This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

Name of company Schering-Plough Research Institute **Name of active substance** Org 25935 (SCH 900435)	**Synopsis / Tabular Format**	

Title of the clinical trial

A multicenter, double-blind, flexible-dose efficacy trial with Org 25935 versus placebo as add-on therapy in subjects with predominant, persistent negative symptoms of schizophrenia treated with a stable dose of a second generation antipsychotic (GIANT).
Clinical Trial Report on Protocol 172003

Investigators

Prof Dr A Bertoldi [AR_017], Prof Dr R Fahrer [AR_037], Prof Dr A Mega [AR_046], Dr E Amado Cattaneo [AR_049], Dr A Hofer [AT_042], Dr V Larach [CL_022], Dr G Vergara [CL_024], Dr H Matlakova [CZ_079], Dr T Rektor [CZ_084], Dr J Rektor [CZ_085], Dr S Pietrucha [CZ_086], Dr J Jääskeläinen [FI_111], Dr H Katila [FI_112], Prof J Tiihonen [FI_116], Dr E Sailas [FI_118], Dr G Badet (replaced by Dr Girod) [FR_109], Prof T Bougerol [FR_213], Dr B Bonnaffoux [FR_309], Dr OJ Høyberg [NO_155], Dr S Heskestad [NO_164], Dr V Vilyanov [RU_008], Prof A Okhapkin [RU_013], Dr M Sheyfer [RU_014], Prof A Bukhanovsky [RU_086], Dr V Tadtayev [RU_087].
The number in brackets refer to the center codes (see next section).

Clinical trial centers

Argentina
[AR_017] Clínica Privada Neuropsiquiátrica San Agustín, Calle 55, N° 763, B1900BHE La Plata;
[AR_037] FLENI, Montañeses 2325, C1428AQK Buenos Aires;
[AR_046] Clínica Psiquiátrica San Jorge, Av. Eva Perón 1536, B1824IBR Lanús Este;
[AR_049] Clínica Privada Banfield, Azara 1780, B1828CKR Banfield, Provincia de Buenos Aires.

Austria
[AT_042] Universitätsklinikum Innsbruck, Abteilung für Psychiatrie, Anichstr. 35, 6020 Innsbruck.

Chile
[CL_022] Cipam – Clínica Pedro Montt, Lord Cochrane 779, Santiago;
[CL_024] Centro de Estudios y Tratamiento de Enfermedades Psiquiátricas, San Pío X 2460, Of. 1506, Providencia, 7510041 Santiago.

Czech Republic
[CZ_079] Nestátni zdravotnické zarizeni, Bezrucova 187, 276 01 Melnik;
[CZ_084] TERAPIE.INFO, s.r.o., Narodni trida 11, 110 00 Praha 1;
[CZ_085] TELEMENS, s.r.o., nam. Prerovskeho povstani 2803/1, 750 01 Prerov;
[CZ_086] Psychiatricka ambulance, Kourimska 915, 284 01 Kutna Hora.

Finland
[FI_111] Privater, Asemakatu 28 B, II krs, FI-70100 Kuopio;
[FI_112] Paloniemen sairaala, Paloniementie 52, FI-08450 Hormajärvi;
[FI_116] Niuvanniemen sairaala, FI-70240 Kuopio;
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France
[FR_109] CHS La Chartreuse – Service de Psychiatrie 4eme secteur, 1 boulevard du Chanoine Kir, 21033 Dijon Cedex;
[FR_213] CHU de Grenoble – Hôpital Sud, 38042 Grenoble Cedex 09;
[FR_309] Centre Medico Psychologique, 5 Avenue Aristide Briand, 39100 Dole.

Norway
[NO_155] Brattvåg Legekontor, 6270 Brattvåg ;
[NO_164] Jæren DPS, Austbøveien 16, 4340 Bryne.

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Russian Federation
[RU_008] City Psychiatric Hospital #2, clinical facility of Saratov State Medical University, 141, Chernyshevskogo str., 410028 Saratov;
[RU_013] Psychoneurological Hospital, clinical facility of Smolensk State Medical Academy, 5A, Rylenkova str., 214019 Smolensk;
[RU_014] Samara Psychiatric Hospital, 78, Nagornaya str., 443016 Samara;
[RU_086] Treatment and Rehabilitation Research Center "Phoenix", 40/128 Voroshilovsky Pr., 344010 Rostov-on-Don;
[RU_087] Psychoneurology Health Center #10, 3, Matveeva per., 190121 Saint-Petersburg.

Report/publication (ref)

Not applicable

Studied period (years)

April, 2007 – September, 2008

Clinical phase

IIB

Objectives

Primary objective

- To demonstrate clinical and statistical superiority of Org 25935 over placebo on the amelioration of negative symptoms in subjects with schizophrenia who are concurrently treated with a stable dose of a second generation antipsychotic (SGA).

