and 4 had portacaval shunts. No subjects withdrew during the crossover treatment period.

Efficacy: forced-titration period
A summary of the key efficacy findings from the forced-titration period is presented in Table I.

Table I  Summary of key efficacy findings for the first 18 weeks of treatment; forced-titration period (LOCF on ITT population)

<table>
<thead>
<tr>
<th>Efficacy variable</th>
<th>Overall (N = 42)</th>
<th>Rosuvastatin 20/40/80 mg</th>
<th>Receptor defective (N = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-C</td>
<td>3.07 (–3.45, 9.60)</td>
<td>0.87 (–5.33, 7.08)</td>
<td></td>
</tr>
<tr>
<td>TG</td>
<td>3.28 (–11.31, 17.87)</td>
<td>11.29 (–8.52, 31.10)</td>
<td></td>
</tr>
<tr>
<td>LDL-C/HDL-C</td>
<td>–20.52 (–29.11, –11.93)</td>
<td>–22.52 (–30.21, –14.84)</td>
<td></td>
</tr>
<tr>
<td>ApoB</td>
<td>–20.0 (–25.9, –14.0)</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>ApoA-I</td>
<td>5.2 (–0.6, 11.1)</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>ApoE</td>
<td>–7.7 (–16.9, 1.4)</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>ApoB/ApoA-I</td>
<td>–20.71 (–28.57, –12.86)</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Lp(a)</td>
<td>5.7 (–2.6, 13.9)</td>
<td>ND</td>
<td></td>
</tr>
</tbody>
</table>

Median percentage change from baseline (min, max) to Week 18c in serum and urinary mevalonic acid, and inflammatory markers and in

<table>
<thead>
<tr>
<th>Efficacy variable</th>
<th>Overall (N = 42)</th>
<th>Number of subjects for % change from baseline at Week 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum mevalonic acid</td>
<td>-70.84 (-91.1, -11.1)</td>
<td>36</td>
</tr>
<tr>
<td>Urinary mevalonic acid</td>
<td>-48.17 (-88.0, 60.5)</td>
<td>36</td>
</tr>
<tr>
<td>CRP</td>
<td>–47.7 (-99, 9300)</td>
<td>36</td>
</tr>
<tr>
<td>IL-6</td>
<td>–4.32 (-98.68, 782.61)</td>
<td>37</td>
</tr>
<tr>
<td>E-Selectin</td>
<td>–14.62 (–59.8, 53.3)</td>
<td>37</td>
</tr>
</tbody>
</table>

aData for 1 subject were excluded from all group mean % change from baseline at Week 18 calculations (blood samples taken <7 days of apheresis at Week 0, 6 and 12).

b LDL-C data for 1 subject (unknown receptor status) were excluded from group mean % change from baseline at Week 18 calculation (LDL-C levels had been mistakenly determined by Friedewald equation instead of by β-quantification).

c Analysis of observed data.

95% CI = 95% Confidence Interval, ND = not done.

At Week 18 (LOCF data from the ITT population) there was a clinically relevant reduction from baseline in LDL-C (the primary objective of this trial); ≥15% reduction in LDL-C is considered
as a clinically relevant response. There were also clinically relevant reductions from baseline in LDL-C at Weeks 6 and 12 (observed data); the majority of the overall reduction was achieved by Week 6. Most subjects (29) were responders, having achieved a ≥ 15% reduction in LDL-C at Week 18 (including 2 receptor receptor negative status and 2 apheresis subjects). There were decreases from baseline in TC and lipid ratios (LDL-C/HDL-C, TC/HDL-C and non HDL-C/HDL-C) and ApoB and apolipoprotein ratio (ApoB/ApoA-I) at Weeks 6, 12 and 18. Changes in HDL-C and ApoA-I were slight, as were changes in ApoE; changes in TG were variable. There were slight changes from baseline at Week 18 in Lp(a), HDL-C, ApoA-I, TG and ApoE; results from these parameters were inconclusive. Data for the inflammatory markers CRP, IL-6 and E-selectin were generally highly variable. There were decreases in serum mevalonic acid at Weeks 6, 12 and 18; urinary mevalonic acid data were highly variable. The number of evaluable subjects in the receptor negative and receptor unknown subgroups were too small (N=5 and N=8, respectively) and data were generally too variable to draw inferences on mean percentage change from baseline data. There was a smaller decrease from baseline in LDL-C in the apheresis subgroup (N=9) compared with portacaval shunt (N=4) and neither portacaval shunt nor apheresis (N=29) subgroups; however, data were variable and there were small numbers of subjects in some of the subgroups. Results from the analyses of observed data from the PP population and Week 18 observed ITT data were consistent with results from the ITT efficacy analysis. Exploratory analyses did not show any clinically relevant impact of demographic factors (age, weight, race, sex) on change in LDL-C levels over time; no inferential statistical analysis was performed.

