SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL NC22703)

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

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	A phase IIIB multicenter, double-blind, randomized, placebo controlled study, evaluating the effect of treatment with dalcetrapib 600 mg on atherosclerotic disease as measured by I. coronary intravascular ultrasound (IVUS), quantitative coronary angiography II, carotid B-mode ultrasound intima medial thickness (IMT) and total plaque volume in subjects undergoing coronary angiography who have coronary artery disease (CAD). Report No. [redacted], December 2012. Synopsis format report due to no further clinical development of dalcetrapib .		
INVESTIGATORS / CENTERS AND COUNTRIES	Canada (39 centers), United States (29), Poland (11), Germany (8), Switzerland (2)		
PUBLICATION (REFERENCE)	NA		
PERIOD OF TRIAL	19Dec2009 to 23Sep2011	CLINICAL PHASE	IIIb
OBJECTIVES	The primary objective was to evaluate the effect of dalcetrapib treatment for 2 years on atherosclerotic disease progression - as assessed by coronary intravascular ultrasound (IVUS) and carotid B-mode ultrasound - in patients with coronary artery disease (CAD). Secondary objectives were to: • Evaluate the effect of dalcetrapib treatment for 2 years on atherosclerotic disease progression - as assessed by quantitative coronary angiography (QCA) - in patients with CAD. • Explore the effect of dalcetrapib on lipid metabolism and biomarkers of inflammation, oxidation and cardiovascular risk. • Evaluate the long-term safety profile of dalcetrapib. • Correlate the status and the rate of progression in atherosclerotic disease in the coronary vasculature with the rate of progression in atherosclerotic disease in the carotid vasculature - as assessed by coronary IVUS and carotid B-mode ultrasound in patients with CAD. • Evaluate the effect of dalcetrapib on clinical outcomes as part of a pooled outcome analysis across the entire phase IIb and phase III program.		
STUDY DESIGN	This was a phase IIIb multicenter, double-blind, randomized, placebo controlled, parallel group study		

	consisting of a pre-randomization (screening) phase of up to 2 months, a 24-month double blind treatment period and a 1-month safety follow-up period. Baseline assessment and month-24 end of treatment assessment consisted of QCA, coronary IVUS and carotid B-mode ultrasound. In addition, carotid B-mode ultrasound endpoints were assessed at month 6 and month 12. The off-line measurements of the different imaging modalities were to be used to evaluate status and rate of atherosclerotic disease progression and its correlations between coronary and carotid vascular beds. Patients received study drug on a background of contemporary evidence-based medical care for CAD. The end of study was defined as either the date of the last visit of the last patient to complete the study or the date at which the last data point from the last patient, which was required for statistical analysis, was received, whichever was the later.
NUMBER OF SUBJECTS	Approximately 900 patients were to be randomized to either 600 mg active dalcetrapib or placebo in a 1:1 ratio, with the expectation that 680 patients would complete the study.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	The target population consisted of patients with angiographic evidence of CAD, an IMT of $\geq$0.65 mm in either or both common carotid arterial segments as assessed by B-mode ultrasound. Potential patients who provided written informed consent underwent a clinically indicated cardiac catheterization and baseline IVUS and carotid B-mode ultrasound assessment. In order to be included in the trial, patients had to fulfill all of the inclusion and not meet any of the exclusion criteria specified in the protocol (page 644).
TRIAL DRUG / STROKE (BATCH) No.	Dalcetrapib was provided as 300 mg film-coated tablets.
DOSE / ROUTE / REGIMEN / DURATION	Two tablets (600 mg) were to be taken once daily, preferably with the largest meal of the day for the duration of the double-blind treatment period (24 months).
REFERENCE DRUG / STROKE (BATCH) No.	Matching placebo was provided as film-coated tablets.
DOSE / ROUTE / REGIMEN / DURATION	Two tablets were to be taken once daily, preferably with the largest meal of the day for the duration of the double-blind treatment period (24 months).
CRITERIA FOR EVALUATION	
EFFICACY:	There were 2 co-primary efficacy endpoints, for the assessment of atherosclerotic disease progression based on the 2 modes of measuring atherosclerotic plaque. They were defined for a patient as: • Nominal change from baseline to study end in coronary percent atheroma volume (PAV) for all anatomically comparable slices in a 30-mm segment of the target coronary artery assessed by IVUS. • Rate of change from baseline to study end in carotid intima media thickness (CIMT) using B-mode ultrasound, where CIMT as the primary measure of effect on carotid atherosclerosis is defined as the per

