SYNOPSIS OF RESEARCH REPORT [redacted]
(PROTOCOL WN22018)

COMPANY: Hoffmann-La Roche Ltd. NAME OF FINISHED PRODUCT: N/A NAME OF ACTIVE SUBSTANCE(S): RO5313534	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	A dose ranging, randomized, double-blind, parallel-group placebo-controlled multi-center study of RO5313534 used as add-on to donepezil treatment in patients with mild to moderate symptoms of Alzheimer's disease / Research Report [redacted] / May 2011. [redacted]		
INVESTIGATORS / CENTERS AND COUNTRIES	Multicenter study conducted at 61 centers in 13 countries (Argentina, Australia, Canada, France, Germany, Italy, Mexico, Poland, Romania, Slovakia, Spain, UK, USA) **Principal Investigator**: [redacted] [redacted] France		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	30 Apr 2009 - 19 Nov 2010	CLINICAL PHASE	IIb
OBJECTIVES	**Primary Objective**: • To evaluate efficacy of 24 weeks treatment of 3 fixed doses of RO5313534 (1, 5 and 15 mg/day) added to donepezil (5 or 10 mg/day) on a cognitive endpoint (measured with the ADAS-Cog) as compared to placebo added to donepezil. **Secondary Objectives**: • To evaluate the tolerability and safety of 24 weeks treatment of the 3 fixed doses of RO5313534 (1, 5 and 15 mg/day) as adjunctive therapy of donepezil (5 or 10 mg/day). • To evaluate efficacy on behavioral, global and functional aspects as compared to placebo added to donepezil (measured with Behave-AD-FW, ADCS-ADL, CGIC and ZARIT).		

	• To evaluate efficacy on cognitive endpoints measured with the cognitive battery, the Cambridge Neuropsychological Test Automated Battery (CANTAB) and the Mini Mental State Examination (MMSE) as compared to placebo added to donepezil. • To evaluate maintenance of efficacy (primary and secondary variables) 4 weeks after discontinuation of treatment. • To investigate by a population PK analysis approach the pharmacokinetics of RO5313534 in the target population, including the influence of covariates such as age, gender, body-weight and renal function. • To explore the relationship between PK exposure and response using population PK-PD methods. • To evaluate whether the genetic markers of APOEε4, nicotinic alpha7 and duplicated alpha 7 are predictive of response (efficacy and safety) to RO5313534 treatment.
STUDY DESIGN	Multicenter, randomized, double-blind placebo-controlled, parallel-group dose ranging 4-arm study. The study had a 14 ± 7 day screening period, followed by a 24 week double-blind treatment period and then a 4 week follow-up period that includes a final visit after 4 weeks. Following the 14 ± 7 day screening period, patients were randomized (in equal ratio) to one of the following 4 treatments: placebo, RO5313534 1 mg, RO5313534 5 mg or RO5313534 15 mg with the background therapy of donepezil (5 or 10 mg).
NUMBER OF SUBJECTS	Patients screened: 510; Patients randomized: 389 Placebo: 97 patients RO5313534 1 mg: 97 patients RO5313534 5 mg: 98 patients RO5313534 15 mg : 97 patients
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Male or female patients with mild to moderate Alzheimer's Disease according to NINCDS-ADRDA and DSM-IV criteria: Age ≥ 50; MMSE 22-13 inclusive and on a stable dose of donepezil (5 or 10 mg) for 4 months prior to baseline.
TRIAL DRUG / STROKE (BATCH) No.	RO5313534 capsules for oral dosing (using combinations of 1 mg and 5 mg capsule strengths). For blinding to treatment groups, all patients received a total of 3 capsules (in a combination of active and placebo) which made up the randomized dose RO5313534 1 mg: Batch No. [redacted] RO5313534 5 mg: Batch No. [redacted]
DOSE / ROUTE / REGIMEN / DURATION	RO5313534 1 mg, 5 mg, 15 mg / oral / daily / 24 weeks
REFERENCE DRUG / STROKE (BATCH) No.	RO5313534 placebo: Batch No. [redacted]
DOSE / ROUTE / REGIMEN / DURATION	RO5313534 placebo / oral / daily / 24 weeks

