SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL NN20372)

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

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	NN20372 - Randomized, double-blind, placebo-controlled add-on trial of the safety and efficacy of RO4917838 in outpatients on olanzapine, quetiapine, risperidone or paliperidone with prominent negative or disorganized thought symptoms. Report No [redacted]. Version 1: September 2010. Version 2: July 2014.		
INVESTIGATORS / CENTERS AND COUNTRIES	66 centers in the following countries: Austria (1 site), Brazil (6), Germany (5), France (3), Hungary (8), Japan (13), Mexico (2), Poland (6), Russia (8), USA (14). ***Version 2 Change:*** *The dm04 List of Investigators output was replaced by a detailed List of Investigators and study sites. This change did not have any impact on the overall results and conclusions of the study.*		
PUBLICATION (REFERENCE)	na		
PERIOD OF TRIAL	1st screening to last follow up visit: 8 February 2008 to 28 September 2009	CLINICAL PHASE	2
OBJECTIVES	To study the safety and efficacy of RO4917838 in patients with schizophrenia who are stable on current antipsychotic treatment (See below for safety and efficacy assessments)		
STUDY DESIGN	Parallel group, double-blind, placebo controlled After a screening period the study had a one month run-in period, before an eight week double-blind treatment period. The four treatments were placebo or RO4917838 10 mg, 30 mg, or 60 mg given orally once a day. The treatment period was followed by a four week follow-up period that included a visit two weeks after the end of study treatment and a final visit after a further two weeks. The end of the study was considered to be the date of the last visit (including the last follow-up visit) of the last patient in the study. A data safety monitoring board (DSMB) monitored the safety of patients in the study.		

	One or two administrative analyses (AA) were planned in the protocol before the final database closure and analysis, mainly for planning of the phase III program. One administrative analysis was performed after all randomized patients had completed the Week 8 assessment or had been withdrawn from treatment or the study. This report presents the final analysis of the study based on the database of 25 November 2009.
NUMBER OF SUBJECTS	320 patients were planned and 323 were randomized to treatment.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Patients who are stable on olanzapine, quetiapine, risperidone, paliperidone or aripiprazole with prominent negative or disorganized thought symptoms
TRIAL DRUG / STROKE (BATCH) No.	RO4917838. 10 mg capsules, formulation F03-03, batch number [redacted] 25 mg capsules, formulation F06-02, batch number [redacted]
DOSE / ROUTE / REGIMEN / DURATION	10, 30, and 60 mg, oral, once daily
REFERENCE DRUG / STROKE (BATCH) No.	Placebo, formulation F01-03, batch number [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Oral, once daily
CRITERIA FOR EVALUATION	
EFFICACY:	**Primary:** PANSS Negative Symptom Factor Score **Secondary:** Percentage of PANSS negative symptom factor score responders, defined as ≥ 20% improvement from baseline at week 8 CGI-S and CGI_I of negative symptoms PANSS total score PANSS subscale scores PANSS factor scores CGI-S and CGI-I of overall symptoms Cognition Cognitive Test Battery PSP SQLS
PHARMACODYNAMICS:	NA
PHARMACOKINETICS:	Apparent clearance CL/F, L/h Volume of distribution of central compartment V2/F, L Absorption rate KA, 1/h Inter-compartmental clearance Q/F, L/h Volume of distribution of peripheral compartment V3/F, L Exposure at steady state AUC, C_{max} Elimination half life, $t_{1/2}$

BIOMARKERS	All analyses of potential molecular markers will be reported separately
SAFETY:	Adverse events Vital signs (blood pressure, heart rate), 12-lead electrocardiogram, Physical examination, Weight Movement rating scales: Barnes Akathisia Scale (BAS), Simpson-Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS) Laboratory Parameters: hematology, blood chemistry, urinalysis, pregnancy test, drugs of abuse test
ROCHE SAMPLE REPOSITORY	All patients were asked to participate in the Roche Sample Repository (RSR) Project in countries where RSR sampling was undertaken. The RSR project involved taking a 9 mL blood sample for pharmacogenetic and genetic research. Taking part in the RSR project was entirely optional and subject to a separate signed Informed Consent.
STATISTICAL METHODS	All efficacy data were analyzed including intent-to-treat patients and per-protocol patients (only when more than 10% of the ITT patients do not qualify for the PP). The mITT population, which was specified in the DRAM before the administrative interim analysis, also excluded in total sixteen patients: three patients treated at a site with critical findings, and thirteen patients whose efficacy assessments were carried out by raters who failed the recertification test. The efficacy parameters of continuous variables were analyzed using a mixed effects covariance pattern model to utilize all the data collected over time. The model included independent variables of the fixed, categorical effects of treatment, assessment visit week, and treatment-by-week interaction, along with the continuous effects of baseline and baseline-by-week interaction. An unstructured covariance matrix was used to model the within-patient errors and different variance-covariance structures were tried for goodness-of-fit exploration. As a supportive analysis, the PANSS total, PANSS positive subscale, PANSS negative subscale, cognitive battery, and CGI Severity of illness scores were also analyzed at endpoint (i.e., week 8 or last observation carried forwarded) and week 8 (i.e., observed cases) by analysis of covariance (ANCOVA) adjusting for baseline values (covariate) and study center (main fixed effect). Categorical data, such as the percentage of responders, was evaluated by the Cochran-mantel-Haenszel (CMH) method with stratification by region. All safety variables (e.g., adverse events, lab tests including hemoglobin, ECG, vital signs) were summarized for each assessment time (including follow-up) using descriptive statistics. The special safety parameters of interest (i.e., SAS, BAS, AIMS) were also analyzed using ANCOVA techniques for change from