**Efficacy: crossover period**

A summary of the key efficacy findings from the crossover period is presented in Table II.
Table II  Summary of key efficacy findings during the 12-week crossover treatment period (observed data from the PP population)

<table>
<thead>
<tr>
<th>Efficacy variable</th>
<th>Rosuvastatin 80 mg</th>
<th>Atorvastatin 80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>lsmean of percentage change (SE) from baseline to Week 24 or 30 in lipids, lipid ratios, and lipoproteins</td>
<td>Overall (N = 22)</td>
<td>Overall (N = 22)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>-19.05 (1.93)a</td>
<td>-17.95 (1.93)a</td>
</tr>
<tr>
<td>TC</td>
<td>-17.64 (1.61)</td>
<td>-17.88 (1.61)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>2.51 (4.61)</td>
<td>-4.94 (4.61)</td>
</tr>
<tr>
<td>LDL-C/HDL-C</td>
<td>-14.74 (4.35)</td>
<td>-7.50 (4.35)</td>
</tr>
<tr>
<td>TC/HDL-C</td>
<td>-16.09 (3.93)</td>
<td>-10.23 (3.93)</td>
</tr>
<tr>
<td>non HDL-C/HDL-C</td>
<td>-17.05 (4.11)</td>
<td>-10.75 (4.11)</td>
</tr>
<tr>
<td>TG</td>
<td>-6.33 (4.44)</td>
<td>-13.93 (4.44)</td>
</tr>
<tr>
<td>ApoB</td>
<td>-11.39 (1.98)</td>
<td>-11.71 (1.98)</td>
</tr>
<tr>
<td>ApoA-I</td>
<td>4.07 (2.33)b</td>
<td>-7.53 (2.33)</td>
</tr>
<tr>
<td>ApoB/ApoA-I</td>
<td>-7.48 (3.95)</td>
<td>-0.33 (3.95)</td>
</tr>
<tr>
<td>ApoE</td>
<td>-20.55 (2.40)</td>
<td>-23.41 (2.40)</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>25.51 (3.14)c</td>
<td>4.78 (3.14)</td>
</tr>
</tbody>
</table>

median percentage change (min, max) from baseline to Week 24 or 30 in serum and urinary mevalonic acid, and in inflammatory markers (observed data from the ITT population)

<table>
<thead>
<tr>
<th></th>
<th>Overall (N = 38)</th>
<th>Overall (N = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum mevalonic acid</td>
<td>-67.54 (-95.6, 20.8)</td>
<td>-70.40 (-88.8, 0.6)</td>
</tr>
<tr>
<td>Urinary mevalonic acid</td>
<td>-60.16 (-150.0, 142.1)</td>
<td>-57.92 (-88.8, 118.8)</td>
</tr>
<tr>
<td>CRP</td>
<td>-41.4 (-99.6, 625)</td>
<td>-46.8 (-98, 352)</td>
</tr>
<tr>
<td>IL-6</td>
<td>-12.61 (-98.46, 398.34)</td>
<td>-18.19 (-91.87, 137.76)</td>
</tr>
<tr>
<td>E-Selectin</td>
<td>-17.48 (-66.7, 55.8)</td>
<td>-14.04 (-62.0, 35.8)</td>
</tr>
</tbody>
</table>

lsmean = Least squares mean.

a LDL-C data for 1 subject were excluded from group mean % change from baseline at Week 24 or 30 in LDL-C calculations (LDL-C levels had been mistakenly determined by Friedewald equation instead of by β-quantification).
b p=0.001, c p<0.001 versus atorvastatin 80 mg.

