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 Organon N.V. **Name of active substance** Org 34517	**Synopsis / Tabular Format** **referring to**	

Title of the clinical trial

Prospective, double-blind, randomized, placebo-controlled dose finding study of the efficacy and safety of 2 target doses of Org 34517 used as adjunctive therapy in subjects with psychotic major depression (major depressive episode, severe, with psychotic features).
Clinical Trial Report on Protocol 28130

Investigators

[redacted]

Center codes are provided between brackets

Clinical trial centers

Belgium

[redacted]

Czech Republic

[redacted]

Germany

[redacted]

India

[redacted]

[redacted]

[redacted]

United Kingdom

[redacted]

United States

[redacted]

Report/publication (ref)

Not applicable

Studied period (years)

October 2004 (first patient in) to July 2006 (last patient out)

Clinical phase

Phase II

Objectives

Primary objective:

- To demonstrate superiority of adjunctive treatment with 900 mg Org 34517, as compared to placebo, in alleviating psychotic symptoms in patients with psychotic depression on "usual treatment", as measured by the PANSS positive symptoms scale.

Secondary objectives:

- To demonstrate superiority of adjunctive treatment with 900 mg Org 34517, as compared to placebo, in alleviating depressive symptoms in patients with psychotic depression on "usual treatment", as measured by the HAMD 17-item scale.
- To demonstrate superiority of adjunctive treatment with 300 mg Org 34517, as compared to placebo, in alleviating psychotic symptoms in patients with psychotic depression on “usual treatment”, as measured by the PANSS positive symptoms scale.
- To demonstrate superiority of adjunctive treatment with 300 mg Org 34517, as compared to placebo, in alleviating depressive symptoms in patients with psychotic depression on "usual treatment", as measured by the HAMD 17-item scale.
- To demonstrate superiority of adjunctive treatment with 900 mg Org 34517, as compared to placebo, in alleviating global severity of illness, as measured by the Clinical Global Impression of Severity (CGI-S).
- To study the effects on cognition after 2 weeks of adjunctive therapy with Org 34517 in subjects with psychotic depression.
- To study the early onset of efficacy, as measured by the PANSS and the HAMD-17, of Org 34517 in subjects with psychotic depression at Day 5 of adjunctive therapy.
- To study the maintenance of the treatment effect.
- To measure safety and tolerability of Org 34517 during treatment and up to 4 weeks after discontinuation of adjunctive treatment.
- To explore population pharmacokinetic data.
- To collect safety data on the effects of Org 34517 on spermatogenesis in a subset of male subjects participating in this trial.

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Methodology

Prospective, multi-center, multinational, randomized, double-blind, placebo-controlled, dose finding trial with Org 34517 in an adjunctive treatment paradigm.

Number of subjects (total and for each treatment)

According to the protocol, at least 300 subjects with severe major depressive disorder (MDD) with psychotic features were to be randomized to 1 of the 3 treatment groups (300 mg (low dose, LD) Org 34517, 900 mg (high dose, HD) Org 34517 or placebo (P)) in a 1:1:1 algorithm. A total of 274 subjects received a dose of investigational product; 88 from the 300 mg Org 34517 group, 92 from the 900 mg Org 34517 group, and 94 from the placebo group.

Diagnosis and criteria for inclusion

Voluntary written informed consent for trial participation; able to speak, read, understand, respond to questions, and follow instructions in English or their native language, if the investigator was fluent in that language and any required documents, including informed consent, could be translated into that language; DSM-IV severe depressive episode with psychotic features, as diagnosed by the MINI for single or recurrent episodes (296.24 or 296.34); score on PANSS item "Delusions" and/or "Hallucinatory behavior" of ≥4 at Screening and Baseline; PANSS Positive Scale score of ≥16 at Screening and Baseline; total score of ≥18 on the HAMD 17 item scale at Screening and Baseline; on a stable dose of "usual treatment", which had to consist of an antidepressant, an antipsychotic, a mood stabilizer or any combination of these 3 drug classes; ≥18 and ≤75 years of age at Screening (per Amendment III); willing to be hospitalized for at least 11 days from Screening onwards (Interval between Screening and Baseline was 2 - 3 days and 1 day was needed for confirmation of the diagnosis and subsequent randomization. Subjects were treated as inpatients for at least 1 week after Randomization. After this period subjects could be treated on an outpatient basis if the investigator was of the opinion that it was safe to do so).
Before randomization, a qualified psychiatrist from Quintiles was to decide whether a subject was eligible for randomization, based on information collected by the investigator at Screening and Baseline.

