SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL BC21144)

COMPANY: NAME OF FINISHED PRODUCT: NAME OF ACTIVE SUBSTANCE(S):	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	Clinical Study Report – Protocol No. BC21144: A Phase IIB, Multi-center, Double-blind, Randomized, Placebo-controlled Study, Evaluating the Safety, Tolerability and Efficacy of Dalcetrapib by Measuring Flow Mediated Dilatation in the Brachial Artery, 24 hour Ambulatory Blood Pressure, Lipids, Lipoproteins and Markers Vascular Inflammation, Oxidation and CV risk in Patients with Coronary Heart Disease (CHD) or CHD Risk Equivalents. Report No. [redacted], March 2011.		
INVESTIGATORS / CENTERS AND COUNTRIES	19 centers in western Europe		
PUBLICATION (REFERENCE)	Kastelein et al. Rationale and design of dal-VESSEL: a study to assess the safety and efficacy of dalcetrapib on endothelial function using brachial artery flow-mediated vasodilatation. Curr Med Res Opin.2011;27(1):141–150.		
PERIOD OF TRIAL	2 May 2008 - 6 May 2010	CLINICAL PHASE	IIB
OBJECTIVES	The primary efficacy objective of this study was to evaluate the effect of dalcetrapib on endothelial function as measured by Flow Mediated Dilatation (FMD) of the brachial artery in patients with CHD or CHD risk equivalents at 12 weeks. The primary safety objective of this study was to evaluate the effect of dalcetrapib on blood pressure (BP) as measured by 24 hour Ambulatory Blood Pressure Monitoring (ABPM) at 4 weeks. The secondary safety and efficacy objectives of this study were: • To evaluate the effect of dalcetrapib on endothelial function as measured by FMD of the brachial artery in patients with CHD or CHD risk equivalents at 36 weeks • To evaluate the effect of dalcetrapib on BP as measured by 24 hour ABPM at 12 and 36 weeks • To explore the effect of dalcetrapib on biomarkers of inflammation, oxidation and cardiovascular (CV) risk such as high sensitivity C-reactive protein (hsCRP), interleukin 6 (IL6), sP-Selectin, sE-Selectin, soluble intracellular adhesion molecule (sICAM), soluble vascular cell adhesion molecule (sVCAM), lipoprotein-associated phospholipases A2 (Lp-PLA2), matrix metalloproteinase (MMP)-3, MMP-9, adiponectin, myeloperoxidase (MPO), tissue plasminogen activator (TPA) and plasminogen activator inhibitor 1 (PAI-1). • To explore the effect of dalcetrapib on clinical and laboratory parameters including blood lipid, lipoprotein and apolipoprotein levels, cholesteryol ester transfer protein (CETP) mass and activity, and insulin sensitivity • To evaluate the safety profile of dalcetrapib		