Following an 18-week forced-titration of rosvastatin 20/40/80 mg there was a clinically relevant reduction from baseline (≥15%) in LDL-C, the primary lipid of interest; similarly, there was a clinically relevant reduction from baseline in LDL-C after 6-weeks treatment each of rosuvastatin 80 mg and atorvastatin 80 mg in the crossover period. The effect of rosuvastatin 80 mg on the reduction from baseline in LDL-C was non-inferior to that of atorvastatin 80 mg (non-inferiority test with a 6% limit) and there was no significant difference between treatments. Following rosuvastatin 80 mg and atorvastatin 80 mg treatment there was an overall improvement in atherogenic profile: there were reductions from baseline in TC, TG and lipid ratios (LDL-C/HDL-C, TC/HDL-C and non HDL-C/HDL-C). Changes in HDL-C were small after both treatments. Following rosuvastatin 80 mg and atorvastatin 80 mg treatment there were also reductions from baseline in apolipoprotein ApoB and ApoE, and apolipoprotein ratio (ApoB/ApoA-I), while for ApoA-I there was an increase from baseline following rosuvastatin 80 mg treatment compared with a decrease after atorvastatin 80 mg treatment (statistically significant difference between treatments; p=0.001). There was a significantly greater increase from baseline in Lp(a) following rosuvastatin 80 mg treatment compared with the increase...
following atorvastatin 80 mg treatment (p<0.001). Results of the ITT analysis of the lipid and lipid fraction data generally supported the findings obtained from the PP analysis. Data for inflammatory makers (CRP, IL-6 and E-Selectin) were variable. There were marked reductions from baseline following both treatments in serum mevalonic acid levels; urinary mevalonic acid data were variable and inconclusive. Exploratory analyses did not show any clinically relevant impact of demographic factors (age, weight, race or sex) on change in LDL-C levels over time; no inferential statistical analysis was performed.

**Safety: forced-titration and crossover periods**

In the forced-titration period the safety population comprised 44 subjects entering the trial at Week 0, while in the crossover period the safety population comprised 38 subjects who received randomised treatment.

Rosuvastatin 20/40/80 mg was well tolerated during the forced-titration period, and rosuvastatin and atorvastatin were well tolerated at the 80 mg dose during the crossover period. There were no adverse events leading to withdrawal and no deaths reported. During the forced-titration period, the types and incidences of treatment-emergent adverse events suggested no change in the adverse events profile of rosuvastatin to that observed in previous trials. There was no apparent increasing incidence of onset/worsening of adverse events as the forced-titration period progressed. Four subjects out of 44 (9.1%) experienced 6 serious adverse events. During the crossover period there were 15 out of 38 (39.4%) subjects who experienced 20 events during rosuvastatin 80 mg treatment and 6 (15.7%) subjects who experienced 10 events during atorvastatin 80 mg treatment. The majority of events occurred as single incidents and 2 subjects experienced > 2 events. Two subjects out of 38 (5.3%) experienced 3 serious adverse events. Two subjects taking concomitant warfarin experienced 3 incidents of high INR with associated adverse events during the forced-titration period: gum haemorrhage (serious and unrelated to treatment) and epistaxis (serious, treatment related) in 1 subject and decreased prothrombin (non-serious, treatment related) in another subject. The INR was stabilised in both subjects, who were reported as recovered; the individual with high INR and with associated bleeding was able to continue in the trial on a modified (lower) warfarin scheme and completed the crossover period, while the other subject withdrew during the forced-titration period due to reasons unrelated to the high INR (protocol non-compliance). INR data in subjects receiving concomitant warfarin were unremarkable throughout the crossover period. Two subjects experienced clinically raised ALT (>3x ULN). In 1 subject the raised ALT levels started during the forced-titration period and continued in the crossover period throughout both rosuvastatin 80 mg and atorvastatin 80 mg treatments (described as “resolving”). In the second subject, the raised ALT occurred in the crossover period after Week 24 during rosuvastatin 80 mg treatment (described as “worsening”). There were 2 incidents of myalgia (1 during the forced-titration period and 1 during atorvastatin 80 mg treatment in the crossover period). Other clinical biochemistry; haematology; and urinalysis data; and data from other safety assessments (vital signs, physical examination and ECGs) were all generally unremarkable over the trial period with no apparent treatment-related patterns during either the forced-titration or crossover periods.
OVERALL CONCLUSIONS
During the forced-titration period of this trial investigating the efficacy and safety of rosuvastatin 20/40/80 mg in subjects with homozygous familial hypercholesterolaemia, there was a clinically relevant reduction from baseline in LDL-C at Week 18 (the primary objective). The main efficacy analyses were based on LOCF data at Week 18 from the ITT population (overall ITT population). Overall rosuvastatin 20/40/80 mg was safe and well tolerated.

During the crossover period of this trial, which compared the safety and efficacy of rosuvastatin 80 mg and atorvastatin 80 mg, there were clinically relevant reductions in LDL-C from baseline following both treatments. There was an overall improvement in atherogenic profile from baseline following both rosuvastatin 80 mg and atorvastatin 80 mg treatment. The main efficacy analysis was based on observed data from the PP population. Both treatments were safe and generally well tolerated.

