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Safety and tolerability of dalcetrapib (RO4607381/JTT-705): results from a 48-week trial

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Aims Co-primary objectives were to evaluate dalcetrapib (JTT-705/RO4607381), which targets cholesteryl ester transfer protein (CETP), effects on high-density lipoprotein cholesterol (HDL-C) in participants with coronary heart disease or risk equivalents and to evaluate potential changes in mesenteric lymph nodes.

Methods and results Double-blind trial with participants randomized (2:1) to dalcetrapib 900 mg/day (higher than 600 mg phase III dose) or placebo, both with atorvastatin, for 24 weeks ($n = 135$; one without post-baseline efficacy data was excluded from intent-to-treat population); a subset continued for 24-week extension ($n = 77$). Lipid changes and safety parameters were assessed. Mesenteric lymph nodes were evaluated by magnetic resonance imaging. Dalcetrapib increased HDL-C (33.4%, Week 24; 33.8%, Week 48), decreased CETP activity (−53.5%, Week 24; −56.5%, Week 48), and increased apolipoprotein A-I (11.4%, Week 24; 16.4%, Week 48). Dalcetrapib showed no clinically relevant differences vs. placebo in adverse events, laboratory parameters including aldosterone, electrocardiograms, and vital signs including blood pressure (BP). Dalcetrapib had no measurable, clinically relevant effect on lymph node size.

Conclusion Dalcetrapib 900 mg administered for up to 48 weeks showed no clinically relevant changes in lymph nodes, BP, or other safety parameters. Dalcetrapib effectively increased HDL-C over 48 weeks of treatment.

Keywords CETP • Dalcetrapib • HDL-C • Lymph node

Introduction

Targeting high-density lipoprotein cholesterol (HDL-C) may potentially reduce cardiovascular disease (CVD) events and risk beyond the reduction already achieved with the standard of care, which includes statins. This is based on the strong epidemiological inverse relationship between HDL-C and CVD risk[1–3] together with suggestive evidence from clinical trials with drugs that both raise HDL-C and lower low-density lipoprotein cholesterol (LDL-C).[4–6] However, current HDL-C-raising therapies have either limited efficacy or tolerability issues.[7]

One potential strategy towards raising HDL-C is through inhibition of cholesteryl ester transfer protein (CETP). Decreased plasma levels of CETP are associated with increased levels of HDL-C and, in turn, decreased risk of coronary artery disease (CAD).[8–10] These effects have been correlated also with specific mutations in the CETP gene.[8,11,12]

Torcetrapib, the first inhibitor of CETP activity to enter extensive evaluation in humans, was associated with increases in blood pressure (BP) in several clinical trials, which appears to be a compound-specific, off-target effect.[13–17] Notably, the phase III Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial of torcetrapib in combination with atorvastatin was halted very early due to increased CVD events and all-cause mortality compared with atorvastatin alone;[13] further development of torcetrapib was terminated.

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Clinical studies have shown that dalcetrapib either alone or with pravastatin was associated with increased HDL-C but no effect on BP.[18,19] A recent analysis of safety data at 4 and 12 weeks from five phase II trials further reinforces the safety of dalcetrapib both alone and in combination with statins[20] and supported further clinical study of dalcetrapib. One potential safety concern from pre-clinical studies surrounds dalcetrapib binding to lipoproteins, lipids, and chylomicrons and ingestion by macrophages in mice and rats, and to a lesser extent in monkeys and hamsters. Although deposition of foamy macrophages in mesenteric lymph nodes is not anticipated in humans, clinical studies are necessary to confirm this.

Although dalcetrapib 600 mg/day is the dose selected for phase III development, the 900 mg/day dose[18,20] was chosen for this study in order to provide a robust assessment of safety and tolerability.

Methods

Participants

Participants were aged 18–75 with coronary heart disease (CHD) or CHD risk equivalents based on National Cholesterol Education Program Adult Treatment Panel III guidelines (atherosclerosis, diabetes, or 10-year risk of CHD events >20%). For full inclusion/exclusion criteria, see the Supplementary material online.

All participants provided written informed consent. Protocols (core and extension periods) were approved by appropriate Institutional Review Boards and Ethics Committees. The study was conducted in 10 centres in the USA and 5 in Germany in conformance with the principles of the Declaration of Helsinki and International Conference of Harmonization Good Clinical Practice guidelines.

Study design

This double-blind, randomized, placebo-controlled, parallel-group, phase II trial included a 5–12-week pre-randomization phase, a 24-week core treatment phase (ClinicalTrial.gov identifier: NCT00353522), and an optional 24-week extension phase (ClinicalTrial.gov identifier: NCT00400439). Participants received atorvastatin 10–80 mg daily during the run-in period, those achieving LDL-C <100 mg/dL were randomized to dalcetrapib 900 mg or placebo (2:1) daily co-administered with atorvastatin 10–80 mg for 24 weeks. Participants continuing in the extension phase received allocated treatment for a further 24 weeks. The double-blind treatment period included both core and extension phases.

Efficacy

Primary efficacy parameters were percent and absolute change from baseline in HDL-C, measured at 24 weeks (core phase) and 48 weeks (extension phase) using standard methods.[21] Secondary efficacy parameters included changes in lipids, apolipoprotein A-I, CETP mass and activity and high-sensitivity (hs) C-reactive protein (more details are provided in the Supplementary material online).