	baseline at endpoint (i.e., week 8 or last assessment). To assess whether efficacy and safety results of the patients enrolled in Japan were similar to those enrolled in North and South America and Europe, selected key data were analyzed by patients enrolled in the two geographical regions. The comparability was assessed descriptively.

METHODOLOGY:

Screening followed by 4 weeks of run-in. On treatment assessments at Week 1, 2, 4, 6 and 8. Follow-up visits at Week 10 and Week 12. PANSS, CGI-S, and CGI-S for negative symptoms at screening, week -2, baseline, each on-treatment visit and at the Week 12 follow-up visit. CGI-I and CGI-I for negative symptoms at Weeks 1, 2, 4, 6, 8 and 12. PSP at screening, baseline, week 4 and week 8. Cognitive battery and SQLS at screening, baseline, and week 8.

EFFICACY RESULTS:

The primary efficacy variable of NN20372 was the PANSS negative symptom factor score. The extent of the decrease from baseline (improvement) at Week 8 was greater in the RO4917838 10 mg and 30 mg treatment groups than in the placebo group.

Treatment effects on the negative symptom parameters were greater in the RO4917838 10 mg and 30 mg treatment groups than in the placebo group. The results of CGI-I of negative symptoms (score and responders) at Week 8 were significantly better than placebo in the RO4917838 10 mg group.

The treatment effects on overall PANSS and CGI parameters and the remaining PANSS symptom factor scores and subscales were generally larger with RO4917838 10 mg and /or RO4917838 30 mg than with placebo but not significantly different from placebo

The PSP total score increased from baseline in all four treatment groups, with the greatest improvements in the 10 mg RO4917838 treatment group.

The SQLS Total, Psychosocial Domain and Vitality Domain Scores decreased, ie improved, from baseline to Week 8 in all four treatment groups. The mean decreases from baseline in the Vitality Domain Scores were larger in the RO4917838 treatment groups

The results in patients at Japanese and non-Japanese sites were similar.

Table 1 NN20372: Overview of Primary Endpoint and Secondary Endpoints at Week 8 (ITT Population)

	Placebo N=77	RO4917838 10 mg N=81	RO4917838 30 mg N=77	RO4917838 60 mg N=77
Primary Efficacy Variable: PANSS NSFS[1]				
adjusted mean change from baseline (SE)	-5.11 (0.530)	-6.45 (0.519) #	-6.40 (0.541) #	-5.03 (0.536)
Secondary Negative Symptoms Variables				
PANSS NSFS responders (LOCF)[2, 3]				
No (%)	34 (44.2%)	47 (58.0%)#	40 (51.9%)	34 (44.2%)
CGI-I of negative symptoms				
Difference from placebo: p-value[6]		0.0207 *	0.2590	0.8046
responders (LOCF) No (%)[2,4]	49 (63.6%)	63 (77.8%) *	51 (66.2%)	46 (59.7%)
CGI-Severity of negative symptoms				
adjusted mean change from baseline (SE) [1]	-0.73 (0.098)	-0.95 (0.096)	-0.98 (0.100) #	-0.79 (0.099)
Other Clinical Secondary Efficacy Variables				
PANSS total, factor scores and subscales				
adjusted mean (SE) change from baseline [1]				
PANSS total score	-10.70 (1.375)	-13.22 (1.345)	-13.35 (1.400)	-10.49 (1.389)
PANSS PSFS	-1.18 (0.389)	-1.80 (0.380)	-1.15 (0.396)	-1.30 (0.393)
PANSS DTCFS	-3.21 (0.398)	-3.70 (0.391)	-3.92 (0.405)	-3.24 (0.404)
PANSS UHEFS	-0.44 (0.174)	-0.39 (0.171)	-0.81 (0.178)	-0.32 (0.178)
PANSS ADFS	-0.76 (0.231)	-0.89 (0.227)	-1.30 (0.236)	-0.88 (0.235)
PANSS NSS	-4.57 (0.490)	-5.65 (0.479)	-5.42 (0.499)	-4.59 (0.495)
PANSS PSS	-1.56 (0.339)	-1.67 (0.332)	-1.41 (0.346)	-1.24 (0.343)
PANSS GSS	-4.54 (0.715)	-5.96 (0.700)	-6.54 (0.730) #	-4.80 (0.723)
CGI Overall Scores				
CGI-I responders (LOCF) (%)[2, 4]	48 (62.3%)	57 (70.4%)	45 (58.4%)	41 (53.2%)
CGI-S adjusted mean change from baseline (SE) [1]	-0.47 (0.085)	-0.55 (0.083)	-0.60 (0.087)	-0.45 (0.086)
PSP Total Score (LOCF)[5]				
adjusted mean change from baseline (SE)	6.30 (1.108)	8.42 (1.080)	6.26 (1.142)	6.88 (1.106)
SQLS Total Score(LOCF) [5]				
SQLS adjusted mean change from baseline (SE)	-3.87 (1.425)	-4.62 (1.375)	-4.49 (1.448)	-4.47 (1.450)