	scan and subject average of the far wall MEAN IMT values of the right and left common carotid, carotid bulb and internal carotid far walls of the arterial segments (MEAN CIMT). Secondary endpoints included coronary IVUS, coronary QCA and carotid ultrasound endpoints and are defined in detail in the protocol (page 654). Other secondary efficacy endpoints included: • Blood lipid (total cholesterol [TC] and triglyceride [TG]) levels, lipoprotein (low density lipoprotein cholesterol [LDL-C], very low density lipoprotein cholesterol [VLDL-C] and high density lipoprotein cholesterol [HDL-C]) levels, and apolipoprotein levels (apoA1 and apoB). • Ratios of these lipid, lipoprotein and apolipoprotein values. • A composite endpoint of CHD death, resuscitated cardiac arrest, non-fatal myocardial infarction, hospitalization for documented acute coronary syndrome (ACS) (electrocardiogram [ECG] abnormalities without biomarkers), stroke, coronary revascularization procedure, and hospitalization for heart failure was to be evaluated as part of the overall dalcetrapib development program. The components of the composite clinical endpoint were to be adjudicated by an independent clinical endpoint committee (CEC).
PHARMACODYNAMICS:	NA
PHARMACOKINETICS:	NA
SAFETY:	Safety of the treatment was evaluated by adverse events (AEs), laboratory tests, vital signs and ECG.
STATISTICAL METHODS	Planned statistical analysis of efficacy endpoints is described in the protocol (page 666)). Due to termination of the clinical development program by the Sponsor the available efficacy data are presented using descriptive statistics by treatment group. No hypothesis testing or estimates of treatment effects are reported. AEs, SAEs and treatment withdrawals due to AEs are summarized by treatment group. For classification purposes, preferred terms were assigned by the Sponsor to the investigator's original terms using the Medical Dictionary for Regulatory Activities (MedDRA) (version 15.0) terminology for AEs and diseases and the International Non-proprietary Name (INN) Drug Terms and Procedures Dictionary for treatments and surgical and medical procedures (page 732, page 781, page 817). Safety laboratory data are reported in SI units. Mean and median values over time using both actual values and changes from baseline are reported for each treatment group. Vital signs parameters (diastolic and systolic blood pressure, pulse rate) are summarized for each treatment group.

METHODOLOGY

The investigator ensured that the study was conducted in accordance with the principles of the Declaration of Helsinki or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. Written informed consent

was obtained from each patient before they participated in the study. Documented approval of the protocol was obtained from an independent ethics committee (IEC)/institutional review board (IRB) before starting the study (see page 717).

Study assessments and procedures were carried out according to the schedule of assessments described in the protocol (page 649).

During the pre-randomization phase potentially eligible study subjects, who fulfilled the clinical and laboratory entry criteria at screening, underwent a clinically-indicated catheterization and angiography, followed by IVUS assessment of the coronary arteries and B-mode ultrasound assessment of the carotid arteries. After a 24-month period of double-blind treatment with dalcetrapib or matching placebo, patients had repeat QCA, coronary IVUS, and carotid B-mode ultrasound measurements. In addition, carotid B-mode ultrasound measurements were conducted at month 6 and month 12.

STUDY POPULATION

Disposition of Patients

A total of 936 patients were randomized between January 13, 2010 and September 23, 2011; 474 patients were randomized to dalcetrapib 600 mg and 462 patients were randomized to matching placebo.

At the point of study termination 75% of patients had completed at least 12 months of the study, 40% had completed 18 months and 11% had attended the 2-year scheduled visit (page 17).

Premature Withdrawals

Seventy-nine patients (40 placebo and 39 dalcetrapib) withdrew from the study prematurely (page 20). Most withdrawals were due to patient decision (failure to return, withdrawal of consent). Overall, 4 patients who were protocol violators withdrew from the study. Twenty-five patients withdrew from study medication due to an AE (page 180) and 7 patients withdrew due to death (see Table 3 for all deaths).