The efficacy and safety conclusions from the forced-titration and crossover periods were based on the following:

**Efficacy conclusions from the forced-titration period**

**Primary Efficacy Endpoint**
- There was a clinically relevant reduction from baseline in LDL-C at Week 18 (≥15% change in LDL-C is considered as a clinically relevant response).

**Secondary Efficacy Endpoints**
- There was a clinically relevant reduction from baseline in LDL-C at Weeks 6 and 12.
- The majority of subjects at Week 18 were responders, having achieved an LDL-C reduction of ≥15%.
- The number of evaluable receptor negative and receptor unknown status subjects was too small and data too variable for any inference to be drawn on the mean percentage change data.
- There were decreases from baseline in TC and in all lipid ratios investigated (LDL-C/HDL-C, TC/HDL-C, non-LDL-C/HDL-C), and in the lipoprotein ApoB and ratio ApoB/ApoA-I at all time points at which they were investigated.
- Changes in HDL-C and ApoA-I were slight.
- Changes in TG were variable.
- Changes in ApoE were slight; results for change from baseline in Lp(a) were inconclusive.
- Data for inflammatory markers (CRP, IL-6 and E-selectin) were generally highly variable.
- There were decreases in serum mevalonic acid at Weeks 6, 12 and 18. Urinary mevalonic acid data were highly variable.
Efficacy conclusions from the crossover period

**LDL-C efficacy endpoint (primary lipid of interest)**

- Following both treatments the reductions from baseline in LDL-C were clinically relevant (≥ 15%).

- Rosuvastatin 80 mg was statistically non-inferior to atorvastatin 80 mg in the reduction of LDL-C from baseline (non-inferiority test with 6% limit); there was no significant difference between the effect of rosuvastatin 80 mg and atorvastatin 80 mg on the reduction from baseline in LDL-C.

**Other efficacy endpoints during the crossover period**

- There was no significant difference between the effect of rosuvastatin 80 mg and atorvastatin 80 mg on reductions from baseline in TC, TG and in lipid ratios (LDL-C/HDL-C, TC/HDL-C and non HDL-C/HDL-C) and on change from baseline in HDL-C.

- There was no significant difference between the effect of rosuvastatin 80 mg and atorvastatin 80 mg in the reductions from baseline in ApoB, ApoB/ApoA-I ratio and ApoE. There was a significant difference between the effect of the 2 treatments on change from baseline in ApoA-I, which was increased following rosuvastatin 80 mg treatment, and was decreased following atorvastatin 80 mg treatment.

- There was a significantly greater increase from baseline in lipoprotein Lp(a) following rosuvastatin 80 mg treatment than the increase following atorvastatin 80 mg treatment.

- Data for inflammatory markers CRP, IL-6 and E-Selectin were variable.

- There were considerable reductions in serum mevalonic acid following rosuvastatin 80 mg and atorvastatin 80 mg treatment; urinary mevalonic acid data were variable and inconclusive.

Safety conclusions from the trial

- During the forced-titration period the overall incidence and types of adverse events (including serious adverse events) were not unexpected for this trial population and were not suggestive of any changes in the adverse event profile of rosuvastatin compared with those observed in previous rosuvastatin trials. During the crossover period there were 15 subjects who experienced 20 treatment-emergent events during treatment with rosuvastatin 80 mg and 6 subjects who experienced 10 treatment-emergent events during atorvastatin 80 mg treatment. The majority of events were of mild or moderate intensity and occurred as single incidents. The incidence, nature and type of events reported during the crossover period would not be unexpected.
for this trial population. There were no adverse events leading to withdrawal throughout the trial.

- During the forced-titration period there were 4 subjects who experienced 6 serious adverse events (epistaxis was the 1 treatment related event); during the crossover period 2 subjects experienced 3 serious adverse events (none treatment related).

- Overall, INR data from the subjects taking concomitant warfarin during the forced-titration and crossover periods fitted the pattern of manageable mild, potentiation of anticoagulant effect of warfarin by rosuvastatin. There were 3 bleeding events (including the serious incident of epistaxis) associated with high INR in 2 subjects that occurred during the forced-titration period. All events were satisfactorily controlled with adjustment of warfarin dose.

- Two subjects had clinically significant elevation in ALT (>3 xULN). There were no clinically significant elevations in CK (>10 times ULN) and there were 2 subjects with myalgia.

- Throughout the trial, data from vital signs, ECGs and other laboratory tests were generally unremarkable with no suggestion of treatment related patterns during either the forced-titration or crossover periods.