Safety

Safety was assessed by monitoring of adverse events (AEs), vital signs, physical examination, and laboratory safety measures (further details are provided in the Supplementary material online). Patients who did not return for a follow-up visit were contacted by the investigator by telephone, personal visit, or via a responsible relative to determine the reason for withdrawal.

Effect on mesenteric lymph nodes

One primary safety objective was to investigate the effect of longer-term high-dose dalcetrapib on the size of mesenteric lymph nodes. Unenhanced magnetic resonance imaging (MRI) (without oral or intravenous contrast administration) was performed using standardized high resolution MRI scanners (≥1.5 T). MRI scans were performed during pre-randomization and at 12, 24, 36, and 48 weeks. In addition to assessment by a local radiologist, two independent blinded reviewers assessed the MRI scans and determined the size of individual lymph nodes based on the dimension of the shortest axis, with <2 mm considered undetectable. Nodes were categorized according to size change relative to previous visits.

Statistical analyses

Efficacy

The primary efficacy analysis was based on the intent-to-treat core and extension populations. These included all randomized participants with one or more post-baseline efficacy measurements. For missing data at Weeks 12 and 24, the last available post-randomization visit data were carried forward for percentage change calculation (last observation carried forward analysis). Treatment differences with respect to mean values for the primary variable were estimated by standard linear model methods (analysis of covariance), where dependent variables included treatment, centre, baseline value of the primary variable, and their interaction terms as appropriate. Ninety-five per cent two-sided confidence interval estimates and associated *P*-values for treatment differences were calculated for model-based exploratory parameters. The non-parametric Wilcoxon two-sample test was used to test for differences in hs-C-reactive protein between treatment groups. No adjustments were made for multiple comparisons.

Safety

The safety population included all randomized participants who received one or more doses of study medication and had a safety follow-up visit. Descriptive statistics are presented. No inferential statistical analyses were performed.

Sample size

Since the primary purpose of the study was exploratory to examine potential effects on mesenteric lymph nodes, it was not possible to calculate sample size based upon formal power calculations relative to the expected effects on this end point. Accordingly, the study sample size was based upon being able to evaluate changes in HDL-C over a 24-week period (due to its importance as an efficacy end point in establishing benefit to patients); thus, the sample size was planned on the basis of studies conducted to date. An initial sample of 105 patients (70 on active treatment, 35 receiving placebo) was anticipated to ensure adequate precision for estimating differences with regard to efficacy between treatment groups.

Statistical analyses were performed with SAS software (SAS Institute Inc.).

Results

Analysis populations

Overall, 135 participants (89 dalcetrapib and 46 placebo) were enrolled. All 135 patients were included in the 24-week core safety population, with 134 in the intent-to-treat population (placebo, $n = 1$ excluded as no post-baseline efficacy data) (*Figure 1*). Patients defined as withdrawn from the study