Analysis Populations

All randomized patients were included in the intention to treat (ITT) population. Five patients (4 placebo, 1 dalcetrapib) who did not receive any study medication are excluded from the safety analysis population (SAP) (page 19).

Demographic Data and Baseline Characteristics

The 2 groups were similar with respect to gender, race, ethnicity, age and body mass index (BMI) (page 21) and also with respect to previous cardiovascular disease (CVD) and risk factors (page 23). Blood lipid, lipoprotein and apolipoprotein means at baseline were similar in the 2 groups (page 25). The incidence at baseline of metabolic syndrome (defined as having 3 of 5 specified criteria) was 63.7% in the placebo group and 66.0% in the dalcetrapib group (page 26).

Previous and Concomitant Diseases and Medications

Previous and concomitant treatments were similar in the 2 groups. Most patients reported the use of a statin (97% placebo, 96% dalcetrapib) and over 90% of patients reported the use of salicylates (page 43). Diseases other than CVD, type II diabetes, hypertension or dyslipidemia were similar in the 2 treatment groups. The most frequently reported diseases were in the Musculoskeletal and Connective Tissues Disorders system organ class (SOC), followed by the Gastrointestinal Disorders SOC, including gastrooesphageal reflux disease reported by 17% of patients overall (page 27).

EFFICACY RESULTS

For the derivation of the numerical imaging endpoints the baseline and follow-up scans need to be matched by location. For this reason the amount of available IVUS & QCA data is very limited. The less invasive carotid ultrasound was performed at 6 and 12 months, and was additionally requested at the time of study termination providing considerably more data.

The numbers of patients included in the image analyses is shown on page 76 .

Changes from baseline in PAV are and total atheroma volume (TAV) are shown on page 77 . Other IVUS endpoints are presented on page 78 (atheroma volume in the most and least

diseased segment), page 79 (plaque characterization indices) and page 80 (total vessel volume and total lumen volume).

Changes from baseline in IMT endpoints are summarized on page 81 , page 83 , page 85 and page 87 . The per-patient means over all segments and changes from baseline of mean IMT and maximum IMT are summarized in Table 1.

Table 1 IMT Endpoints – Per-Patient Means Over All Segments

imt_all_a_ITT IMT Endpoints - Per-Patient Means Over All Segments - Mean cIMT, Max cIMT

Protocol: NC22703 (dal-Plaque 2)
Analysis Population: INTENT-TO-TREAT (ITT)

	Mean Intima-Media Thickness Mean over all Segments [mm]		Maximum Intima-Media Thickness Mean over all Segments [mm]	
	Placebo N = 462	Dalcetrapib 600mg N = 474	Placebo N = 462	Dalcetrapib 600mg N = 474
Reported Values:				
Baseline				
n	396	411	396	411
mean	0.874	0.858	1.029	1.008
sd	0.1549	0.1495	0.1765	0.1659
median	0.857	0.847	1.005	0.997
Q1 - Q3	0.767 - 0.956	0.743 - 0.948	0.908 - 1.136	0.882 - 1.112
min - max	0.585 - 1.635	0.568 - 1.562	0.686 - 1.835	0.675 - 1.692
Month 6				
n	390	408	390	408
mean	0.878	0.861	1.032	1.012
sd	0.1562	0.1543	0.1760	0.1712
median	0.859	0.845	1.013	0.991
Q1 - Q3	0.773 - 0.956	0.744 - 0.950	0.910 - 1.126	0.885 - 1.115
min - max	0.587 - 1.686	0.567 - 1.498	0.695 - 1.952	0.652 - 1.675
Month 12				
n	365	377	365	377
mean	0.875	0.858	1.031	1.010
sd	0.1549	0.1498	0.1737	0.1673
median	0.860	0.843	1.008	1.000
Q1 - Q3	0.772 - 0.957	0.738 - 0.952	0.913 - 1.120	0.888 - 1.115
min - max	0.594 - 1.787	0.573 - 1.532	0.686 - 2.038	0.653 - 1.742
Month 18				
n	125	133	125	133
mean	0.884	0.867	1.042	1.021
sd	0.1722	0.1326	0.1969	0.1484
median	0.860	0.870	1.006	1.025
Q1 - Q3	0.768 - 0.958	0.760 - 0.962	0.906 - 1.116	0.903 - 1.122
min - max	0.615 - 1.792	0.618 - 1.290	0.727 - 2.072	0.710 - 1.460
Month 24				
n	61	54	61	54
mean	0.880	0.850	1.043	1.008
sd	0.1311	0.1428	0.1449	0.1642
median	0.873	0.843	1.045	0.996
Q1 - Q3	0.807 - 0.930	0.742 - 0.938	0.962 - 1.113	0.880 - 1.125
min - max	0.666 - 1.492	0.618 - 1.365	0.802 - 1.650	0.707 - 1.550
Last Value				
n	388	408	388	408
mean	0.876	0.861	1.033	1.013
sd	0.1577	0.1461	0.1791	0.1636
median	0.860	0.843	1.004	0.998
Q1 - Q3	0.771 - 0.953	0.747 - 0.952	0.912 - 1.120	0.895 - 1.119
min - max	0.594 - 1.792	0.573 - 1.433	0.686 - 2.072	0.653 - 1.702