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

Subjects randomized to Org 34517 treatment received either LD or HD Org 34517 for 2 weeks as adjunctive therapy. Trial medication was provided in blisters with capsules containing 150 mg of Org 34517 (and). The starting dose for both Org 34517 arms was 300 mg once daily. The HD group was titrated upwards to 600 mg once daily on Day 2 and to 900 mg once daily on Day 3. The LD group had a corresponding increase in the number of capsules consumed on Days 2 and 3 to maintain the double-blindness. If subjects could not tolerate 900 mg, the investigator was allowed to reduce the dose to 600 mg. For blinding purposes, this dose reduction from 6 to 4 capsules was possible in all treatment groups.
On Day 15, all subjects received single-blind placebo treatment until Day 29.
Medication was to be taken orally in the evening, with dinner (starting on the evening of Randomization).

Duration of treatment

The duration of treatment was 4 weeks; 2 weeks active treatment, 2 weeks placebo, and 2 weeks follow-up.

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

Subjects randomized to placebo received visually indistinguishable placebo capsules for 2 weeks as adjunctive therapy ( ). The placebo group had a corresponding increase in the number of capsules consumed on Days 2 and 3 as those in the Org 34517 dosing groups to maintain the double-blindness. The dose reduction from 6 to 4 capsules was also possible in this treatment group.
On Day 15, all subjects received single blind placebo treatment until Day 29.
Medication was to be taken orally in the evening, with dinner (starting on the evening of Randomization).

Criteria for evaluation

Efficacy: Positive And Negative Syndrome Scale (PANSS), HAMD-17 total score, and Clinical Global Impression (both CGI Severity (CGI-S) and CGI Change (CGI-C)); Pharmacokinetics: total plasma Org 34517 concentrations; Other parameters: cognition testing by means of a computerized test battery from Cogtest; measurement of morning saliva cortisol to determine the activity of the HPA axis (in selected centers the afternoon cortisol test (ACT) was also applied to measure hypercortisolemia); Safety: (Serious) adverse events ((S)AEs); routine laboratory measurements; assessment of pro-inflammatory cytokine IL6, testosterone (T), progesterone (P), Prostate-Specific-Antigen (PSA)[2],

[2] Only for male subjects with a past history (3 months or more) of symptoms of prostate hypertrophia.

alpha-1-acid glycoprotein (AAG), and the thyroid panel; vital signs, ECGs and physical examinations. Semen analysis at participating sites.

Statistical methods

The efficacy analysis for the primary and secondary variables was performed for both the ITT and PP group. For all assessments, statistical analysis was performed both on LOCF and OC values for the ITT group, and for the PP group. The results of the LOCF analysis for the ITT group are considered as the primary evidence for efficacy. The results for the PP group and the results of the OC analysis are considered supportive. For categorical variables, a (polytomous, if applicable) logistic regression model was applied per assessment, if applicable, with the baseline value and 'usual treatment' as covariates and with treatment group and center as fixed factors. If more appropriate, categories were combined in order to avoid low frequencies. Treatment differences between each of the two Org 34517 groups and the placebo group were expressed in terms of odds ratios, resulting from the logistic regression including all treatments. For continuous variables, the changes from baseline were analyzed per assessment using an ANCOVA model with the baseline value and 'usual treatment' as covariates and with treatment group and center as fixed factors.

The PANSS positive symptoms and HAMD-17 responder rate were analyzed using a logistic regression model. To deal with multiplicity, statistical test results for the LOCF/ITT analysis of the HAMD 50% responder rate at both Day 8 and Day 43 were interpreted according to the stepwise procedure. The morning cortisol changes from baseline were analyzed using an ANCOVA.

Descriptive statistics for the Org 34517 plasma concentrations were calculated by assessment and dose (dose reduction as a result of poor tolerability was taken into account).

Descriptive statistics was used for safety analysis.

Summary

Efficacy: In subjects with psychotic depression, stable on usual treatment, 900 mg Org 34517 failed to show a statistically significant difference from placebo (p=0.14) on the primary endpoint of sustained response on the PANSS positive symptoms scale (the proportion of subjects with a change from baseline of at least 50% at both Days 8 and 43). The important secondary endpoints (900 mg Org 34517 versus placebo response on the HAMD and 300 mg Org 34517 versus placebo response on the PANSS positive scale and the HAMD) did not show any statistically significant difference from placebo. The CGI-S data suggested that there is an effect as early as Day 5, as it showed that subjects who received 900 mg Org 34517 had an improvement over placebo. Analysis of the efficacy data on a visit-by-visit basis indicated that 300 mg Org 34517 is similar to placebo. In contrast, 900 mg Org 34517 was numerically superior to placebo on the PANSS total score, the PANSS-derived BPRS, and the PANSS positive symptom score, reaching statistical significance on Day 8 (BPRS) and Day 22 (BPRS and PANSS positive symptom score).

