Efficacy and Safety of Roluperidone for the Treatment of Negative Symptoms of Schizophrenia

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Background: This is a placebo-controlled multi-national trial of roluperidone, a compound with antagonist properties for 5-HT2A, sigma 2, and α1A-adrenergic receptors, targeting negative symptoms in patients with schizophrenia. This trial follows a previous trial that demonstrated roluperidone superiority over placebo in a similar patient population. Methods: Roluperidone 32 mg/day, roluperidone 64 mg/day, or placebo was administered for 12 weeks to 513 patients with schizophrenia with moderate to severe negative symptoms. The primary endpoint was the PANSS-derived Negative Symptom Factor Score (NSFS) and the key secondary endpoint was Personal and Social Performance scale (PSP) total score. Results: NSFS scores were lower (improved) for roluperidone 64 mg compared to placebo and marginally missing statistical significance for the intent-to-treat (ITT) analysis data set (P ≤ .064), but reached nominal significance (P ≤ .044) for the modified-ITT (m-ITT) data set. Changes in PSP total score were statistically significantly better on roluperidone 64 mg compared to placebo for both ITT and m-ITT (P ≤ .021 and P ≤ .017, respectively). Conclusions: Results of this trial confirm the potential of roluperidone as a treatment of negative symptoms and improving everyday functioning in patients with schizophrenia. Study registration: Eudra-CT: 2017-003333-29; NCT03397134.

Key words: schizophrenia/negative symptoms/treatment
symptoms. A thorough meta-analysis did not find significant advantages for any medication in the treatment of negative symptoms, and to date, there are no medications approved for the treatment of negative symptoms by the FDA.

The realization that negative symptoms constitute a major unmet need has stimulated researchers in academia and in the pharmaceutical industry to search for a solution beyond interference with DA neurotransmission. Attempts to target N-methyl-D-aspartic acid (NMDA)/glutamate neurotransmission, via glycine re-uptake inhibition and other strategies were initially encouraging, but the results were not replicated in a subsequent larger trial. Pharmacological manipulations of the trace amine-associated receptor 1 (TAAR1), or PDE10A inhibition have not yet produced conclusive results. Therefore, developing well-tolerated drugs, with innovative mechanisms of action (MoA), which can ameliorate negative symptoms, remains a priority.

Roluperidone is a novel cyclic amide derivative with antagonistic properties for serotonergic 5-HT2A, sigma, and α1A-adrenergic receptors, and to a lesser extent, α1B-adrenergic receptors. Roluperidone has no affinity for DA, cholinergic, or histaminergic receptors (data on file). Although roluperidone has no affinities for pre- or postsynaptic DA receptors, dopaminergic neurotransmission might be modulated by both the 5-HT2A and sigma, antagonisms. Antagonism at the sigma2 receptors might also modulate glutamatergic pathways, and affect calcium neuronal modulation. Taken together, it could be hypothesized that sigma2 receptors are involved in counteracting dysregulations in key DA and glutamate neurotransmitter pathways. It should be noted that several antipsychotic drugs such as haloperidol possess sigma binding activities, but the role of sigma receptors in affecting schizophrenia symptoms has not been fully elucidated. Finally, the α1A-adrenergic antagonistic activity might contribute to improve synaptic efficacy and plasticity, thus facilitating learning and memory functions.

A previous placebo-controlled, 12-week trial, which enrolled 244 patients with stable positive symptoms of schizophrenia, reported that roluperidone was superior to placebo in decreasing the negative symptoms as measured by the pentagonal model structure negative symptoms scores of the Positive and Negative Syndrome Scale (PANSS) for both the 32 mg and 64 mg dose (P ≤ .024, ES = 0.45, and ≤ .004, ES = 0.57). Significant improvements were also found on the Personal and Social Performance (PSP) total score for the 64 mg dose (P ≤ .003, ES = 0.59). The aim of this large, multi-site trial presented here was to confirm the results of the previous trial using similar methodology.

Methods

Between December 2017 and February 2020, 513 patients 18–55 years of age, received roluperidone or placebo at 61 sites in Europe, Israel, and the USA. Patients were recruited from outpatient clinics, supervised residential facilities, and psychiatric hospital wards. The trial protocol was approved by Institutional Review Boards, local ethics committees, and national regulatory bodies and all participants signed an informed consent form.