Secondary objectives

- To establish the safety and tolerability of oral doses up to and including 32 mg Org 25935 per day in subjects with schizophrenia who are concurrently treated with a stable dose of a SGA;
- To evaluate the effects of Org 25935 on overall disease severity;
- To evaluate the effects of Org 25935 on positive symptoms;
- To evaluate the effects of Org 25935 on depressive symptoms;
- To evaluate the effects of Org 25935 on cognitive functions;
- To evaluate the effects of Org 25935 on neurological soft signs;
- To evaluate the effects of Org 25935 on extrapyramidal symptoms;
- To evaluate the effects of Org 25935 on level of functioning;
- To collect population pharmacokinetic data;
- To evaluate whether particular patient characteristics influence treatment efficacy or safety.

Methodology

This was a prospective, multiple dose, parallel group comparison of add-on treatment with two non-overlapping dose ranges Org 25935 and placebo, to demonstrate proof of concept in the add-on treatment of negative symptoms in schizophrenia. The phases of the trial were: screening (3-7 days), add-on treatment (81-87 days, randomized double-blind treatment), and follow-up (7 and 30 days) after last dose of trial medication.

Number of subjects (total and for each treatment)

In total, 246 subjects were screened of which 215 subjects were actually randomized (Org 25935 4-8 mg BID: 72; Org 25935 12-16 mg BID: 73; placebo: 70). In total, 214 subjects were treated (Org 25935 4-8 mg BID: 71; Org 2593512-16 mg BID: 73; placebo: 70). There was no stratification for SGA treatment. Subjects could be either outpatient or hospitallized prior to and/or during trial participation.

Diagnosis and criteria for inclusion

Subjects had to: provide written informed consent after the scope and nature of the investigation, including recording of interviews for second opinion, have been explained to them before screening; be between 18 and 55 years of age inclusive at screening; be (if female) surgically sterile, post menopausal ≥1 year at screening, or when of childbearing potential, using one of the following contraceptive methods: an intra uterine device (IUD), hormonal contraceptives in

combination with a barrier method, or a condom, used in combination with a spermicidal paste or prepared with such a paste; be able to speak, read, understand, and possess the ability to respond to questions and follow simple instructions in a language in which the investigator is fluent and into which any required documents and instructions, including the informed consent, have been translated; be diagnosed at the screening interview with non-first-episode schizophrenia meeting DSM-IV criteria; be treated with an oral or intramuscular stable dose of one of the following second generation antipsychotics (SGAs): aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone; be in the non-acute phase of their illness and clinically stable for the past 3 months at the time of screening, as demonstrated by: treatment with the current SGA for at least 12 weeks prior to screening, no dose change of the SGA or change in medication to treat clinical symptoms of schizophrenia in the past 4 weeks prior to screening, no increase in level of psychiatric care due to worsening of symptoms of schizophrenia in the past 12 weeks prior to screening, and no jailing or imprisonment in the past 12 weeks prior to screening; present a score ≥ 4 on three or more of the following PANSS items (Marder factors for negative symptoms) at screening: blunted affect (N1), emotional withdrawal (N2), poor rapport (N3), passive social withdrawal (N4), lack of spontaneity (N6), motor retardation (G7), active social avoidance (G16); present an overall PANSS negative subscale (Marder factors) score > 20; be medically stable and receiving standard therapies at a stable dose in the past 4 weeks prior to screening for treatment of their medical condition if they have hypothyroidism, diabetes, high blood pressure or chronic respiratory conditions; have a caregiver or an identified responsible person (e.g., family member, social worker or nurse) considered reliable by the investigator in providing support to the subject to ensure compliance with study treatment and protocol procedures.

Test product, dose and mode of administration, batch No.

Twice daily oral administration of 4-8 mg Org 25935, 12-16 mg Org 25935, or placebo. Modifications to the dosing schedule included truncation of upward titration and, if necessary, the allowance for downward titration to the starting dose in case of unacceptable adverse events. The actual dose at which the subject was treated was at the discretion of the investigator. Subjects maintained on the dose to which they were titrated to at week 6 for the remainder of the trial period.
Org 25935 was prepared as white tablets for oral use. Each tablet contained 4 mg (Batch number CA047) or 8 mg (Batch number CA048) Org 25935. The composition of the tablet was lactose monohydrate, maize starch, hydroxypropylcellulose, croscarmellose sodium, colloidal silica and magnesium stearate as excipients. Manufactured by NV Organon.

Duration of treatment

The subjects had a screening visit 3 to 7 days prior to baseline. The duration of active treatment on trial medication was 12 weeks ± 3 days. A post-treatment phase included out-patient follow-up visits in person or by phone at 7 and 30 days after the last dose of trial medication.

Reference therapy, dose and mode of administration, batch No.

Twice daily oral administration of placebo tablets (Batch number CA049). The composition of the tablet was lactose monohydrate, maize starch, hydroxypropylcellulose, croscarmellose sodium, colloidal silica and magnesium stearate as excipients. Manufactured by NV Organon.
Formulation of test and reference treatment was indistinguishable with respect to appearance, shape, smell and taste.