NSFS negative symptom factor score, PSFS, positive symptoms factor score, DTCFS disorganized thoughts/cognition factor score, UHEFS: uncontrolled hostility/excitement factor score, ADFS: anxiety/depression factor score, NSS: negative symptom subscale, PSS: positive symptom subscale, GSS: general psychopathology (GPS) symptom subscale, CGI-I: Clinical Global Impression - Improvement, CGI-S : Clinical Global Impression - Severity, PSP: personal and social performance scale. SQLS: Schizophrenia Quality of Life Scale

Difference from placebo: #0.05 < p <= 0.1 trend level significant; * p=<0.05 statistically significant.

1: Estimates are from analysis based on mixed-effect model of repeated measures using unstructured covariance matrix: Change = baseline + week + treatment + baseline*week +treatment*week (repeated values over week)

2: Analysis based on Cochran-Mantel-Haenszel test with study region as stratification variable.

3. PANSS NSFS responder is defined as a 20% or greater improvement.

4: CGI-I score of 1 (very much improved) or 2 (much improved) or 3 (minimally improved) at Week 8.

5: Estimates are from Analysis of Covariance model: Change = Baseline + Treatment + Region

6: Van Elteren's test

PHARMACOKINETIC RESULTS:

RO4917838

There was no effect of the following covariates on RO4917838 CL/F and V2/F: gender, body weight (BW), age, smoking status, renal function (creatinine clearance, CLcr), race, geographic location of study site (Japan/rest of world [RoW]), and antipsychotic background therapy.

There was a statistically significant effect of BMI on the apparent central volume V2/F. However, the effect was minor and did not lead to relevant changes in RO4917838 Cmax.

RO4917838 Metabolites

There was no obvious influence of gender, location (Japan vs ROW), or smoking on plasma concentration or on metabolite / parent ratio for any of the four metabolites, RO5008459, RO5008582, RO5200126, and RO5011173.

Exploratory Investigation of the RO4917838 Exposure – Efficacy Relationship

Model-based simulations indicated that 20 mg RO4917838 is expected to have the greatest change from baseline in PANSS negative symptom factor score at week 8, and 15 mg and 30 mg RO4917838 to have almost the same performance as 20 mg.

SAFETY RESULTS:

During the period from the first dose of medication to premature withdrawal or completion of the 8-week treatment period, adverse events occurred in 40% to 46% of patients. Most AEs were mild or moderate in intensity, and the majority were considered not to be related to the study treatment (Table 2).

There were six SAEs with onset during the treatment period, all in the RO4917838 treatment groups, three of which were considered related to treatment (one in each of the RO4917838 treatment groups). There was one AE leading to withdrawal in each of the placebo and RO4917838 10 mg groups (1% of patients), while 9% of the patients in the RO4917838 30 mg and 60 mg groups withdrew due to AEs. AEs of special interest were observed only in the RO4917838 30 mg and 60 mg groups.