Eligibility Criteria

To be eligible, patients had to meet DSM-5 criteria for schizophrenia confirmed by Mini International Neuropsychiatric Interview, diagnosed with schizophrenia for at least one year, be symptomatically stable by history, and manifest negative symptoms for ≥ 6 months prior to entering the trial. Patients had to be either outpatients, or inpatients admitted for social reasons and not for symptomatic worsening. Patient must have had a score of > 20 on the PANSS negative symptoms subscale (N-1 Blunted affect, N-2 Emotional withdrawal, N-3 Poor rapport, N-4 Passive/apathetic social withdrawal, N-5 Difficulty in abstract thinking, N-6 Lack of spontaneity & flow of conversation, N-7 Stereotyped thinking) with no change between screening and baseline of more than 3 points. There was no severity limit on the total positive symptoms score, but patients had to have scores ≤ 4 on PANSS items related to agitation (P4 Excitement, P6 Suspiciousness/Persecution, P7 Hostility, G8 Uncooperativeness, and G14 Poor impulse control). Patients were excluded if they had a California Depression Scale for Schizophrenia (CDSS) total score > 6, at least a moderate degree of akathisia based on the Barnes Akathisia Rating Scale (BARS), or a BMI ≥ 35 kg/m2. Patients were also excluded if they had a personal or familial history of long QT syndrome, a QTc (Fridericia-corrected) > 430 ms for males and > 450 ms for females, or if they were poor or intermediate metabolizers for P450 CYP2D6, as determined by genotyping. Patients with an Axis I diagnosis of another mental disorder, significant risk of suicide, a positive urine test for illicit drugs, history of substance abuse, or unstable medical disorders were also excluded.

Study Design

Eligible patients had their depot antipsychotic medications discontinued for at least a treatment cycle (1 to 3 months depending on the drug formulation) and all their psychotropic drugs were discontinued at least 2 days prior to randomization and throughout the study duration hence, patients received roluperidone monotherapy throughout the study. Patients were assigned to roluperidone 32 mg/day, 64 mg/day, or placebo in a 1:1:1 ratio for a 12-week study duration. Patients were randomized based on a computer-generated randomization schedule prepared before the study. The randomization was balanced by using randomly permuted blocks and were stratified by region (United States, all other sites in Europe, Israel, and the USA). Patients were recruited from outpatient clinics, supervised residential facilities, and psychiatric hospital wards. The trial protocol was approved by Institutional Review Boards, local ethics committees, and national regulatory bodies and all participants signed an informed consent form.
countries). Investigators, patients, and the sponsor were blinded to assignment at all times during the study. After randomization, patients had to be hospitalized for at least 36 hours and then could remain hospitalized or be discharged at the discretion of the investigator. No psychotropic medications were allowed during the duration of the trial except for rescue medications given for insomnia or agitation in doses allowed by the local regulations (oral lorazepam, zolpidem). Anticholinergic medications were discontinued at baseline in all patients but were allowed during the trial to treat emergent EPS. Patients were evaluated in person at screening, baseline, and Weeks 1, 2, 3, 4, 8, and 12 (end of double-blind study). Patients who completed the 12-week double-blind trial could continue to receive the same dose of roluperidone or, if receiving placebo, be switched at random to either dose of roluperidone for 40 additional weeks in an open-label extension. The roluperidone dose was blinded through the extension phase; data are not presented here.

Outcome Measures

Primary Outcome Measure. Primary outcome measure was the change from baseline to week 12 on the NSFS (N1 to N4, N6, G7, and G16) of the PANSS.22,23

Key Secondary Outcome Measure. Key secondary outcome measure was the PSP total score,24 a scale that assesses socially useful activities, personal and social relationships, self-care, and disturbing and aggressive behaviors.

Secondary Outcome Measures. Secondary outcome measures were the Clinical Global Impression—Severity Scale (CGI-S), Clinical Global Impression—Improvement Scale (CGI-I), other PANSS-derived subscales and domains, assessment of cognitive function measured by verbal fluency test, and of depressive symptoms measured by CDSS.

Safety and Tolerability. Safety and tolerability were evaluated by monitoring the frequency, severity, and timing of adverse events, clinical laboratory test results, ECG, vital signs, body weight, abnormal involuntary movement scale (AIMS), BARS, Simpson-Angus Scale (SAS), and Sheehan Suicidality Tracking Scale.