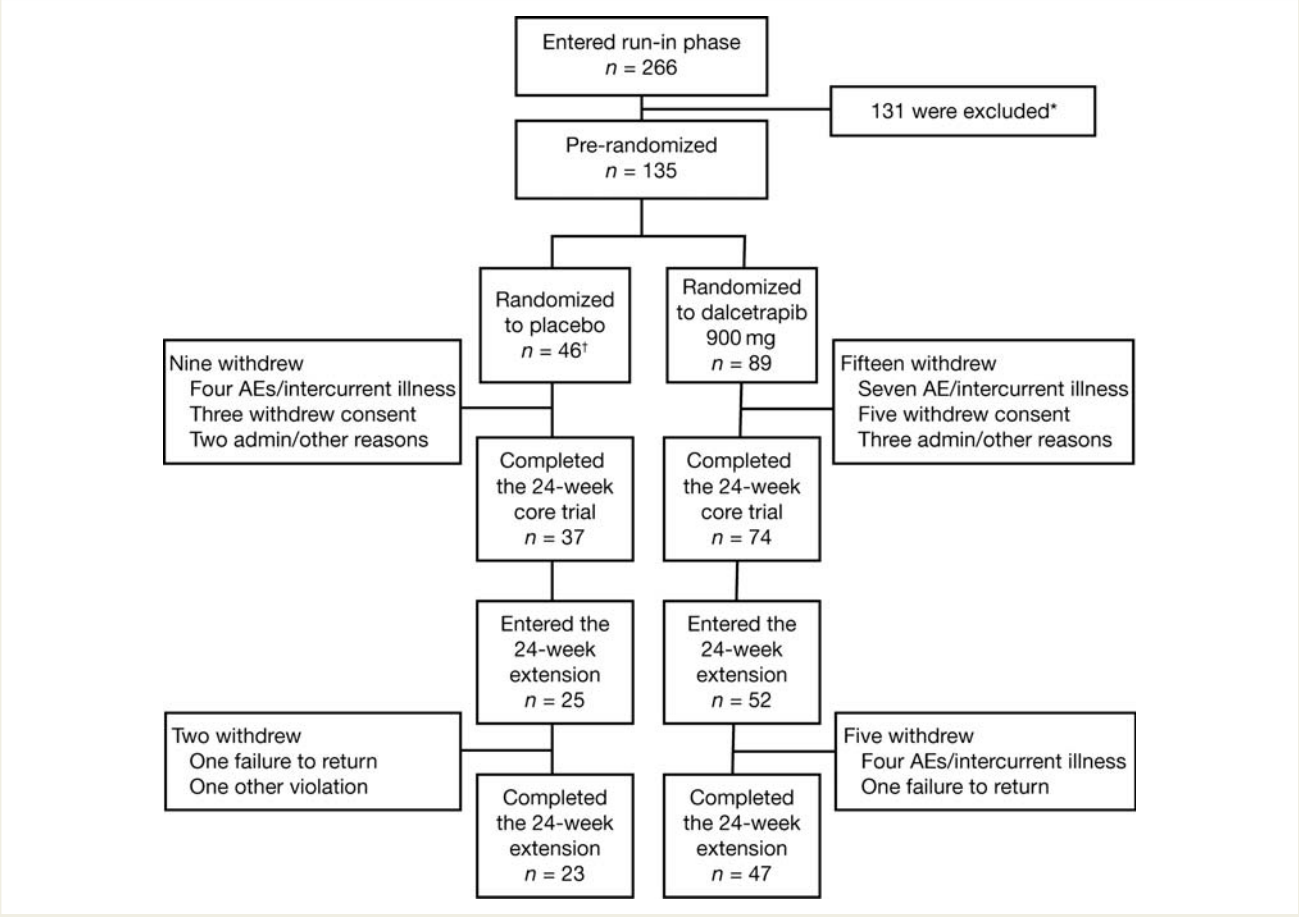

Figure 1 Participant disposition. Asterisk indicates the most common reason for exclusion (51%) pre-randomization was disqualification on the basis of non-detection of lymph nodes; †$n = 45$ for intent-to-treat; one participant in the placebo group was excluded from the intent-to-treat population due to lack of post-baseline efficacy data.

(*Figure 1*) were included in the analysis on the basis of last observation carried forward. During the first month of treatment, two patients in each group withdrew from the study (one due to AE/intercurrent illness, one withdrew consent). There were no apparent differences between the two groups in terms of when patients were withdrawn. The 24-week extension phase included 77 participants in both the intent-to-treat and safety extension populations (52 dalcetrapib and 25 placebo) and was limited to US sites as the extension protocol lacked approval from the German Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte) based on available data. Treatment groups were generally comparable with regard to baseline characteristics (*Table 1*). Slightly more dalcetrapib participants in both phases had previous coronary disease or atherosclerosis vs. placebo; a similar trend was seen in this group in the core period regarding previous hypertension.

Efficacy

There was a significantly greater increase in HDL-C from baseline with dalcetrapib at Weeks 24 and 48 (each $P < 0.0001$ vs. placebo; *Table 2*). The absolute change in HDL-C (least squares mean) with dalcetrapib was 12.8 mg/dL at Week 24 and 13.8 mg/dL at Week 48 from baseline levels of 41.4 and 42.4 mg/dL, respectively. The absolute change for placebo was 0.5 mg/dL at Week 24 and 1.4 mg/dL at Week 48 from baseline 41.0 and 41.8 mg/dL, respectively. Percent change in HDL-C was 33.4% for dalcetrapib vs. 3.5% for placebo at Week 24, and 33.8 vs. 3.7% at Week 48 (each $P <$ 0.0001 vs. placebo; *Table 2*). High-density lipoprotein cholesterol levels reached a plateau at Week 2 with dalcetrapib and were sustained throughout both treatment phases (*Figure 2*). In the dalcetrapib group, CETP activity decreased (−53.5% at Week 24; −56.5% at Week 48) and CETP mass increased (80.8% at Week 24; 86.5% at Week 48) from baseline (each $P < 0.0001$ vs. placebo; *Table 2*).

At Weeks 24 and 48 with dalcetrapib, there were no clinically relevant changes from the already low baseline LDL-C levels on atorvastatin of 76.9 and 74.2 mg/dL, respectively (*Table 2*). At Week 24, triglyceride levels were elevated with placebo but not dalcetrapib (19 vs. −1.5%; $P = 0.006$; *Table 2*) from baseline 131.7 and 150.2 mg/dL, respectively; this difference between groups was not consistently observed (data not shown). Apolipoprotein A-I increased from baseline in both groups; this was significantly greater for dalcetrapib vs. placebo at both Week 24 (11.4 vs. 4.4%; $P = 0.006$) and Week 48 (16.4 vs. 8.2%; $P = 0.025$; *Table 2*).