CRITERIA FOR EVALUATION	
EFFICACY:	Primary • ADAS-Cog score change from baseline at week 24 Secondary • CANTAB tests of MOT, SRT, CRT, PAL, DMS, RVP (and potentially composite score) • Mini Mental State Exam (MMSE) total score • Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (ADCS CGIC) • Behavioral Pathology in Alzheimer's Disease Frequency Weighted (Behave-AD-FW) • Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL) • Zarit Burden Interview
CLINICAL GENOTYPING:	• Assessment of apolipoprotein E CHRNA7 and duplicated CHRNA7
PHARMACOKINETICS:	• Plasma concentrations of RO5313534 • CL/F – apparent clearance • V/F – apparent volume of distribution • C_{max} – maximun plasma concentration • C_{trough} – trough plasma concentration • $AUC_{0-\tau}$ – Area under the plasma concentration time curve
SAFETY:	• Adverse events and suicidality risk assessed at weeks 1, 2, 4, 6, 8, 12, 18, 24 and 28 (follow-up). • Vital signs (blood pressure and heart rate) assessed at weeks 1, 2, 4, 6, 8, 12,18, 24 and 28 (follow-up) and orthostatic changes at week 1, 8, 24 and 28. • 12-lead ECG at baseline and post baseline day 1, weeks 1, 2, 4, 6, 12, 18, 24 and 28 (follow-up). • Routine labs at baseline, weeks 2, 4, 8, 12, 18, 24 and 28 (follow-up).
STATISTICAL METHODS	The efficacy data analysis was performed on the ITT and PP population. The primary statistical analysis method applied was a mixed effects model for repeated measures, and a supportive analysis was done using ANCOVA with LOCF imputation for missing data. For PK data, nonlinear mixed effects modeling was used to analyze the sparse sampling dose-concentration time data of RO5313534. The PK data of this study was to be pooled with more extensive data from other studies in patients and reported separately. All safety parameters were summarized using descriptive statistics.

METHODOLOGY:

Signed informed consent from each patient was obtained prior to the patient participating in the study.

The study had a 14 ± 7 day screening period followed by a 24 week double-blind treatment period and then a 4 week follow-up period that included a final visit 4 weeks after the last dose (i.e. at week 28 for those completing the treatment).

Eligible patients were randomized to one of the 4 treatment groups in equal ratio. Randomization was done centrally using IVRS with the intent to achieve the best possible balance across the treatment groups. Further balancing of treatment groups was done for MMSE score (≤ 18 vs. > 18), age (< 65 vs. ≥ 65) and geographical region of the study site and the patients evaluated over the 24 weeks of the treatment period and subsequent 4 weeks of treatment-free follow up with a series of clinical assessments, safety evaluations, PK and biomarker sampling. Clinical assessments included ADAS-Cog, CANTAB, MMSE, Behave-AD-FW, ADCS-ADL, CGIC and ZARIT. Safety parameters included adverse events, laboratory tests and vital signs.

A total of 10 blood samples for PK analysis were collected at baseline, post baseline day 1, week 1, 2, 4, 12, 18 and 24.

EFFICACY RESULTS:

Study WN22018 did not meet its primary endpoint. RO5313534 did not show any treatment benefit over placebo added on to stable background donepezil treatment in patients with mild to moderate Alzheimer's Disease. The extent of the change from baseline to Week 24 in ADAS-Cog total score was small in all treatment groups. The biggest treatment difference versus placebo in the ITT population was shown in the 5 mg group: -0.05 vs. 0.89. Similar results were shown for the PP population and for all other efficacy parameters.

PHARMACODYNAMIC RESULTS:

n/a

PHARMACOKINETIC RESULTS:

Results of the population pharmacokinetic analysis are provided in a separate report.

SAFETY RESULTS:

During the treatment period, the number of patients experiencing AEs did not vary greatly between the placebo (60/97 patients [62%]), RO5313534 1 mg (55/96 patients [57%]), and RO5313534 5 mg (63/98 patients [64%]) groups. A higher number of patients in the RO5313534 15 mg treatment group (70/97 patients [72%]) reported at least one AE. However, there was no marked difference in the overall number of AEs experienced by patients in any of the treatment groups.

Constipation (mainly assessed as mild in intensity) was the most common AE and the only event that was clearly related to treatment with RO5313534. Constipation was reported in 13%, 11% and 15% of patients win the RO5313534 treatment groups, respectively with a placebo rate of 5%. There was also a trend for a slightly higher reporting frequency of events of diarrhea, fatigue and fall in patients receiving active treatment compared with those receiving placebo although no obvious relationship to treatment dose was observed. No prominent CNS events of note were identified on active treatment.

