SYNOPSIS OF RESEARCH REPORT [redacted]
(PROTOCOL NC19453 / NC20716)

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. NC19453 / NC20716: A Phase II, Double-blind, Randomized, Placebo-controlled, Parallel Group Study, Assessing Long-term Safety and Efficacy of RO4607381 in Patients with CHD or a CHD Risk Equivalent. Report No. [redacted] September 2008.		
INVESTIGATORS / CENTERS AND COUNTRIES	15 centers in USA and Germany		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	NC19453: 20 July 2006 to 28 August 2007 NC20716: 09 June 2007 to 17 January 2008	CLINICAL PHASE	II

OBJECTIVES

NC19453

The primary objectives of this study were:

- to evaluate the effect of RO4607381 (900 mg daily) on high density lipoprotein cholesterol (HDL-C) in patients with coronary heart disease (CHD) or a CHD risk equivalent
- to evaluate the 24-week safety profile of RO4607381. In addition to assessing the general safety profile of RO4607381, Magnetic Resonance Imaging (MRI) was performed to evaluate potential changes in mesenteric lymph nodes.

The secondary objectives of this study were:

- to assess the effects of RO4607381 on lipoprotein metabolism through determinations of change in blood lipid, lipoprotein, apolipoprotein (Apo) A1 and Apo B levels during the 24-week period of double-blind treatment
- to explore changes in other tissues using MRI, including small bowel mucosa, liver and abdominal aorta
- to investigate the relationship between RO4607381 plasma concentrations and efficacy parameters
- to explore a potential relationship between RO4607381 plasma concentrations and changes in mesenteric lymph nodes
- to evaluate the effects of RO4607381 on blood lymphocyte and lymphocyte subtype counts and highly sensitive C-reactive protein (hsCRP) levels.

NC20716 (extension study)

The primary objective of this study was to characterize the long-term safety profile of RO4607381, particularly with respect to potential changes in mesenteric lymph nodes assessed by un-enhanced MRI imaging.

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	The secondary objective of this study was to evaluate effects of RO4607381 on lipoprotein metabolism through determination of levels of blood lipid, lipoprotein, Apo A1 and Apo B levels. In addition, the effect of RO4607381 on lesions of the abdominal aorta was evaluated in an exploratory manner using MRI.
STUDY DESIGN	This was a multicenter, randomized, double-blind, placebo-controlled, parallel group study in CHD or CHD risk equivalent patients. The total study duration was up to 64 weeks and the study consisted of 3 parts: 1. a pre-randomization phase of 5 to 12 weeks when the majority of patients were required to have a) a measurable lymph node on an initial MRI scan and b) a low density lipoprotein cholesterol (LDL-C) level of <100 mg/dL with diet on a background therapy of 10 to 80 mg atorvastatin; 2. a 24-week double-blind treatment phase with 900 mg RO4607381 daily or placebo 3. and either an additional visit 4 weeks after discontinuation of double-blind treatment for those patients electing not to enter the extension study (NC20716) or a further 24 weeks of trial treatment and an additional visit 4 weeks after discontinuation of double-blind treatment for those patients entering the extension study.
NUMBER OF SUBJECTS	135
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Male and female patients aged 18 – 75 years with CHD or a CHD risk equivalent based on National Cholesterol Education Program, Adult Treatment Panel III (NCEP ATPIII) (eg, atherosclerosis, diabetes or a 10 year risk of CHD events >20%), body weight <125 kg at Visit 1, triglycerides <600 mg/dL at each pre-randomization visit and LDL-C <100 mg/dL prior to randomization.
TRIAL DRUG / STROKE (BATCH) No.	RO4607381 (dalcetrapib) 300 mg tablets / Formulation No. [redacted] / Batch Nos [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Patients received daily oral doses of 900 mg RO4607381 for 24 weeks (NC19453) or 48 weeks (NC20716). RO4607381 was taken with food and it was recommended that RO4607381 was administered following the largest meal of the day, although it could be taken after any meal. The drug was always to be taken at approximately the same time of the day.