Sample Size and Statistical Analysis

The sample size for this study was based on the assumption of a treatment difference of 3 points in the mean change from baseline to Week 12 in NSFS between any roluperidone dose and placebo. A standard deviation of 6.5 in the change in NSFS score from baseline was hypothesized. Assuming an equal allocation to placebo and each of the 2 roluperidone doses, 167 patients in each treatment group, adjusted for 40% noncompleters, were required to detect the treatment difference with a power of 90% at an overall 2-sided significance level of .05 (P-value)

Statistical Methods

The primary efficacy endpoint was the change in the NSFS from baseline to Week 12 (the 12-week double-blind treatment phase). This endpoint was analyzed using MMRM with fixed effects for treatment group (roluperidone 64 mg, roluperidone 32 mg, and placebo), region (USA, rest of the world), visit, and treatment-by-visit interaction, a random effect for patient within treatment group, and baseline NSFS as covariate. An unstructured covariance matrix was used to model the covariance of within-patient scores. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. These analyses were performed based on all post-Baseline scores using only the observed cases without imputation of missing values. Comparison against placebo was performed with the roluperidone 64 mg and 32 mg doses.

The truncated Hochberg method for adjustment of multiplicity to control the type I error rate at the 2-sided 0.050 alpha level within the family of primary and the key secondary hypotheses was utilized and was chosen based on the phase 2b results.

Responder analysis based on pre-defined changes from baseline in NSFS, PANSS total score, and PSP total score was performed, and the treatment groups were compared using logistic regression model with treatment and Baseline values as covariate.

All analyses were performed using the safety and ITT sets. Before the database was locked and unblinded, a data quality review with the help of AI revealed that one site reported data that were behaviorally and physiologically implausible. Throughout the 12 weeks of the trial, the 17 patients recruited at the site had none or negligible variations in terms of symptoms severity as reflected by CGI or blood pressure measurement, no reports of adverse effects, and no dropout from the trial. Therefore, efficacy analyses were repeated both as ITT and as modified ITT (m-ITT) set which excluded from the ITT set the 17 patients from the site.

Results

A total of 857 patients were screened, 515 patients were randomized, and 513 patients received at least one dose of roluperidone or placebo. Of the 513 patients, 172 received placebo, 170 received the 32 mg roluperidone dose, and 171 received the 64 mg roluperidone dose. A total of 379/513 patients completed 12-week of double-blind treatment: 76% in the placebo group, 72% in the 32 mg group, and 74% in the 64 mg group (figure 1). The most frequent reason for study discontinuation in all treatment groups was withdrawal of consent. All demographics and disease characteristics were comparable for the 3 groups (tables 1 and 2). Before the wash-out period required prior to randomization, 434 (84.6%) patients received oral antipsychotics, 32 (6.2%) patients depot antipsychotics, and 47 (9.2%) patients received no antipsychotic medication. The
Table 1. Demographic data

|                      | Placebo (N = 172) | Roluperidone 32 mg (N = 170) | Roluperidone 64 mg (N = 171) | Total (N = 341) | Overall (N = 513) |
|----------------------|------------------|-------------------------------|-----------------------------|----------------|-------------------|
| **Age at informed consent (years)** |                  |                               |                             |                |                   |
| Mean (SD)            | 41 (8.7)         | 41 (9.4)                      | 41 (9.3)                    | 41 (9.3)       | 41 (9.1)          |
| Median               | 41               | 42                            | 42                          | 42             | 42                |
| Min, max             | 18, 55           | 18, 55                        | 18, 55                      | 18, 55         | 18, 55            |
| **Sex, n (%)**       |                  |                               |                             |                |                   |
| Male                 | 106 (62%)        | 106 (62%)                     | 103 (60%)                   | 209 (61%)      | 315 (61%)         |
| Female               | 66 (38%)         | 64 (38%)                      | 68 (40%)                    | 132 (39%)      | 198 (39%)         |
| **Race, n (%)**      |                  |                               |                             |                |                   |
| American Indian or Alaska Native | 0 | 1 (<1%) | 0 | 1 (<1%) | 1 (<1%) |
| Asian                | 0                | 1 (<1%)                       | 1 (<1%)                     | 2 (<1%)        | 2 (<1%)           |
| Black or African American | 20 (12%) | 19 (11%) | 18 (11%) | 37 (11%) | 57 (11%) |
| Native Hawaiian or other | 0 | 2 (1%) | 1 (<1%) | 3 (<1%) | 3 (<1%) |
| Pacific Islander     |                  |                               |                             |                |                   |
| White                | 152 (88%)        | 147 (86%)                     | 151 (88%)                   | 298 (87%)      | 450 (88%)         |
| Other                | 0                | 0                             | 0                           | 0              | 0                 |
| **BMI (kg/m²)**      |                  |                               |                             |                |                   |
| N                    | 172              | 170                           | 170                         | 340            | 512               |
| Mean (SD)            | 25.8 (4.14)      | 25.6 (4.31)                   | 25.7 (4.04)                 | 25.6 (4.17)    | 25.7 (4.16)       |
| Median               | 24.7             | 25.2                          | 25.5                        | 25.4           | 25.1              |
| Min, max             | 18.6, 34.8       | 16.8, 34.7                    | 17.6, 34.7                  | 16.8, 34.7     | 16.8, 34.8        |
| USA                  | 27 (16%)         | 27 (16%)                      | 27 (16%)                    | 54 (16%)       | 81 (16%)          |
| Rest of World        | 145 (84%)        | 143 (84%)                     | 144 (84%)                   | 287 (84%)      | 432 (84%)         |