Criteria for evaluation

Safety/tolerability:
- (Serious) adverse events ((S)AEs), routine laboratory parameters, hormones (gonadotrophins, testosterone, SHBG and prolactin), physical examination, vital signs, electrocardiogram, ophthalmologic assessments (optional);
- Extrapyramidal symptoms: abbreviated Extrapyramidal Symptom Rating Scale (ESRS-A).

Efficacy:
- Negative symptoms:
  - Primary: Scale for the Assessment of Negative Symptoms (SANS);
  - Secondary: Positive and Negative Syndrome Scale (PANSS subscale);
- Positive symptoms: Positive and Negative Syndrome Scale (PANSS subscales);
- General: Global Assessment of Functioning (GAF) and PANSS (total score).

Other variables:
- Depressive symptoms: Calgary Depression Scale for Schizophrenia (CDSS);
- Cognitive functions: Cognitive battery composite and individual test measures;
- Neurological Soft Signs (NES);
- Level Of Function scale (LOF);

- Org 25935 plasma concentrations;
- Pharmacogenetics.

Statistical methods

The efficacy analysis for the primary and secondary variables was performed for the ITT week 8 completers group, since it was not expected that subjects improve from their negative symptoms early during in the trial. The ITT group was also analyzed, but considered additional. To account for missing data statistical analyses were performed both on LOCF and OC values. The results of the LOCF analysis were considered as the primary evidence for efficacy, the other analyses were considered supportive. The primary endpoint was after 12 weeks of treatment.
For continuous variables, the changes from baseline were analyzed per assessment using an ANCOVA model with baseline value as covariates and with treatment and center as fixed factors.
Descriptive statistics was used for safety analysis.

Summary

In total, 215 subjects were randomized of which 214 were treated. A slight majority of the trial population was male, which was consistent in all treatment groups. Almost all subjects were of the white race, mean age was 38.1 years, mean body height was 171.7 cm, mean body weight was 79.6 kg, and mean BMI was 27.0 kg/m^2. In total, 187 subjects completed the trial and 28 discontinued prematurely, of which 24 before Week 8.

Efficacy conclusions:
- Treatment with Org 25935 (4-8 mg BID and 12-16 mg BID) provided a modest benefit when added to the standard treatment with second generation antipsychotics during 12 weeks.
- Treatment with Org 25935 was not more effective than placebo in alleviating negative symptoms of schizophrenia.
- The overall (negative) trial outcome appears to be unbiased.

Safety conclusions:
- Org 25935 was overall well tolerated within the tested dose range (4-16 mg BID) with no unusual AEs.
- Transient, mostly mild, visual AEs were reported in a minority (up to 5%) of subjects.
- AEs of which the incidence appeared to increase with dosage included (percentages for subjects on placebo, 4-8 mg BID Org 25935, and 12-16 mg BID Org 25935, respectively): dizziness (0.0 - 2.8 - 9.6%), nasopharyngitis (1.4 – 4.2 – 9.6%), anxiety (2.9 – 2.8 – 5.5%), somnolence (1.4 – 2.8 – 5.5%), and blurred vision (0.0 – 1.4 – 4.1%).
- No effects were seen on any safety parameters, including routine laboratory panels, ECGs, vital signs, body weight, and ophthalmology assessments that can be interpreted as clinically meaningful.

Conclusions

The following conclusions can be drawn from this study:
- A modest (17-37%) improvement (or relative change from baseline) in overall disease severity, negative symptoms, positive symptoms, depressive symptoms, cognitive functions, neurological soft signs, and level of functioning was seen in all treatment arms.
- Org 25935 was not superior to placebo in the amelioration of negative symptoms in subjects with schizophrenia who were concurrently treated with a stable dose of a second generation antipsychotic.
- Background treatment and presence of neurological soft signs at baseline did not seem to have influenced treatment efficacy.
- Org 25935 appeared to be well tolerated in the tested dose ranges (4-8 mg BID and 12-16 mg BID), with a relatively low incidence of AEs or drop-outs due to AEs.
- Most commonly reported AEs on placebo, 4-8 mg BID Org 25935 and 12-16 mg BID Org 25935 respectively, included insomnia (8.6 – 8.5 – 6.8%), headache (10.0 – 4.2 – 6.8%), dizziness (0.0 – 2.8 – 9.6%), nasopharyngitis (1.4 – 4.2 – 9.6%), anxiety (2.9 – 2.8 –5.5%), somnolence (1.4 – 2.8 – 5.5%), and blurred vision (0.0 – 1.4 – 4.1%).
- No notable effect of treatment with Org 25935 on extrapyramidal symptoms was observed.
- No effects were seen on any safety parameters, including physical examination, laboratory, ECG, and ophthalmology assessments that can be interpreted as clinically meaningful.