	• To assess the effect of dalcetrapib on clinical outcomes as part of an outcome analysis across the entire phase IIb and phase III program (results will be reported separately).
STUDY DESIGN	This was a double-blind, randomized, placebo-controlled, multi-center study in patients with CHD or CHD risk equivalent. After a screening period of up to 8 weeks, eligible study participants received double-blind treatment with dalcetrapib or a matching placebo for 36 weeks followed by a 2-week safety follow-up. FMD was assessed at baseline, 12 and 36 weeks. Blood pressure assessed during one 24-hour period and electrocardiograms (ECGs) were assessed at baseline, 4, 12, and 36 weeks. Changes in antihypertensive treatment and/or dosage (e.g., thiazide diuretics, calcium antagonists, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor antagonist and beta-blockers) were not permitted from the baseline ABPM to the Week 4 ABPM assessments (Visit 3).
NUMBER OF SUBJECTS	476 total; 238 patients randomized to each study arm.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Both male and female patients aged 18-75 years (inclusive) at Visit 1, with CHD or CHD risk equivalent based on National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII), e.g., atherosclerosis, diabetes or >20% 10-year risk of CHD events, with high density lipoprotein cholesterol (HDL-C) <50 mg/dL (<1.3 mmol/L), TG level ≤ 400 mg/dL (<4.5 mmol/L) at screening and appropriately treated with statin and/or other LDL-C lowering drug to a stable LDL-C level (<100mg/dL) unless taking maximum tolerated doses of therapy based on their medical condition or intolerant to statin.
TRIAL DRUG / STROKE (BATCH) No.	Dalcetrapib 300 mg / formulation No. 460-7381/F51 / lot numbers: [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Patients received daily oral doses of 600 mg dalcetrapib (2 tablets of 300 mg) with food for 36 weeks
REFERENCE DRUG / STROKE (BATCH) No.	Placebo / formulation No. 460-7381/F52 / lot numbers: [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Placebo matching the investigational product given orally, once daily with food
CRITERIA FOR EVALUATION	
EFFICACY:	**Primary parameter:** change from baseline in %FMD as measured in the right brachial artery 5 to 10 cm proximal to the antecubital fossa with a high resolution ultrasound probe after 12 weeks of treatment. **Secondary parameters:** • Change from baseline in %FMD as measured in the right brachial artery 5 to 10 cm proximal to the antecubital fossa with a high resolution ultrasound probe after 36 weeks of treatment. • Blood lipid (total cholesterol [TC] and TG levels), lipoproteins (high density lipoprotein [HDL] and low density lipoprotein [LDL]), apolipoprotein (Apo) levels (ApoA1 and ApoB) and lipoprotein sub-fractions. • Ratios of these lipid, lipoprotein and apolipoprotein values • CETP mass and activity • Biomarkers of inflammation, oxidation and CV risk (hsCRP, IL6, sP-Selectin, sE-Selectin, sICAM, sVCAM, PLA2, MMP-

	3, MMP-9, Adiponectin, MPO, TPA, PAI-1) • Insulin sensitivity based on fasting glucose and insulin measurements • A composite endpoint of CHD death, non-fatal myocardial infarction (MI), hospitalization for documented acute coronary syndrome (ACS) (ECG abnormalities without biomarkers), resuscitated cardiac arrest, stroke, hospitalization for congestive heart failure and any revascularization procedure are evaluated as part of the overall dalcetrapib development program.
PHARMACODYNAMICS:	N/A
PHARMACOKINETICS:	Reported separately
SAFETY:	**Primary parameter:** change from baseline in mean BP at 4 weeks determined by 24-hour period ABPM. **Secondary parameters:** • change from baseline in mean BP at 12 and 36 weeks determined by 24-hour period ABPM; • diurnal rhythm of BP at 4, 12, and 36 weeks; • daytime mean BP at 4, 12, and 36 weeks; • nighttime mean BP at 4, 12, and 36 weeks. Other safety parameters were adverse events (AEs), serious adverse events (SAEs), laboratory safety assessments, vital signs, ECGs and physical examinations.
STATISTICAL METHODS	Treatment differences with respect to mean values of the primary variable were initially estimated by standard linear models methods, where the independent variables included treatment, center, and the baseline value of the primary variable. Based on the absolute change from baseline, non-inferiority was tested first. A 2-sided significance level of 5% was used. For %FMD, a non-inferiority margin of -0.65% was used and non-inferiority was to be concluded if the lower limit of the 95% two-sided confidence interval for the placebo corrected absolute change form baseline did not cross -0.65%. For BP, the non-inferiority was to be concluded of the upper limit of the 95% two-sided confidence interval for the placebo corrected absolute change form baseline did not exceed 2 mmHg. For the secondary efficacy endpoints, only tests for differences were performed. Diurnal rhythm, dipping status and abnormality status were summarized descriptively using frequency counts.

METHODOLOGY:

After a screening period of up to 8 weeks, eligible study participants received double-blind treatment with dalcetrapib or a matching placebo for 36 weeks followed by a 2-week safety follow-up. FMD was assessed at baseline, 12 and 36 weeks. In a subset of patients the FMD was performed twice with at least 1 night in between the investigations. Biomarkers of inflammation, oxidation and CV risk were assessed at baseline and at Weeks 12 and 36. Blood pressure (24 hour continuous monitoring) and ECGs were assessed at baseline, 4, 12, and 36 weeks. Lipids and Hemoglobin A1c (HbA1c) were assessed at screening, baseline and Weeks 4, 12, 24 and 36. Apo A1 and B, CETP mass and activity, fasting plasma glucose and insulin were assessed at baseline and Weeks 4, 24 and 36. Physical examination was performed at screening, baseline and Week 36. Height and weight were assessed at baseline and Week 36. Safety laboratory parameters and vital signs were assessed at screening, baseline, Weeks 4, 8, 12, 18, 24, 30, 36 and follow-up. Adverse events were collected and monitored throughout the study.