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REFERENCE DRUG / STROKE (BATCH) No.	Placebo tablets / Formulation No. [redacted] / Batch Nos [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Placebo matching the investigational product to be given orally, once daily with food.
CRITERIA FOR EVALUATION	
EFFICACY:	**Primary parameter:** Percentage and absolute change from baseline to Week 24 (NC19453) and Week 48 (NC20716) in HDL-C level. **Secondary parameters:** Changes from baseline during the 24-week (NC19453) and 48-week (NC20716) period of double-blind treatment in total cholesterol (TC), triglycerides, HDL-C, LDL-C, cholesteryl ester transfer protein (CETP) mass and activity, Apo A1 and Apo B and selected ratios.
PHARMACODYNAMICS:	N/A
PHARMACOKINETICS:	Reported separately (Report No. [redacted]
SAFETY:	MRI scans, medical history, adverse events (AEs), clinical laboratory tests: serum chemistry (including aspartate aminotransferase, alanine aminotransferase and creatine phosphokinase), hematology and urinalysis parameters, 12-lead electrocardiogram (ECG, including QTc), vital signs (temperature, seated blood pressure and pulse), body weight and body mass index, physical examination.
STATISTICAL METHODS	There was no formal hypothesis testing. **Analysis of Primary and Secondary Efficacy Parameters:** Treatment differences with respect to mean values were estimated by standard linear models methods, where the dependant variables included treatment, center, the baseline value of the primary variable and their interaction terms as appropriate. Hypothesis testing was not performed directly; however for the various model-based exploratory analyses, 95% two-sided confidence interval (CI) estimates were computed for the model parameters. Depending on the model, these CIs could be used to test hypotheses of interest. **Safety Analysis:** Descriptive statistics were used to analyze all safety data. Safety analyses and baseline/demographic variables were primarily based on descriptive summary and include frequencies and percentages for categorical variables and statistics such as the number of available observations, mean, median, standard deviation, minimum and maximum for continuous variables.

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METHODOLOGY:

After a 5 to 12-week pre-randomization phase (to wash out any previous statin other than atorvastatin), patients with CHD or a CHD risk equivalent were randomized to receive RO4607381 900 mg daily or placebo in a 2:1 ratio and atorvastatin (dose at investigator's discretion). Patients were treated for 24 weeks or 48 weeks if they participated in the extension phase of the study (Protocol No. NC20716). A follow-up visit was conducted 4 weeks after the last dose of RO4607381 or placebo and the patients continued taking atorvastatin during this period of time. Efficacy parameters were assessed at baseline and at Weeks 2, 6, 12, 18, 24, 36 and 48. MRI scans were performed at screening, Weeks 12, 24, 48 and follow-up (if required). Blood and urine samples were collected for laboratory assessments at screening, baseline, Weeks 2, 6, 12, 18, 24, 36 and 48 and follow-up. Adverse events and vital signs were monitored throughout the study. Physical examination was conducted at screening and Weeks 24 and 48. Body weight was measured at screening, randomization, Weeks 24, 48 and follow-up.

EFFICACY RESULTS:

Treatment with RO4607381 and atorvastatin for 24 weeks resulted in mean changes from baseline in HDL-C of 33.4% versus 3.5% in the placebo/atorvastatin group. The magnitude of the effect of RO4607381 on HDL-C levels was similar at all time points when it was assessed throughout the study, including the extension period. At Week 48 the increase in HDL-C was 33.8% in the active treatment group versus 3.7% in the placebo group. RO4607381 was equally effective in raising HDL-C irrespective of the HDL-C and triglycerides levels at baseline. CETP activity decreased (-53.5% at Week 24 and -56.5% at Week 48) and the CETP mass increased (80.8% at Week 24 and 86.5% at Week 48) from baseline in the RO4607381/atorvastatin group.