Table 1 Demographics and baseline characteristics following pre-randomization phase

Parameter[a]	24-week core phase		24-week extension phase	
	Placebo	Dalcetrapib 900 mg	Placebo	Dalcetrapib 900 mg
n	46	89	25	52
Age (years)	60.2 ± 7.50	61.2 ± 7.76	60.8 ± 7.83	60.6 ± 7.03
Gender, male (%)	38 (83)	68 (76)	22 (88)	40 (77)
Body mass index (kg/m^2)	30.1 ± 5.59	30.5 ± 4.73	29.7 ± 6.04	30.1 ± 4.64
Systolic BP (mmHg)	125.2 ± 14.31	128.1 ± 13.57	125.2 ± 13.57	126.7 ± 14.11
Diastolic BP (mmHg)	75.8 ± 7.25	75.6 ± 8.19	76.2 ± 7.68	76.0 ± 8.92
HDL-C (mg/dL)	41.0 ± 11.4	41.4 ± 9.31	41.8 ± 12.5	42.4 ± 9.42
LDL-C (mg/dL)	76.9 ± 20.7	76.9 ± 16.4	78.9 ± 23.7	74.2 ± 17.1
Total cholesterol (mg/dL)	144.2 ± 26.03	147.3 ± 22.26	150.6 ± 29.25	143.8 ± 19.86
Triglyceride (mg/dL)	131.7 ± 69.72	150.2 ± 92.57	149.9 ± 80.46	136.0 ± 56.48
Apolipoprotein A-I (mg/dL)	131.9 ± 23.41	137.1 ± 17.07	133.8 ± 23.75	138.4 ± 16.59
hs-C-reactive protein (mg/L)[b]	1.30 (2.45)	1.27 (2.86)	1.57 (4.49)	1.44 (3.04)
CETP activity (pmol/μL/h)	26.1 ± 8.30	26.3 ± 7.87	27.0 ± 7.95	27.1 ± 8.79
CETP mass (μg/mL)	1.7 ± 0.4	1.7 ± 0.4	1.7 ± 0.4	1.6 ± 0.4
Cigarette smoker (%)	4 (9)	14 (16)	3 (12)	6 (12)
Hypertension (%)	30 (65)	65 (73)	18 (72)	36 (69)
Diabetes (%)	25 (54)	48 (54)	13 (52)	28 (54)
Coronary disease (%)	19 (41)	49 (55)	11 (44)	28 (54)
Atherosclerosis (%)	15 (33)	35 (39)	7 (28)	23 (44)

BP, blood pressure; CETP, cholesteryl ester transfer protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
[a]Mean ± SD values unless otherwise stated.
[b]Median values (inter-quartile range).

Table 2 Change from baseline for efficacy parameters

Parameter[a]	Change (% change) from baseline					
	24-week core phase			24-week extension phase		
	Placebo	Dalcetrapib 900 mg	*P*-value	Placebo	Dalcetrapib 900 mg	*P*-value
HDL-C (mg/dL)	0.5 (3.5)	12.8 (33.4)	<0.0001 (<0.0001)	1.4 (3.7)	13.8 (33.8)	<0.0001 (<0.0001)
LDL-C (mg/dL)	1.5 (5.6)	−1.1 (0.5)	0.466 (0.270)	−0.9 (3.0)	1.6 (4.8)	0.585 (0.781)
Triglyceride (mg/dL)	3.9 (19.0)	−12.5 (−1.5)	0.116 (0.006)	−9.0 (4.1)	−2.5 (0.9)	0.807 (0.801)
Apolipoprotein A-I (mg/dL)	4.2 (4.4)	14.8 (11.4)	0.002 (0.006)	9.8 (8.2)	22.0 (16.4)	0.010 (0.025)
hs-C-reactive protein (mg/L)[b]	−0.24 (−24.2)	0.05 (5.7)	0.010 (0.008)	−0.24 (−26.1)	0.01 (3.2)	0.114 (0.146)
CETP activity (pmol/μL/h)	−0.1 (2.0)	−14.4 (−53.5)	<0.0001 (<0.0001)	−2.2 (−5.7)	−15.3 (−56.5)	<0.0001 (<0.0001)
CETP mass (μg/mL)	−0.02 (−0.8)	1.4 (80.8)	<0.0001 (<0.0001)	−0.1 (−4.9)	1.4 (86.5)	<0.0001 (<0.0001)

CETP, cholesteryl ester transfer protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
[a]Least squares mean change (% change) from baseline, unless otherwise stated.
[b]Median (per cent change) from baseline.

There was a small but statistically significant difference between treatment groups in median percent change in hs-C-reactive protein from baseline at Week 24 ($P = 0.010$ absolute change; $P = 0.008$ percent change) but not at Week 48 (*Table 2*). These data proved difficult to interpret due to differences in the median hs-C-reactive protein values at baseline between dalcetrapib (1.44 mg/L) and placebo (1.57 mg/L) groups in the 48-week study, with hs-C-reactive protein levels possibly attenuated by atorvastatin treatment (*Table 1*).