EFFICACY RESULTS:

The lower limit of the 95% confidence interval (CI) for the placebo corrected absolute change from

baseline in %FMD to Week 12 did not cross the pre-defined non-inferiority threshold of -0.65%. An analysis based on change from baseline to Week 36 led to the same conclusions and was also confirmed by an "as treated" analysis. The robustness of the primary analysis was also confirmed by an analysis accounting for predefined prognostic factors as well as analyses imputing missing post-baseline values. The mean absolute change from baseline in %FMD was positive at all time points in both treatment arms. The placebo corrected HDL-C increase was 30.8% at Week 36. ApoA1 increased by 10.2% and ApoB decreased by 4.7%. Reductions by 23.3% to 31.6% were observed in the ratios of TC, low density lipoprotein cholesterol (LDL-C), and non-HDL-C divided by HDL-C, although for neither LDL-C nor for TC had clinically meaningful or statistically significant results been observed.

PHARMACODYNAMIC RESULTS:

N/A

PHARMACOKINETIC RESULTS:

Will be reported separately.

SAFETY RESULTS:

Two analyses ("as treated" and "as randomized") were performed for the primary safety endpoint, absolute change from baseline in 24 hour ABPM to Week 4. In the "as randomized" analysis, the primary safety objective was met for both systolic BP (SBP) and diastolic BP (DBP). Dalcetrapib was non-inferior to placebo in terms of change from baseline for these two parameters. The placebo corrected changes from baseline were 0.65 mmHg (95% CI [-0.68, 1.99]) for SBP and 0.64 mmHg (95% CI [-0.18, 1.45]) for DBP. In the "as treated" analysis, in which 1 patient randomized to placebo but treated with dalcetrapib throughout the course of the study is allocated to the dalcetrapib arm, the corresponding results were 0.69 mmHg (95% CI [-0.64, 2.03]) for SBP and 0.64 mmHg (95% CI [-0.18, 1.45]) for DBP. The mean changes resulting from the two analyses were similar. While in the "as randomized" analysis the upper limit of the 95% CI was below the non-inferiority threshold of 2 mmHg (falling beneath by 0.01 mmHg), it exceeded the non-inferiority threshold by 0.03 mmHg in the "as treated" analysis of SBP. The results of the primary analyses were confirmed by including prognostic factors in the model. Treatment effects in subgroups were not inconsistent with the overall results.

The total number of patients with at least one AE and the total number of AEs were similar between the two study arms. One patient taking placebo died during the study. The number of patients experiencing SAEs or AEs leading to withdrawal from treatment was similar between the study arms. The most common AEs during the study were nasopharyngitis and influenza, diarrhea, back pain and headache. The incidence of those AEs was similar between the study arms. Overall, there was no clear difference in the incidence or pattern of AEs between the study arms. However, the incidence of diarrhea considered by the investigator to be possibly or probably related to study treatment was higher in the dalcetrapib arm (19 [8%] patients versus 12 [5%] in the placebo arm), and there were more withdrawals for diarrhea in the dalcetrapib arm (5 [2%] patients versus 2 [<1%] in the placebo arm).

There were no clinically relevant findings with regards to the other safety parameters such as laboratory parameters, ECGs or vital signs.

CONCLUSIONS:

- The endothelial function was unchanged following 12 and 36 weeks of treatment with dalcetrapib as measured by FMD
- Dalcetrapib neither showed a clinically relevant nor a statistically significant change in BP compared to placebo as measured by ABPM. Supported by:
    - 24h BP pattern similar to placebo (nocturnal dipping)
    - Vital signs profile similar to placebo (SBP, DBP and pulse)
    - No imbalance in reporting of AEs related to hypertension
- After placebo correction, there was a 30.8% increase in HDL-C, a 10.2% increase in ApoA1, and changes in lipid profile were generally considered as beneficial.
- Dalcetrapib was generally well tolerated, with incidence of AEs, SAEs and withdrawals from study drug similar between dalcetrapib and placebo arms.