SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL NC20971)

COMPANY: F. Hoffmann-La Roche Ltd NAME OF FINISHED PRODUCT: NAME OF ACTIVE SUBSTANCE(S): Dalcetrapib	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	A phase III, double-blind, randomized placebo-controlled study, to evaluate the effects of dalcetrapib on cardiovascular (CV) risk in stable coronary heart disease (CHD) patients, with a documented recent Acute Coronary Syndrome (ACS). Report [redacted], December 2012 Synopsis format due to no further clinical development of dalcetrapib.		
INVESTIGATORS / CENTERS AND COUNTRIES	935 Centers in 27 Countries in Europe (AT, BE, CH, DE, DK, CZ, ES, FR, FI, GB, HU, IE, IL, IT, NL, PL, SE, SK) Australasia/Asia (AU, CN, KR, NZ), Americas (AR, BR, CA, US), South Africa.		
PUBLICATION (REFERENCE)	Schwartz GG, Olsson AG, Abt M et al., N Engl J Med 2012 (see page 10)		
PERIOD OF TRIAL	April 2008 to September 2012	CLINICAL PHASE	III
PRIMARY OBJECTIVE	To evaluate the potential of dalcetrapib to reduce cardiovascular morbidity and mortality in stable CHD patients, with a documented recent ACS.		
STUDY DESIGN	Double-blind, randomized, placebo-controlled, parallel group, multi-center study		
NUMBER OF SUBJECTS	15,871		
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Patients recently hospitalized for an ACS (between 4 and 12 weeks after the index event).		
INVESTIGATIONAL DRUG/COMPARATOR DOSE / ROUTE / REGIMEN	Dalcetrapib 600 mg or matching placebo oral once daily (two 300 mg film-coated tablets) on a background of contemporary evidence-based medical care for ACS		
DURATION	The study was an event-driven trial designed to run until 1,600 events occurred and 80% of patients had completed a minimum of 2.5 years of treatment. All patients were to be followed up for at least 2 years unless the patient died, was lost to follow-up or withdrew consent.		
CRITERIA FOR EVALUATION			
EFFICACY:	**Primary endpoint:** the time to first occurrence of a composite of death from coronary heart disease, major non-fatal coronary event (myocardial infarction, hospitalization for unstable angina with objective evidence of acute myocardial ischemia, or cardiac arrest with resuscitation), or ischemic stroke (as adjudicated by the Clinical Endpoints Committee).		

	Secondary endpoints: included individual composite endpoints, each component of the primary composite end point, unanticipated coronary revascularization (not including revascularization for restenosis at the previous intervention site), all-cause mortality and changes in lipoproteins and inflammatory markers
SAFETY:	Adverse events, safety laboratory tests, ECG and vital signs
STATISTICAL METHODS	Two interim analyses, including an analysis for futility, were performed after approximately 800 and 1120 primary end-point events had occurred. Estimates of hazard ratios and 95% CIs for comparisons of dalcetrapib with placebo were calculated with the use of Cox proportional hazards models stratified according to region and type of index event.
METHODOLOGY	Full details of the study design and methods are provided in the protocol on page 273

STUDY POPULATION

A total of 15871 patients were randomized (ITT population), of whom 15819 received at least one dose of study medication (Safety population).

Treatment groups were well balanced for baseline characteristics. At time of randomization patients were on average 60 years old, 19% were female, 88% Caucasian (page 26), 68% had hypertension, 25% diabetes (page 24 , 87% had a myocardial infarction as index event (page 27 and ninety-one percent of patients had a revascularization for the index event.

In total, 97% of the patients were treated with aspirin and statins, 89% with clopidogrel, ticlopidine or prasugrel, 88% with beta-blockers and 79% with an ACE inhibitor or ARBs at time of randomization (page 29 and page 31). Patients were randomized within 61 days of the index event (page 39).

In total, 3412 patients discontinued study medication early (21% on placebo, 22% on dalcetrapib, including deaths) and 577 patients withdrew consent, were lost to follow-up or had an unknown status at the time of the interim cut for efficacy (3.3% on placebo, 3.9% on dalcetrapib; page 28).

There was similar overall patient-years of treatment and follow up in each arm (page 40), with a median duration of treatment of approximately 31 months (schwartz et al page 10).

EFFICACY RESULTS At the second pre-specified interim analysis, which included 1135 primary end-point events (71% of the number of events projected for the final analysis), the independent data and safety monitoring board recommended termination of the trial for futility, in accordance with pre-specified criteria outlined in the statistical analysis plan. The sponsor and executive steering committee accepted this recommendation and terminated the trial.