Per-patient mean of the mean IMT values over all (6) far wall segments.
Per-patient mean of the maximum IMT values over all (6) far wall segments.
Additional 'end of study' IMT scans were taken at the early termination visit.

Program : $PROD/cdp12036/nc22703/imt_all_a.sas
Output : $PROD/cdp12036/nc22703/reports/imt_all_a_ITT.lst
23OCT2012 20:24 Page 1 of 2

Table 1 IMT Endpoints – Per-Patient Means Over All Segments (cont.)

imt_all_a_ITT IMT Endpoints - Per-Patient Means Over All Segments - Mean cIMT, Max cIMT

Protocol: NC22703 (dal-Plaque 2)
Analysis Population: INTENT-TO-TREAT (ITT)

	Mean Intima-Media Thickness Mean over all Segments [mm]		Maximum Intima-Media Thickness Mean over all Segments [mm]	
	Placebo N = 462	Dalcetrapib 600mg N = 474	Placebo N = 462	Dalcetrapib 600mg N = 474
Change from Baseline:				
Month 6				
n	379	393	379	393
mean	0.005	0.002	0.006	0.004
sd	0.0470	0.0540	0.0569	0.0621
median	0.002	0.000	0.002	0.002
Q1 - Q3	-0.016 - 0.016	-0.015 - 0.016	-0.023 - 0.027	-0.022 - 0.025
min - max	-0.202 - 0.234	-0.266 - 0.348	-0.228 - 0.271	-0.273 - 0.383
Month 12				
n	356	363	356	363
mean	0.003	0.003	0.005	0.005
sd	0.0568	0.0588	0.0659	0.0679
median	0.002	0.001	0.005	0.003
Q1 - Q3	-0.017 - 0.025	-0.016 - 0.019	-0.022 - 0.034	-0.021 - 0.030
min - max	-0.302 - 0.255	-0.481 - 0.456	-0.278 - 0.265	-0.487 - 0.450
Month 18				
n	122	130	122	130
mean	-0.002	0.006	0.001	0.007
sd	0.0615	0.0582	0.0724	0.0687
median	-0.005	0.004	-0.005	0.001
Q1 - Q3	-0.025 - 0.023	-0.015 - 0.026	-0.039 - 0.033	-0.018 - 0.043
min - max	-0.286 - 0.249	-0.180 - 0.224	-0.251 - 0.283	-0.205 - 0.226
Month 24				
n	59	53	59	53
mean	0.002	-0.005	0.009	0.001
sd	0.0479	0.0444	0.0587	0.0490
median	0.003	0.003	0.003	0.003
Q1 - Q3	-0.015 - 0.017	-0.016 - 0.010	-0.020 - 0.045	-0.023 - 0.030
min - max	-0.141 - 0.137	-0.197 - 0.139	-0.155 - 0.171	-0.142 - 0.160
Last Value				
n	378	394	378	394
mean	0.002	0.004	0.005	0.008
sd	0.0563	0.0571	0.0677	0.0667
median	0.002	0.003	0.002	0.003
Q1 - Q3	-0.018 - 0.023	-0.016 - 0.020	-0.025 - 0.032	-0.022 - 0.031
min - max	-0.286 - 0.249	-0.197 - 0.456	-0.347 - 0.283	-0.205 - 0.450

Per-patient mean of the mean IMT values over all (6) far wall segments.
Per-patient mean of the maximum IMT values over all (6) far wall segments.
Additional 'end of study' IMT scans were taken at the early termination visit.