Safety

Adverse events

During the double-blind treatment period, which included both the core and extension periods, the percentage of participants

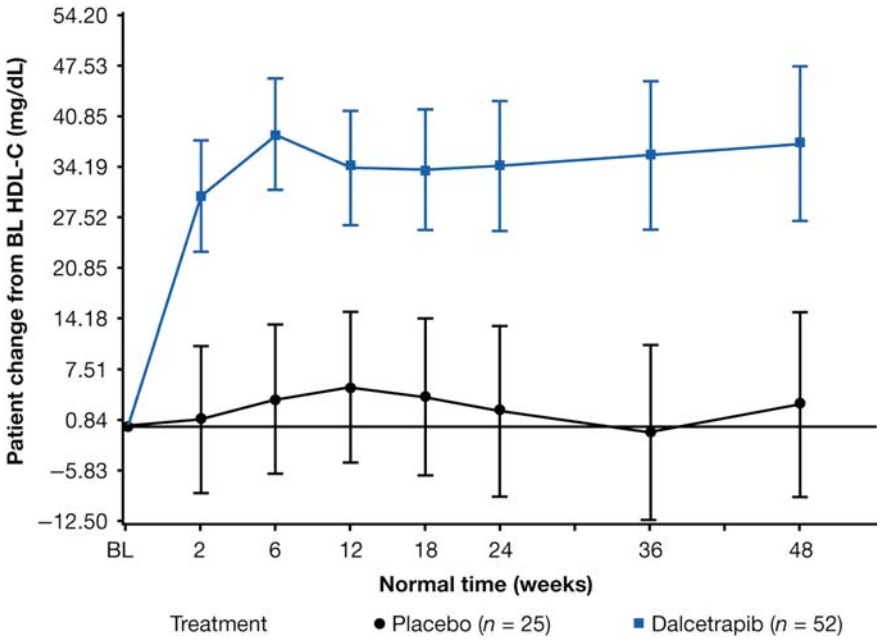

Figure 2 High-density lipoprotein cholesterol per cent change (±95% confidence interval) from baseline (BL) by time over 48 weeks.

Table 3 Overview of adverse events in the double-blind treatment period (core and extension periods)

	Number (%) of participants with ≥1 AE	
	Placebo	Dalcetrapib 900 mg
n	46	89
Any AE	38 (83)	76 (85)
Mild	26 (57)	63 (71)
Moderate	24 (52)	52 (58)
Severe	3 (7)	15 (17)
Treatment-related AEs	15 (33)	35 (39)
Serious AE	4 (9)	10 (11)
Deaths	0	0
Withdrawals due to AEs	3 (7)	11 (12)
Withdrawals due to treatment-related AEs	2 (4)	8 (9)

Table 4 Most frequently reported adverse events (five or more cases in any treatment group)

	Number (%) of participants with ≥1 AE	
	Placebo	Dalcetrapib 900 mg
n	46	89
Diarrhoea	5 (11)	15 (17)
Upper respiratory tract infection	6 (13)	13 (15)
Nasopharyngitis	4 (9)	9 (10)
Pain in extremity	2 (4)	9 (10)
Back pain	4 (9)	7 (8)
Headache	3 (7)	7 (8)
Arthralgia	2 (4)	6 (7)
Abdominal pain	3 (7)	5 (6)
Sinusitis	3 (7)	5 (6)
Hypertension	1 (2)	5 (6)

experiencing at least one AE was comparable between dalcetrapib 900 mg (85%) and placebo (83%), and most AEs were mild or moderate in intensity, with no deaths (*Table 3*). This trend was apparent also between treatment groups for the incidence of commonly occurring AEs (*Table 4*). Diarrhoea was the most common AE with dalcetrapib, occurring more frequently than for placebo (17 vs. 11%; *Table 4*). Although extremity pain was slightly more common with dalcetrapib vs. placebo (10 vs. 4%; ns), the incidence of myalgia was low in each group (4%). The percentage of AEs considered related to treatment was comparable between dalcetrapib (39%) and placebo (33%) (*Table 3*). Diarrhoea and headache were the most common treatment-related AEs reported with dalcetrapib (13 and 6%, respectively).

The percentage of participants experiencing serious AEs (SAEs) was comparable between treatment groups (11% dalcetrapib vs. 9% placebo) (*Table 3*). One case of CAD with dalcetrapib was considered possibly related to treatment by the investigator. All other

SAEs were considered not related to treatment [dalcetrapib: atrial fibrillation (two participants), non-cardiac chest pain (two participants), angina pectoris, glioma, metastatic squamous cell carcinoma, rectal cancer, neurocysticercosis; placebo: CAD, arthritis, osteoarthritis, acute cholecystitis]. The participant with metastatic squamous cell carcinoma had a history of the disease. Adverse events led to the withdrawal of 12% of participants administered dalcetrapib and 7% of participants given placebo (ns; *Table 3*). This included one participant who permanently discontinued dalcetrapib due to an AE (myalgia) which started before the double-blind study. The percentage of participants who withdrew due to treatment-related AEs was 9% for dalcetrapib and 4% for placebo (*Table 3*). Regarding cardiac and vascular AEs, CAD, and two cases of hypertension in the dalcetrapib group were considered possibly treatment-related.

Blood pressure, heart rate, and electrocardiograms

Blood pressure remained stable throughout the 48-week study (*Figure 3*). Mean (SD) BP values for dalcetrapib were (systolic BP/diastolic BP) 127 (14.1)/76 (8.9) mmHg at baseline and 127 (12.6)/77 (11.1) mmHg at study end. Shifts in systolic BP and diastolic BP were of a similar magnitude and direction in both treatment groups. Pulse rates generally remained stable (data not shown). In the dalcetrapib group, increased heart rate and irregular heart rate were each experienced by one participant. Two participants administered dalcetrapib had abnormal electrocardiograms, one of which was considered remotely related to treatment.