The efficacy analyses for events are performed on the full dataset, with a cut-off of May 7 2012, which is the date the study termination was announced. Events after May 7, 2012 are ignored, and patients are censored at this date if they were event-free.

Primary Endpoint:

Dalcetrapib had no significant effect on the primary end point, which occurred in 8.3% of patients in the dalcetrapib group and in 8.0% of patients in the placebo group (HR 1.04; 95% CI, 0.93 to 1.16; p = 0.52), see Table 1.

Secondary Endpoints:

Dalcetrapib also had no statistically significant effect on the rate of any component of the primary end point, on the rate of unanticipated coronary revascularization, or on the rate of death from any cause (see Table below). Prespecified subgroup analyses showed no statistically significant effect of dalcetrapib on the primary end point (page 52).

Table 1 Summary of Efficacy

CEC adjudicated	Patients with event (n %)		Hazard ratio (95% CI)	p value
	Placebo (N=7933)	Dalcetrapib (N=7938)		
Primary composite endpoint	633 (8.0)	656 (8.3)	1.04 (0.93-1.16)	0.52
Coronary heart disease death	125 (1.6)	118 (1.5)	0.94 (0.73-1.21)	0.66
Non-fatal acute myocardial infarction	407 (5.1)	414 (5.2)	1.02 (0.89-1.17)	0.80
Hospitalization for unstable angina	92 (1.2)	84 (1.1)	0.91 (0.68-1.22)	0.54
Resuscitated cardiac arrest	10 (0.1)	14 (0.2)	1.41 (0.63-3.18)	0.40
Stroke of presumed atherothrombotic etiology	73 (0.9)	91 (1.1)	1.25 (0.92-1.70)	0.16
All cause mortality	229 (2.9)	226 (2.8)	0.99 (0.82-1.19)	0.90
Unanticipated coronary revascularization procedure	672 (8.5)	674 (8.5)	1.00 (0.90-1.11)	0.97

Source outputs available from page 43

Treatment with dalcetrapib increased HDL cholesterol levels (placebo corrected, compared to baseline) by 27% to 30% across the assessments made, see page 63). However, neither baseline HDL cholesterol nor change in HDL cholesterol post baseline were predictive of CV outcome (page 50 and Figure 3 in Schwartz et al - see page 10).

Corrected for placebo, hsCRP was increased by 18% under treatment with dalcetrapib at month 3 corresponding to a placebo-corrected median difference of 0.2 mg/L (page 67).

SAFETY RESULTS

Overview of Safety

Dalcetrapib was generally well tolerated. The overall proportion of patients experiencing AEs, SAEs, and deaths was similar in each arm. More patients discontinued treatment because of AEs (primarily diarrhea) in the dalcetrapib arm (7.0%) than in the placebo arm (5.6%) (Table 2).

Table 2 Overview of Safety

	Placebo N = 7907 No. (%)	Dalcetrapib N = 7912 No. (%)
Total Pts with at Least one AE	6543 (82.7)	6572 (83.1)
Total Number of AEs	28913	28588
Deaths	234 (3.0)	232 (2.9)
Deaths up to 30 days after last dose	158 (2.0)	150 (1.9)
Serious AE	1825 (23.1)	1840 (23.3)
AE leading to withdrawal from treatment	442 (5.6)	557 (7.0)

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.
Output : $MARSOUT/cdp12036/nc20971/ae24_summ.dat
AE24 plus dd11b_sap

On average over the first three years of follow-up, systolic blood pressure was slightly increased by 0.6 mmHg and hypertension was reported more frequently as an adverse event (9.2% vs 8.0%) or serious adverse event (0.6% vs 0.3%) in the dalcetrapib group, compared with the placebo group, respectively, for further details see section AEs on focus.

Diarrhea occurred more frequently with dalcetrapib than with placebo (7.1% and 4.5%) and led to discontinuation of study medication in 1.4% and 0.3% of the groups, respectively. There was an excess of insomnia with dalcetrapib (2.1%) compared with placebo (1.7% of patients). However, there were no differences between groups in new diagnoses of, or deaths from malignancies or serious infections. Dalcetrapib had no effect on hematological parameters, measures of hepatic or renal function or on creatinine kinase levels.

Adverse Events

Overall AE profile: The overall proportion of patients experiencing AEs was similar between the treatment arms (placebo 78.9%;dalcetrapib 79.4%) (page 78). The incidence by system organ class (SOC) was generally balanced between treatment arms (page 144) with the most frequently affected SOCs being infections (placebo 28.3%, dalcetrapib 27.8%), general disorders (placebo 25.1%, dalcetrapib 25.5%), musculoskeletal disorders (placebo 24.4%, dalcetrapib 23.8%) and gastrointestinal disorders (placebo 22.3%, dalcetrapib 25.2%) (page 78).