most frequently used concomitant medication administered during the 12-week double-blind portion of the trial were benzodiazepines, in 19 patients (11%) in the placebo group, 31 patients (18%) in the 32 mg roluperidone group, and 31 patients (18%) in the 64 mg roluperidone group.

Fig. 1. Patients distribution.

**Efficacy**

Table 3 presents summary of findings for primary, key secondary, and other secondary and exploratory endpoints. The analysis of the change from baseline to Week 12 in NSFS for the ITT population, showed a
Table 2. Baseline Characteristics

| Assessments at Baseline | Placebo (N = 172) | Roluperidone | Overall (N = 513) |
|-------------------------|------------------|--------------|------------------|
|                         | 32 mg (N = 170)  | 64 mg (N = 171) | Total (N = 341)  |
| **PANSS**               |                  |              |                  |
| **NSFS**                |                  |              |                  |
| N                       | 172              | 170          | 171              | 341              | 513              |
| Mean (SD)               | 24 (3.0)         | 25 (3.4)     | 25 (3.2)         | 25 (3.3)         | 25 (3.2)         |
| Median                  | 24               | 25           | 26               | 25               | 25               |
| Min, max                | 17, 32           | 16, 39       | 19, 36           | 16, 39           | 16, 39           |
| **Total Score**         |                  |              |                  |
| N                       | 172              | 170          | 171              | 341              | 513              |
| Mean (SD)               | 77 (9.9)         | 80 (11.8)    | 79 (10.5)        | 79 (11.1)        | 79 (10.8)        |
| Median                  | 77               | 80           | 79               | 80               | 79               |
| Min, max                | 56, 113          | 53, 117      | 56, 109          | 53, 117          | 53, 117          |
| **Positive Subscore**   |                  |              |                  |
| N                       | 172              | 170          | 171              | 341              | 513              |
| Mean (SD)               | 14 (3.6)         | 15 (4.1)     | 14 (4.0)         | 15 (4.0)         | 14 (3.9)         |
| Median                  | 14               | 15           | 14               | 15               | 14               |
| Min, max                | 7, 23            | 7, 25        | 7, 27            | 7, 27            | 7, 27            |
| **Negative Subscore**   |                  |              |                  |
| N                       | 172              | 170          | 171              | 341              | 513              |
| Mean (SD)               | 26 (3.3)         | 27 (3.6)     | 27 (3.4)         | 27 (3.5)         | 27 (3.4)         |
| Median                  | 26               | 27           | 27               | 27               | 27               |
| Min, max                | 21, 40           | 21, 43       | 21, 39           | 21, 43           | 21, 43           |
| **PSP Scale Total Score** |              |              |                  |
| N                       | 171              | 170          | 171              | 341              | 512              |
| Mean (SD)               | 53 (11.0)        | 53 (12.2)    | 53 (10.5)        | 53 (11.4)        | 53 (11.2)        |
| Median                  | 50               | 51           | 50               | 50               | 50               |
| Min, max                | 21, 80           | 20, 100      | 15, 75           | 15, 100          | 15, 100          |
| **CGI-S Score**         |                  |              |                  |
| N                       | 172              | 170          | 171              | 341              | 513              |
| Mean (SD)               | 4 (0.6)          | 4 (0.6)      | 4 (0.6)          | 4 (0.6)          | 4 (0.6)          |
| Median                  | 4                | 4            | 4                | 4                | 4                |
| Min, max                | 2, 6             | 3, 6         | 3, 6             | 3, 6             | 2, 6             |
| **Verbal Fluency Test (words per min)** | | | | | |