Laboratory tests

Four percent of participants in each treatment group experienced elevations in creatine phosphokinase (CPK), alanine aminotransferase (ALT), or aspartate aminotransferase (AST). In the dalcetrapib group, CPK elevations $>3 \times$ upper limit of normal (ULN) were observed in 2% (2/89) of participants and CPK elevations $>5 \times$ ULN in 1% (1/89) of participants; also with elevated levels at baseline (>1 but $<3 \times$ ULN). In the placebo group, 2% (1/45) of participants experienced CPK elevations $>3 \times$ ULN. Additionally, 1% (1/89) of participants administered dalcetrapib experienced ALT elevations $>3 \times$ ULN, and 2% (1/45) of participants administered placebo experienced elevations in both ALT ($>5 \times$ ULN) and AST ($>5 \times$ ULN). Aspartate aminotransferase elevations $>3 \times$ ULN were not observed with dalcetrapib. No participants with CPK elevations experienced myalgia, and no participant permanently discontinued treatment due to liver enzyme elevations. Treatment was interrupted for one dalcetrapib participant due to increased ($>3 \times$ ULN) levels of alkaline phosphatase (ALP),

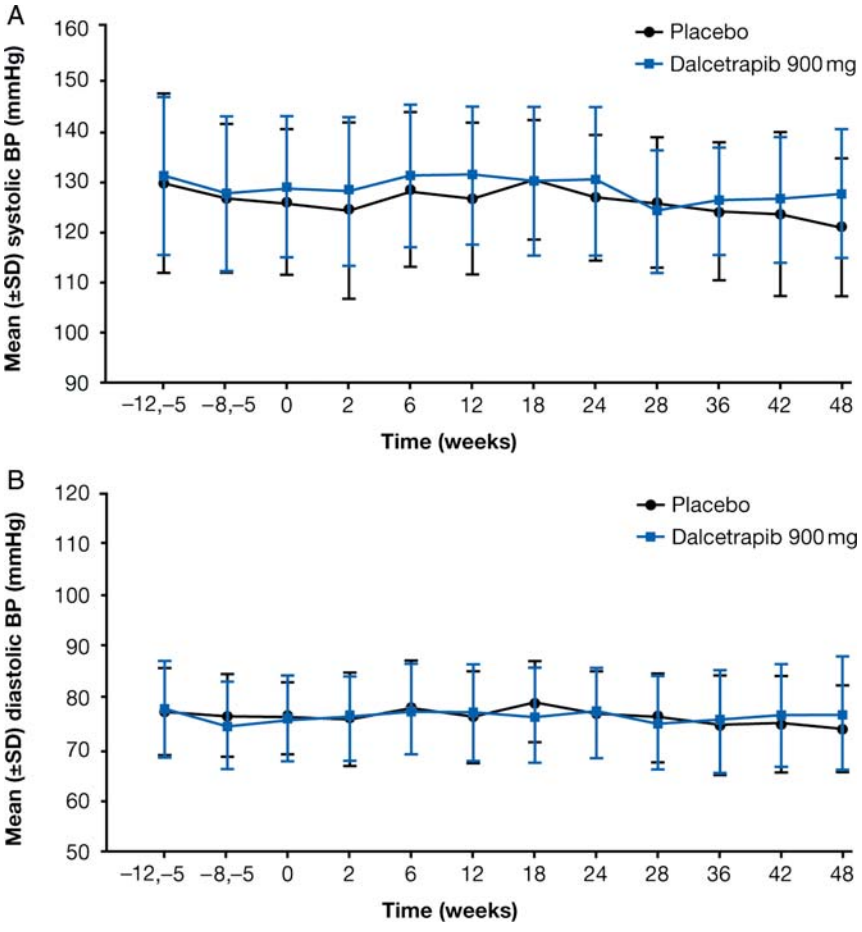

Figure 3 Blood pressure over time in the 24-week core and 24-week extension study.

ALT, and gamma-glutamyl transferase (GGT) on Day 19. This participant also had elevated ALP and GGT levels on Days 22, 28, 37, 55, 70, and 118, which progressively returned to normal. Elevation in ALP $> 3 \times$ ULN on Days 19 and 22 was not considered clinically significant (the definition being ALP and AST $> 3 \times$ ULN on two occasions ≥ 4 days apart). The AE was considered mild and possibly related to treatment by the investigator and resolved without sequelae.

There were no clinically significant changes in electrolytes with dalcetrapib; mean (SD) potassium and sodium levels were 4.3 (0.35) and 141 (2.1) mmol/L, respectively, at baseline and 4.3 (0.42) and 141 (2.3) mmol/L, respectively, at study end. In the placebo group, mean (SD) potassium and sodium levels were 4.3 (0.46) and 141 (2.0) mmol/L, respectively, at baseline and 4.4 (0.45) and 141 (2.8) mmol/L, respectively, at study end.

Aldosterone levels showed no change; median levels at baseline and study end were 76 and 82 pg/mL, respectively, with dalcetrapib, and 100 and 96 pg/mL, respectively, with placebo.