AEs reported more frequently with dalcetrapib than placebo included hypertension (9.2% vs 8.0%) (page 145), diarrhea (7.1% vs 4.5%) (page 146), and insomnia (2.1% vs 1.7% (page 147).

Deaths: Overall cause of death was similar across treatment arms (3.0% placebo vs 2.9% dalcetrapib, page 148). The most common causes of death were CV endpoint events (placebo 1.6% vs dalcetrapib 1.5%), malignancy (0.6% both groups), infections (placebo 0.3%, dalcetrapib 0.2%) and respiratory system events (0.2 % both groups).

Serious AEs: The overall proportion of patients experiencing serious AEs was similar between the treatment arms (placebo 21.4%; dalcetrapib 21.3%) (page 160). Incidence by SOC was similar across arms with the most frequently affected SOCs being cardiac disorders (placebo 4.4%, dalcetrapib 4.3%), infections (placebo 3.6%, dalcetrapib 3.5%), general disorders (placebo 3.5%, dalcetrapib 3.4%), neoplasms (placebo 2.9%, dalcetrapib 2.8%) and gastrointestinal disorders (placebo 2.8%, dalcetrapib 2.7%).

AEs leading to withdrawal: More patients stopped treatment because of AEs in the dalcetrapib arm (7.0%) than in the placebo arm (5.6%) (page 188), the difference primarily accounted for by discontinuation due to diarrhea (1.4% dalcetrapib vs 0.3% placebo).

AEs on focus

Hypertension

Hypertension was reported more frequently as an adverse event (9.2% vs 8.0%) or serious adverse event (0.6% vs 0.3%) in the dalcetrapib group, compared with the placebo group, respectively. While the mean systolic blood pressure was slightly increased (by 0.6 mmHg across all assessments during the first three years of follow-up, see page 198) in the dalcetrapib group, there were no clinically relevant differences in mean diastolic blood pressure, pulse rate (page 212, plasma aldosterone, potassium, bicarbonate (page 215, or the number of prescribed anti-hypertensive medications (page 237).

Malignancies

The total number of patients with malignancies were similar between the 2 treatment groups (for AE and SAE, respectively, 3.6% and 2.6% for placebo and 3.4% and 2.5% for dalcetrapib; page 238 and page 241). Types of cancer were generally balanced across arms. The incidence (placebo vs. dalcetrapib) was 2 vs. 11 patients for rectal cancer, 11 vs. 14 for colon cancer, 11 vs. 7 for breast cancer, 37 vs. 32 for prostate cancer, and 25 vs. 18 for bladder cancer. Total deaths reported due to malignancy were balanced across groups (0.6% in both treatment groups, 47 patients on placebo and 48 patients on dalcetrapib page 148).

Laboratory Values

Mean changes in safety laboratory values were similar between the treatment arms for chemistry (page 215) and haematology (page 244) variables. The incidence of abnormalities was also similar between arms (page 255, and page 262).

Vital Signs

Apart from the slight increase in mean systolic BP over the first three years of follow-up in the dalcetrapib group compared to placebo, there were no clinically relevant differences between groups in mean diastolic blood pressure or pulse rate (page 212) or in the proportion of patients with at least one abnormally high value post baseline (page 265).

No difference in QTcB or QTcF was seen for categorical analysis and change from baseline (see page 267, page 268, page 269, page 270)

CONCLUSIONS

Dalcetrapib was generally well tolerated. The addition of dalcetrapib to standard therapy after acute coronary syndrome raised concentrations of HDL cholesterol by 27 to 30% and apolipoprotein A1 by 10%, which was within the range reported in earlier trials with dalcetrapib. However, this did not translate into any benefit in major cardiovascular outcomes in this study.

Neither HDL cholesterol at baseline nor the increase of HDL cholesterol on treatment was a predictor of cardiovascular risk for patients in either the dalcetrapib group or the placebo group. This is in contrast to epidemiologic data and may indicate that that HDL cholesterol levels are not a determinant of risk when patients are treated with the type of evidence-based therapies that were used in the trial.

Other possible explanations for the neutral effect on CV outcome are a) potential differences in HDL and HDL functionality after an ACS event and b) the slight increases of SBP and hsCRP potentially marking an adverse effect of CETP inhibition and possibly contributing to negating a benefit of raising HDL cholesterol.