| N                       | 172              | 170          | 171              | 341              | 513              |
| Mean (SD)               | 25 (9.3)         | 23 (10.1)    | 23 (9.7)         | 23 (9.9)         | 24 (9.7)         |
| Median                  | 24               | 23           | 22               | 22               | 23               |
| Min, max                | 4, 51            | 0, 47        | 0, 51            | 0, 51            | 0, 51            |
| **CDSS Score**          |                  |              |                  |
| N                       | 172              | 170          | 171              | 341              | 513              |
| Mean (SD)               | 1 (1.5)          | 1 (1.5)      | 1 (1.5)          | 1 (1.5)          | 1 (1.5)          |
| Median                  | 0                | 0            | 0                | 0                | 0                |
| Min, max                | 0, 6             | 0, 6         | 0, 6             | 0, 6             | 0, 6             |
| **AIMS Composite Score** |              |              |                  |
| N                       | 172              | 170          | 171              | 341              | 513              |
| Mean (SD)               | 0 (1.0)          | 0 (1.4)      | 0 (1.0)          | 0 (1.2)          | 0 (1.2)          |
| Median                  | 0                | 0            | 0                | 0                | 0                |
| Min, max                | 0, 11            | 0, 12        | 0, 10            | 0, 12            | 0, 12            |
| **BARS Total Score**    |                  |              |                  |
| N                       | 172              | 170          | 171              | 341              | 513              |
| Mean (SD)               | 0 (0.4)          | 0 (0.4)      | 0 (0.4)          | 0 (0.4)          | 0 (0.4)          |
| Median                  | 0                | 0            | 0                | 0                | 0                |
| Min, max                | 0, 2             | 0, 2         | 0, 3             | 0, 3             | 0, 3             |
| **S-AS**                |                  |              |                  |
| N                       | 172              | 170          | 171              | 341              | 513              |
| Mean (SD)               | 0 (1.0)          | 1 (2.2)      | 1 (1.5)          | 1 (1.9)          | 1 (1.7)          |
| Median                  | 0                | 0            | 0                | 0                | 0                |
| Min, max                | 0, 7             | 0, 15        | 0, 10            | 0, 15            | 0, 15            |
| **STS Total Score**     |                  |              |                  |
| N                       | 171              | 170          | 171              | 341              | 512              |
| Mean (SD)               | 0 (0.1)          | 0 (1.5)      | 0 (0.3)          | 0 (1.1)          | 0 (0.9)          |
| Median                  | 0                | 0            | 0                | 0                | 0                |
| Min, max                | 0, 1             | 0, 20        | 0, 3             | 0, 20            | 0, 20            |

Note: AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; CDSS, Calgary Depression Scale for Schizophrenia; CGI-S, Clinical Global Impression of Severity; Max, maximum; Min, minimum; NSFS, Marder Negative Symptoms Factor Score; PANSS, Positive and Negative Syndrome Scale; PSP, Personal and Social Performance; SAS, Simpson-Angus Scale; SD, standard deviation; STS, Sheehan Suicidality Tracking Scale.
treatment difference versus placebo of \(-0.52\) (95% CI: 
\[-1.42, 0.38\]) for the 32 mg roliperidone group and 
\(-0.85\) (95% CI: 
\[-1.75, 0.05\]) for the 64 mg roliperidone group 
\((P \leq .260 \text{ and } P \leq .064, \text{ respectively}; \text{ figure 2}).\) The analysis 
of the change from Baseline to Week 12 in NSFS for 
the m-ITT population for the 64 mg roliperidone group 
demonstrated nominally statistically significant supe-
riority compared to placebo (difference versus placebo: 
\(-0.96\) [95% CI: 
\[-1.89, -0.03\]], 
\(P \leq .044\); ES = 0.26; \text{ table 3}). \text{ Statistically, significantly more patients had a 20\% reduction from baseline at Week 12 in the 64 mg roliperidone dose (41%}