Effects on mesenteric lymph nodes

At randomization, 70 participants in the dalcetrapib group and 33 participants in the placebo group had a detectable mesenteric lymph node, as anticipated given this was an entry requirement for the trial. When the sizes of mesenteric lymph nodes were compared at various times during the study, similar results were obtained in the placebo and dalcetrapib groups. A comparison of changes in lymph node volume from baseline to Week 48 reported that in the placebo group, of 32 nodes assessed, 56% decreased in size, 3% stayed the same and 41% increased. In the dalcetrapib group where 45 nodes were assessed, similar percentages of lymph nodes increased (42%) and decreased (56%) in size and there was no clinically relevant difference in the proportion of enlarged lymph nodes. The Data Safety Monitoring Board concluded that there were no systematic or significant safety concerns in the MRI data at Week 24. Similarly, data from review of the MRI scans at Week 48 were consistent with the Week 24 data and did not show any trend towards an increase or decrease in lymph node size in either treatment group.

Discussion

Cholesteryl ester transfer protein has been identified as a potential therapeutic target to improve CVD outcomes. However, recent clinical studies with torcetrapib have raised questions regarding the safety of this approach, as torcetrapib has been associated with increases in BP, CVD events, and mortality,[13–16] although studies with other CETP inhibitors have indicated that these are not class effects.[17] Indeed, previous pre-clinical and clinical work with dalcetrapib has shown no effect on mean BP over 12 weeks.[20,22] These findings, with a dose 50% higher than that used in ongoing development, have been extended out to 48 weeks in this study, which is the longest study to date of a CETP-targeting agent with no detected changes in BP. Additionally, in contrast with torcetrapib, the observed increase in HDL-C with dalcetrapib reached a maximum at approximately 2 weeks; torcetrapib showed a continuing increase in HDL-C after 3 months of treatment in the ILLUMINATE trial.[13]

The current study presents additional safety data for an agent that targets CETP ahead of the ongoing large phase III **dal**-OUTCOMES trial.[23] In this analysis, dalcetrapib was found not to be associated with any clinically relevant safety concerns with regard to overall or cardiovascular AEs. The incidence of SAEs in the two treatment groups was comparable between the groups (11% dalcetrapib; 9% placebo); absolute numbers ($n = 10$ dalcetrapib; $n = 4$ placebo) and numbers of participants ($n = 89$ dalcetrapib; $n = 45$ placebo) were greater in the dalcetrapib group mainly due to a 2:1 randomization. The inclusion of only participants with CHD or risk equivalents would also be expected to result in some cardiovascular SAEs. Although cardiovascular SAEs were slightly more common in the dalcetrapib group, this may reflect the greater pre-ponderance of CHD risk factors in the dalcetrapib group at baseline. The slightly higher incidence of reported hypertension in the dalcetrapib group compared with the placebo group may indeed have been due to baseline differences. None of the three carcinoma-associated events in the dalcetrapib group were treatment-related—in two cases these were thought likely to be pre-existing disease (the presence of skin lesions was not an exclusion criteria in the case of the metastatic squamous cell carcinoma, and diagnosis of a case of rectal cancer early in the trial suggested it was present at baseline); glioma was diagnosed in another patient (Day 334) following an episode of dementia. Data from a previous 12-week study showed no cases of cancer with dalcetrapib in combination with pravastatin.[20] Although there were differences in the type of SAEs between the treatment groups, it is difficult to draw any conclusions from these differences due to the relatively small number of participants and the 2:1 randomization.

In this study, the use of dalcetrapib to inhibit CETP activity did not appear to be associated with any off-target, compound-specific, cardiovascular or non-cardiovascular safety concerns, except for an increased incidence of gastrointestinal events and headache. While a pre-clinical lymph node signal observed in some but not all species was considered unlikely to be clinically significant, this study confirmed that dalcetrapib has no effect on lymph nodes in humans. In addition, the dose of dalcetrapib studied (900 mg) was higher than the 600 mg dose chosen for further development and the placebo-controlled phase III **dal**-OUTCOMES trial, in which dalcetrapib is being evaluated in clinically stable patients with recent acute coronary syndrome (ACS) ($n = 15\,600$) in combination with a background of standard ACS medication.[23] The lack of substantial AEs at a 900 mg dose provides support for the safety of dalcetrapib in phase III trials.

The safety data reported here corroborate the results of a safety analysis of five shorter phase II trials examining dalcetrapib at doses of 300, 600, and 900 mg compared with placebo: a 4-week trial of dalcetrapib alone ($n = 193$), three 4-week studies of dalcetrapib in combination with statins ($n = 353$), and a 12-week trial of dalcetrapib in combination with pravastatin ($n = 292$).[20] The analysis showed a similar low incidence of cardiovascular AEs ($\leq 5\%$) in the different treatment groups.[20] In the pooled 4-week trials, the incidence of patients with AEs with the 600 mg dose of dalcetrapib was the same as with placebo, but it was higher with dalcetrapib 900 mg ($P < 0.05$ vs. placebo and vs. dalcetrapib 600 mg).[20] The incidence of SAEs was low (1% in each treatment group including placebo).[20]

The efficacy of dalcetrapib at raising HDL-C is not expected to be substantially reduced with the phase III 600 mg dose compared with the 900 mg dose investigated here. Although there was some degree of dose dependence in the effect of dalcetrapib on HDL-C in other phase II trials,[18–20] the increase in HDL-C observed with dalcetrapib 600 mg in combination with a statin (pravastatin) was as high as 31.4% at 12 weeks of treatment.[20] This is only slightly below the increases observed in the current study with dalcetrapib 900 mg (33.4% at Week 24; 33.8% at Week 48). Significant increases in apolipoprotein A-I for dalcetrapib vs. placebo were also observed in this study. Although hs-C-reactive protein was not significantly increased from baseline after 24 or 48 weeks of dalcetrapib therapy, the placebo group experienced a slight decrease, which at 24 weeks resulted in a statistical difference between the groups which was not present at 48 weeks. The clinical significance of these findings is uncertain.