During the four week follow-up period, 6% to 12% of patients in the four treatment groups reported AEs (placebo 8%, RO4917838 10 mg 12%, 30 mg 6%, 60 mg 12%;). There was one SAE with onset during this period, in the placebo group. and one SAE with onset during the treatment period but after the last

dose, that became serious during the follow-up period.
The pharmacology of RO4917838, the pharmacokinetic profile and the absence of an RO4917838-related increase in AEs of interest in abuse liability evaluation, all support that there is no evidence for RO4917838 having abuse liability. There were no cases of euphoria, well-being, intoxicated state, depersonalization, confusion or disorientation.

Table 2 Overview of Adverse Events During the Treatment Period (Safety Population)

Total No of Patients (%)	Placebo N = 80 No. (%)	RO4917838 10 mg N = 82 No. (%)	RO4917838 30 mg N = 81 No. (%)	RO4917838 60 mg N = 78 No. (%)
Adverse events [1]	32 (40)	34 (41)	33 (41)	36 (46)
severe [2]	0	2 (2)	2 (2)	7 (9)
related [3]	16 (20)	15 (18)	19 (23)	24 (31)
Serious adverse events[1]	0	1 (1)	2 (2)	3 (4)
related [3]	0	1 (1)	1 (1)	1 (1)
AEs leading to discontinuation	1 (1)	1 (1)	7 (9)	7 (9)
Deaths	0	0	0	0
AEs of special interest				
Suicide related AEs	0	0	1 (1)	2 (3)
Dysphoria/ depressed mood	0	0	0	1 (1)
Skin disorders of the hands and feet [4]	0	0	0	0
Eye disorders				
blurred vision[4]	0	0	2 (2)	1 (1)
Hemoglobin decrease[5]	0	0	0	1 (1)

1. Multiple occurrences of the same adverse event in an individual are counted once
2. Multiple occurrences of the same adverse event in an individual are counted once under the highest reported intensity.
3. Sum of AEs considered remotely, possibly and probably related to treatment. Only the closest relationship to treatment is counted for multiple occurrences of the same adverse event in one individual.
4. Identified as an AE of interest based upon AE reported in a 4-month hematology study in healthy volunteers
5. Decrease in hemoglobin concentration that met criteria for a per protocol early discontinuation, and recorded as an AE by the investigator

There were no clinically significant RO4917838-dependant marked abnormalities in laboratory parameters during the treatment and follow-up periods.

- Hemoglobin levels, mean corpuscular hemoglobin, mean corpuscular volume decreased and reticulocyte numbers increased in the active treatment groups in a dose-dependent manner.

Accordingly the proportions of patients with hemoglobin level decreases from baseline >10 g/L were higher in the RO4917838 groups than in the placebo group. Iron and ferritin concentrations increased in the active treatment groups in a dose-dependent manner. None of these changes reached clinical significance and resolved after stopping treatment.

- The proportion of patients with marked abnormalities in triglycerides was higher on RO4917838 than on placebo. No dose-dependence was observed.
- The incidence rate of proteinuria was higher in the RO4917838 60 mg group than in the remaining groups. Hematuria was reported in a higher proportion of both male and female patients in the RO4917838 30 mg and 60 mg groups than in the placebo an 10 mg groups.

There were no clinically relevant changes in vital signs or ECG parameters, and the proportions of patients with orthostatic changes were similar across all treatment groups.
There was a trend to small increases in weight (mean change from baseline 0.6 kg) in the placebo groups and to dose related weight loss in the RO4917838 groups (reaching -0.8 kg in the RO4917838 60 mg group).
There was no worsening of extrapyramidal symptoms; scores in the three movement rating scale (AIMS, BAS and SAS) decreased during the study.

CONCLUSIONS:

This phase II study evaluated the effect of three doses of RO4917838 compared to placebo as an add-on therapy for the treatment of negative symptoms in patients with schizophrenia.

Efficacy

The study demonstrated consistent and robust effects of RO4917838 10 mg compared to placebo on negative symptoms assessed both by continuous and categorical outcome measures. RO4917838 30 mg had similar, but overall weaker effects. The 60 mg dose group did not differ from the placebo group in any outcome measure, suggesting an inverted U-shape dose-effect relationship. Thus, the results of this study demonstrate the utility of a GlyT1 inhibitor in the treatment of predominant and persistent negative symptoms in schizophrenia. Treatment with 10 mg showed the best benefit risk ratio.

Pharmacokinetics

There were no clinically relevant effects of demographic covariates on pharmacokinetics of RO4917838.

Safety

RO4917838 was well tolerated, with a favorable benefit risk profile. The study confirmed the pharmacodynamic and dose-proportional effects of the compound on hemoglobin levels.

Patients at Japanese vs Non-Japanese sites

The efficacy, pharmacokinetic and safety results in patients at Japanese and non-Japanese sites were generally similar.