An increase in concentration of Apo A1 and decreases in LDL-C/HDL-C, non HDL-C/HDL-C, TC/HDL-C (atherogenic index) and Apo B/A1 ratios were observed in the RO4607381/atorvastatin group. There were no clinically relevant changes in LDL-C, TC or triglyceride levels in the RO4607381/atorvastatin group at Weeks 24 and 48. Results of exploratory analyses will be reported separately (Report No. [redacted]).

SAFETY RESULTS:

There were no deaths during the study. Four patients (9%) and 10 patients (11%) in the placebo/atorvastatin and RO4607381/atorvastatin groups respectively experienced serious AEs (SAEs) during the 48-week double-blind treatment phase. One patient (2%) and 3 (3%) patients respectively experienced SAEs during the follow-up phase. One patient in the RO4607381/atorvastatin group experienced a SAE of coronary artery disease considered possibly related to the study drug by the investigator during the double-blind period. This event resolved without sequela and the patient completed the study. All other SAEs were unrelated to the study treatment. Three (7%) and 12 (13%) patients in the placebo/atorvastatin and RO4607381/atorvastatin groups respectively withdrew from treatment during the double-blind phase due to AEs. For 5 (11%) and 8 (9%) patients respectively the dose of the study drug was interrupted due to AEs during the double-blind phase. The most frequent cause for withdrawals from treatment and temporary discontinuations were gastrointestinal disorders.

A total of 38 (83%) and 76 (85%) patients experienced AEs during the double-blind period in the placebo/atorvastatin and RO4607381/atorvastatin groups respectively. Most of the AEs were mild or moderate in intensity. A greater proportion of patients experienced at least 1 AE of severe intensity in the RO4607381/atorvastatin group during the double-blind phase (17% versus 7% in the placebo/atorvastatin group); however, only 2 (2%) AEs of severe intensity experienced by patients taking RO4607381 and atorvastatin were considered possibly related to the study treatment by the investigator. Overall, the most commonly reported AEs belonged to the class of infections and infestations, gastrointestinal disorders,

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musculoskeletal and connective tissue disorders and nervous system disorders. The proportion of patients who experienced at least 1 AE considered related to the study treatment was slightly greater in the RO4607381/atorvastatin group (39% versus 33% for placebo/atorvastatin group). The proportion of patients experiencing gastrointestinal disorders related to the study treatment was higher in the RO4607381/atorvastatin group (28% versus 20% in the placebo/atorvastatin group). Diarrhea and headache were the most common AEs related to the study treatment reported in patients receiving RO4607381/atorvastatin (13% and 6% respectively). They were mild or moderate in intensity.

MRI scans were analyzed by the sites, 2 blinded readers and the Data Safety Monitoring Board (DSMB). There were no systematic or significant safety concerns reported in the MRI data at Week 24 and Week 48. The number of patients experiencing lymph node enlargement reported by the sites as AEs was similar between the 2 treatment groups, 3 (7%) and 2 (2%) in the placebo/atorvastatin and RO4607381/atorvastatin groups respectively. Furthermore, RO4607381 had no measurable effect on the fat content of lymph nodes. Therefore, the conclusion was reached that RO4607381 had no measurable and clinically relevant effect on mesenteric lymph nodes during the study.

There were no clinically relevant differences between the 2 treatment groups in laboratory safety parameters, including lymphocytes and renin-angiotensin aldosterone data, ECGs and vital signs, including blood pressure. One patient receiving RO4607381 and atorvastatin experienced an elevation in hepatic enzyme levels of more than 3x upper limit of normal (ULN). This event was possibly related to the study treatment, was mild in intensity and resolved without sequela.

CONCLUSIONS:

The results of this study show that the CETP inhibitor RO4607381 is effective in raising concentrations of HDL-C over the 48-week treatment period and is overall well tolerated. RO4607381 had no measurable and clinically relevant effect on mesenteric lymph nodes during the study confirming the hypothesis that the pre-clinical findings were species-specific and unlikely to be relevant to humans.