Notably, the number of participants studied to date having taken dalcetrapib is limited and follow-up is relatively short. Accordingly, the possibility of Type II error cannot be ruled out. Additional, larger studies are needed to definitively determine whether there may be important adverse effects associated with the use of dalcetrapib.

In conclusion, this 48-week safety trial, the longest to date, provides additional support that dalcetrapib appears to be a safe and effective HDL-C-raising treatment. An exploratory analysis is planned to analyse a surrogate CHD endpoint, changes in aortic plaque morphology, from the MRI scans obtained in this study. Further study is also underway to determine whether the increases observed in HDL-C with dalcetrapib will lead to improved morbidity and mortality outcomes[23] (ClinicalTrial.gov identifier: NCT00658515).

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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CARDIOVASCULAR FLASHLIGHT

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Simultaneous quadruple kissing stenting of an unprotected left main coronary artery

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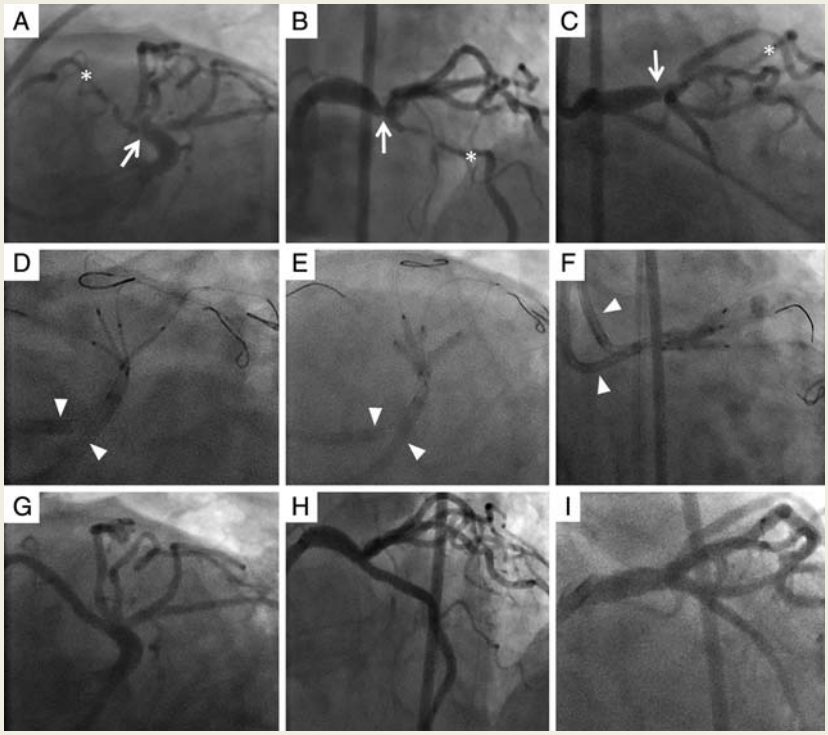

Coronary angiography for non-ST-elevation myocardial infarction in a 83-year-old, obese, hypertensive woman with diabetic nephropathy and hyperlipidaemia revealed a severe stenosis in a very large calibre unprotected distal left main coronary artery (LMCA) (arrows in *Panels A–C*) involving an uncommon quadrifurcation with the left anterior descending (LAD), two intermediate branches, and the Circumflex (Cx) artery. A long segment of the proximal LAD (asterisk) and the ostium of the most medial intermediate branch were also critically diseased. Although diabetic state and anatomic considerations would highly suggest coronary artery bypass graft surgery as the preferred treatment strategy, the patient was rejected for surgery due to morbid obesity, age, and renal failure. Hence, we planned a percutaneous coronary intervention after obtaining informed consent and after checking efficacy of dual antiplatelet treatment by platelet aggregometry and willingness of treatment compliance.

We opted for a simultaneous kissing stenting technique due to the important size mismatch between LMCA and distal branches. To allow simultaneous introduction of four stents in the LMCA, we used a bilateral 8 French arterial access (arrowheads in *Panels D–F*) and wired all branches 2 by 2. First, the LAD was separately treated with a TAXUS Liberté 3.0/38 mm paclitaxel-eluting stent (Boston Scientific), leaving the ostial segment unstented. Consequently, four TAXUS Liberté stents were introduced in the LMCA quadrifurcation (3.0/12, 2.75/16, 2.5/12, and 2.75/12 in LAD, medial and lateral intermediate branch and the Cx, respectively; *Panel D*), followed by simultaneous quadruple kissing stent expansion at 12 atm each (*Panels E* and *F*). Final angiography confirmed wide patency of LMCA and all four branches (*Panels G–I*).