For the cognitive tests, Org 34517 did not demonstrate pro-cognitive effects (i.e., cognitive improvement) during acute (15-day) treatment of patients with psychotic depression. A minority of patients showed cognitive worsening, while the majority were either stable or demonstrated cognitive gains after 15 days of active or placebo treatment.

Other variables: Org 34517 induced a statistically significant dose dependant increase in morning and afternoon saliva cortisol by Day 15. The increase normalized by Day 29. For the 900 mg Org 34517 dose group, the increases in morning and afternoon cortisol levels were statistically significant at Day 15.

Mean Org 34517 plasma concentrations were 20-30 % higher for the 900 mg treatment compared to the 300 mg treatment. An exploratory PK-PD evaluation did not indicate a clear relationship between Org 34517 concentrations and effects on PANSS positive.

Safety: The number of subjects experiencing at least one AE was comparable for all treatment groups; 59 subjects (67.0%) from the 300 mg Org 34517, 63 subjects (68.5%) from the 900 mg Org 34517, and 61 subjects (64.9%) from the placebo. There were no deaths. A total of 8 subjects (9.1%) from the 300 mg Org 34517 group, 3 subjects (3.3%) from the 900 mg Org 34517 group, and 6 subjects (6.4%) from the placebo group experienced SAEs. A total of 4 subjects (4.5%) from the 300 mg Org 34517 group, 3 subjects (3.3%) from the 900 mg Org 34517 group, and 5 subjects (5.3%) from the placebo group were reported to have discontinued due to an AE. A total of 37 subjects (42.0%) from the 300 mg Org 34517 group, 47 subjects (51.1%) from the 900 mg Org 34517 group, and 41 subjects (43.6%) from the placebo group were considered to have drug-related AEs. A total of 5 subjects (5.7%) from the 300 mg Org 34517 group, 4 subjects (4.3%) from the 900 mg Org 34517 group, and 7 subjects (7.4%) from the placebo group were considered to have experienced AEs of severe intensity.

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Exacerbation of major depression that resulted in or prolonged hospitalization was considered to be an SAE. [redacted]

The 3 SOCs with the most frequent incidences of AEs were nervous system disorders, gastrointestinal disorders, and psychiatric disorders. Generally, the incidence of the frequently (≥5%) reported AEs (e.g., nausea, headache, and dizziness) within these SOCs were similar for all 3 treatment groups. Adverse events within the SOC "infections and infestations", had a higher incidence in the 300 mg Org 34517 group (over 9%) than the 900 mg Org 34517 group or placebo (over 4%). Major depression was reported less often as an AE in the 900 mg Org 34517 group (2.2%) when compared to the 300 mg Org 34517 group (6.8%) and the placebo group (5.3%). The SOC "skin and subcutaneuous disorders" showed a higher incidence of AEs, belonging to this SOC, in the placebo group, when compared to the Org 34517 groups. However, the incidence of AEs such as papular rash, eczema, rash, maculo-papular rash, drug eruption, and generalized rash were higher for the 900 mg Org 34517 group when compared with either the 300 mg Org 34517 group or the placebo group.

There was a higher incidence of MALVs for monocytes in the Org 34517 groups when compared with placebo. MALVs for neutrophils showed a dose dependent increase, with an incidence of 12.1% in the 900 mg group. The treatment groups were comparable for hematology parameters. For ALAT, the incidences of increases above the upper safety limit were similar for all 3 treatment groups. Total cholesterol levels above the upper safety limit showed a dose dependent increase in incidence, with more than twice as many subjects in the 900 mg Org 34517 group, compared to the placebo group, having cholesterol levels above the upper safety limit. The incidence of increased plasma glucose MALVs was highest in the 300 mg group, which was more than 2 times the incidence in the other groups. The incidence of increases above the upper safety limit of phosphate was similar in all 3 treatment groups. The differences among the 3 treatment groups in upward shift in bilirubin total were statistically significant (p=0.010). Also the differences in upward shift in Phosphate (P) was statistically significant (p=0.019). For all other biochemistry parameters the shifts were not statistically significant.

Conclusions

- The objectives of this study were not met since 900 mg Org 34517 failed to show superiority over placebo.
- Org 34517 induced a significant dose dependent increase in morning and afternoon saliva cortisol.
- Org 34517 appeared to be safe and well tolerated in the population chosen for this study.

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