Three life-threatening (grade 4) adverse events were reported; cerebral hemorrhage in one patient in the RO5313534 1 mg treatment group (remotely related, outcome of death), pulmonary embolism (unrelated, resolved with sequelae) in one patient in the RO5313534 5 mg group and myocardial infarction (possibly related, resolved without sequelae) in one patient in the RO5313534 15 mg treatment group.

A total of four study patients died. One placebo patient died as a result of pulmonary embolism (unrelated) on Day 229 during follow-up. Two patients in the RO5313534 1 mg group died, one as a result of cerebral hemorrhage (remotely related) on Day 106 and the other due to adenocarcinoma (unrelated) on Day 223 during follow-up. One patient in the RO5313534 5 mg group died as a result of pneumonia (unrelated) on Day 94.

Twenty four patients (5 patients the placebo group, 8 patients in the RO5313534 1 mg group, 7 patients in the RO5313534 5 mg group and 4 patients in the RO5313534 15 mg group) experienced a total of 25 SAEs. The most frequently reported SAEs were cardiac disorders, reported in 5 patients (2 patients in the placebo group and 1 patient in each of the RO5313534 1mg, 5 mg and 15 mg treatment groups). No SAE was reported as more than a single occurrence in any treatment group and all except three were considered by the investigator to be unrelated to trial treatment. One event of cerebral hemorrhage in the RO5313534 1 mg group and one event of anemia in the RO5313534 5 mg group were assessed as remotely related to trial treatment while one event of myocardial infarction in the RO5313534 15 mg group was assessed by the investigator as possibly related to treatment. Twenty-two patients were withdrawn from study treatment due to AEs. Seven patients (7%) discontinued from the placebo group, 3 patients (3%) from the RO5313534 1 mg group, 8 patients (8%) from the RO5313534 5 mg group and 4 patients (4%) from the RO5313534 15 mg group. Constipation (1 patient in each of the RO5313534 1 mg and 5 mg groups) and dizziness (1 patient in each of the RO5313534 5 mg and 15 mg groups) were the only AEs leading to discontinuation which were reported as more than single occurrences.

A total of three patients experienced a suicide related adverse event during the treatment period (1 patient in the placebo group with reported self-injurious behavior and two patients in the RO5313534 15 mg group with reported suicidal ideation). None of the suicide related adverse events were considered related to trial treatment by the investigator.

With regards to laboratory test parameters, no clinically relevant laboratory test value abnormalities were seen and the incidence of marked laboratory test value abnormalities was low. In particular, there was no evidence to suggest that treatment with RO5313534 led to clinically significant changes in cardiac or hepatic function. There was no evidence to suggest that treatment with RO5313534 had any effect on QT interval. There were no differences between the active drug and placebo groups in the incidence of change from baseline QTcF values of >30 to ≤ 60 msec and no patients experienced a QTcF change from baseline of > 60 msec during treatment or follow-up. The incidence of bradycardia was low.

During treatment and follow-up, there was a higher incidence of orthostatic hypotension reported on active treatment, particularly with respect to decreases in diastolic blood pressure. However, these changes were purely barometric and did not result in an increase in AE reporting or an excess of discontinuations.

CONCLUSIONS:

- Study WN22018 did not meet its primary endpoint.
- Baseline characteristics of the patients were comparable among the four treatment groups.
- No efficacy signal was shown in any RO5313534 dose group for any efficacy endpoint
- RO5313534 appears to be safe and well tolerated in combination with donepezil and at a dose ranging from 1 to 15 mg/day
- The main AEs differentiating active from placebo were constipation, diarrhea, fatigue and fall. There were no prominent CNS events on active.
- There was a low incidence of AEs during follow-up, none evocative of withdrawal and no difference in frequency of SAEs or deaths between the treatment groups.
- There was no cardiovascular parameter of concern (QTcF or incidence of bradycardia). In the 15 mg group, there was a purely barometric, asymptomatic trend toward orthostatic lowering of diastolic BP and a higher incidence of systolic BP elevations compared to the other groups.
- There was no signal of clinical relevance in the laboratory tests, particularly in hepatic and renal parameters and in the CPK results.