Program : $PROD/cdp12036/nc22703/imt_all_a.sas
Output : $PROD/cdp12036/nc22703/reports/imt_all_a_ITT.lst
23OCT2012 20:24 Page 2 of 2

Mean and median coronary artery score and cumulative coronary stenosis score at month 24 and changes from baseline are summarized for each treatment group on page 88 .

The median HDL-C level in the dalcetrapib group increased from 44 mg/dL at baseline to 57 mg/dL at Month 6. Corresponding values in the placebo group were 45 mg/dL and 46 mg/dL (page 89), Mean and median values and changes from baseline (absolute and percent changes) of other lipid parameters (TC, non-HDL-C, LDL-C, VLDL-C, LDL-C/HDL-C ratio, non HDL-C/HDL-C ratio, TRI, apoA1, apoB, high sensitivity C-reactive protein (hsCRP) are summarized from page 91 .

Death, major coronary event, stroke or revascularization event was reported by the investigator for 46 (9.7%) patients in the dalcetrapib group and 35 (7.6%) patients in the placebo group.

Following adjudication by the CEC the figures were 36 patients (7.6%) in the dalcetrapib group and 28 (6.1%) in the placebo group (page 113).

SAFETY RESULTS

Overview of Safety

An overall summary of safety profile, including AEs during the double-blind treatment period, deaths and withdrawals, is shown in Table 2.

Table 2 Summary of Adverse Events During Double-Blind Treatment

ae24_summ Summary of Adverse Events During Double-Blind Treatment, Deaths and Withdrawals (Including AE Associated with Efficacy Endpoints)
Protocol(s): NC22703 (NC22703)
Analysis: SAP Center: ALL CENTERS

	Placebo N = 458 No. (%)	Dalcetrapib N = 473 No. (%)
Total Pts with at Least one AE	349 (76.2)	379 (80.1)
Total Number of AEs	1308	1317
Deaths #	1 (0.2)	8 (1.7)
Study withdrawals due to an AE #	4 (0.9)	6 (1.3)
Patients with at least one		
AE leading to Death	1 (0.2)	6 (1.3)
Serious AE	63 (13.8)	62 (13.1)
AE leading to withdrawal from treatment	11 (2.4)	14 (3.0)
AE leading to dose modification/interruption	41 (9.0)	47 (9.9)
Related AE	115 (25.1)	127 (26.8)

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
Deaths derived from Death page, Withdrawals derived from Study Completion page.
AE24 19SEP2012:10:46:14 (1 of 1)

Extent of Exposure to Study Treatment

Median daily dose of dalcetrapib was 590.9 mg over a median treatment duration of 418.0 days. Median daily dose of placebo was 586.7 mg over a treatment duration of 422.5 days (page 115). Total elapsed time was 546.62 patient years in the dalcetrapib group and 537.57 patient years in the placebo group (page 117).

Common Adverse Events

The overall number of patients with at least one AE was similar in the 2 treatment groups (76.2% placebo, 80.1% dalcetrapib).A similar profile of AEs was seen in the placebo and dalcetrapib groups during the double-blind treatment period (page 118, page 210). At the MedDRA-defined system organ class (SOC) level, the most frequently reported AEs were gastrointestinal disorders (placebo 24.7%, dalcetrapib 26.6%), musculoskeletal and connective tissue disorders (placebo 26.9%, dalcetrapib 22.6%), infections and infestations (placebo 22.9%, dalcetrapib 23.7%), general disorders and administration site conditions (placebo 23.1%, dalcetrapib 22.4%) (page 118).

At the level of individual MedDRA preferred terms, the most frequently reported AEs among dalcetrapib treated patients included chest pain (placebo 7.9%, dalcetrapib 10.1%), diarrhea (placebo 5.9%, dalcetrapib 8.7%), hypertension (placebo 4.1%, dalcetrapib 8.0%), angina pectoris (placebo 5.7%, dalcetrapib 6.3%), nasopharyngitis (placebo 4.8%, dalcetrapib 5.7%) headache (placebo 5.0%, dalcetrapib 5.7%), dizziness (placebo 4.8%, dalcetrapib 5.1%). The higher incidence of hypertension in dalcetrapib-treated patients was not reflected in a clinically relevant increase in the mean systolic or diastolic blood pressure (page 136).

The majority of AEs were considered by the investigator to be not related to treatment and a similar pattern of related events was seen in the dalcetrapib and placebo treatment groups (page 139).

Deaths

There were a total of 9 deaths in the safety analysis population during the study; one patient in the placebo group (metastatic small cell lung cancer) and 8 patients in the dalcetrapib group (5 adjudicated endpoint coronary heart disease, 2 neoplasms and 1 suicide) (Table 3 and page 591).

Table 3 Summary of All Deaths

dd11a_sap Summary of All Deaths
Protocol(s): NC22703 (NC22703)
Analysis: SAP Center: ALL CENTERS

Primary Cause of Death	Placebo N = 458 No. (%)	Dalcetrapib N = 473 No. (%)
Total No. of Deaths	1 (<1)	8 (2)
CARDIOVASCULAR ENDPOINT EVENTS		
Total No. of Deaths	-	5 (1)
@CORONARY HEART DISEASE DEATH	-	5 (1)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
Total No. of Deaths	1 (<1)	2 (<1)
BENIGN PANCREATIC NEOPLASM	-	1 (<1)
BRAIN NEOPLASM	-	1 (<1)
SMALL CELL LUNG CANCER METASTATIC	1 (<1)	-
PSYCHIATRIC DISORDERS		
Total No. of Deaths	-	1 (<1)
COMPLETED SUICIDE	-	1 (<1)

Investigator text for Cause of Death encoded using MedDRA version 15.0.
Percentages are based on N.
DD11 19SEP2012:10:53:02 (1 of 1)

Serious Adverse Events

The proportion of patients with at least one serious adverse event (SAEs) reported was similar in the 2 treatment groups (placebo 63 patients [13.8%], dalcetrapib 61 patients [12.9%])) (page 167, page 592). At the MedDRA-defined SOC level, the most frequently reported SAEs were cardiac disorders (2.6% placebo, 2.5% dalcetrapib), neoplasms (2.4% placebo, 1.9% dalcetrapib), general disorders and administration site conditions (2.6% placebo, 1.3% dalcetrapib), vascular disorders (1.1% placebo, 1.5% dalcetrapib) .

The majority of SAEs were considered by the investigator to be not related to treatment and a similar overall pattern of related events was seen in both treatment groups (page 172).

Adverse Events Leading to Discontinuation of Study Treatment

Eleven patients (2.4%) in the placebo group and 14 patients (3.0%) in the dalcetrapib group experienced AEs leading to discontinuation of study medication. The most frequent causes of discontinuation were events observed in the gastrointestinal disorders SOC, with 2 patients on placebo (diarrhea, abdominal pain) and 7 patients on dalcetrapib (3 diarrhea, 2 dyspepsia, 1 epigastric discomfort and 1 gastroesophageal reflux disease) (page 180).

Laboratory Parameters and Vital Signs

Mean and median values and changes from baseline are summarized for each treatment group on page 182 (blood chemistry parameters) and page 201(hematology parameters).

CONCLUSIONS

- Dalcetrapib was generally well tolerated, in spite of a higher incidence of hypertension compared to placebo.
- There was no difference in the incidence of events for the composite CV endpoint of CHD death, major coronary events and stroke between dalcetrapib and placebo-treated patients.
- Dalcetrapib increased HDL-C levels and altered other lipids and lipoproteins consistent with previous studies.
- There was no evidence of progression or regression of plaque burden in carotids as observed by cIMT and IVUS with dalcetrapib compared to placebo, although limited IVUS data were available.