Table 3. Summary of Select Efficacy Endpoints At Week 12

| Change from Baseline (LS Means (SEM)) | MIN-101 | Placebo | 32 mg | 64 mg | MIN-101 versus Placebo | 32 mg | 64 mg | MIN-101 versus Placebo | 32 mg | 64 mg |
|---------------------------------------|---------|---------|-------|-------|------------------------|-------|-------|------------------------|-------|-------|
| **Primary Objective**                 |         |         |       |       |                        |       |       |                        |       |       |
| Marder's NSFS (ITT)                   | \(-3.5\) (0.34) | \(-4.0\) (0.35) | \(-4.3\) (0.34) | .259 | .064 | 0.13 | 0.21 |
| Marder's NSFS (mITT)                  | \(-3.5\) (0.35) | \(-4.0\) (0.35) | \(-4.5\) (0.35) | .286 | .044 | 0.13 | 0.26 |
| **Key Secondary Objectives**          |         |         |       |       |                        |       |       |                        |       |       |
| PSP Total Score (ITT)                 | \(3.9\) (0.73) | \(4.5\) (0.75) | \(6.1\) (0.73) | .542 | .021 | 0.07 | 0.27 |
| PSP Total Score (mITT)                | \(3.8\) (0.75) | \(4.4\) (0.77) | \(6.2\) (0.77) | .551 | .017 | 0.07 | 0.29 |
| **Secondary and Exploratory**         |         |         |       |       |                        |       |       |                        |       |       |
| Clinical Global Impression of Severity| \(-0.3\) (0.06) | \(-0.4\) (0.06) | \(-0.5\) (0.06) | .221 | .073 | 0.12 | 0.24 |
| **PANSS Constructs**                 |         |         |       |       |                        |       |       |                        |       |       |
| Total Score                           | \(-5.5\) (0.84) | \(-7.1\) (0.87) | \(-7.4\) (0.85) | .168 | .098 | 0.17 | 0.20 |
| Negative Symptoms Subscore            | \(-3.8\) (0.35) | \(-4.2\) (0.35) | \(-4.7\) (0.35) | .392 | .046 | 0.10 | 0.23 |
| Positive Symptoms Subscore            | \(-0.2\) (0.25) | \(-0.3\) (0.26) | \(-0.4\) (0.25) | .783 | .478 | 0.04 | 0.07 |
| General Psychopathology Subscore      | \(-1.7\) (0.45) | \(-2.8\) (0.47) | \(-2.3\) (0.46) | \(0.92\) | .380 | 0.22 | 0.12 |
| Marder's Positive Symptoms Factor Score| \(-1.0\) (2.70) | \(-1.5\) (2.65) | \(-1.6\) (2.86) | \(0.19\) | .039 | 0.14 | 0.24 |
| Marder's Anxiety/Depression Factor Score| \(-0.5\) (0.20) | \(-0.6\) (0.20) | \(-0.7\) (0.20) | \(0.62\) | .448 | 0.05 | 0.09 |
| Marder's Disorganized Thought Factor Score| \(-1.2\) (0.24) | \(-1.6\) (0.25) | \(-1.4\) (0.25) | \(0.27\) | .514 | 0.15 | 0.07 |
| Marder's Uncontrolled Hostility/Excitement Factor | \(0.2\) (0.18) | \(0.3\) (0.18) | \(0.5\) (0.18) | \(0.68\) | .153 | \(-0.05\) | \(-0.15\) |
| **Score**                             |         |         |       |       |                        |       |       |                        |       |       |
| NSFS Emotional Experience Score       | \(-1.3\) (0.16) | \(-1.5\) (0.16) | \(-1.8\) (0.16) | \(0.41\) | .020 | 0.11 | 0.28 |
| NSFS Emotional Expression Score       | \(-2.3\) (0.22) | \(-2.6\) (0.22) | \(-2.6\) (0.22) | \(0.35\) | .349 | 0.17 | 0.17 |
| **PSP Domains**                      |         |         |       |       |                        |       |       |                        |       |       |
| Self-Care                             | \(-0.3\) (0.06) | \(-0.4\) (0.06) | \(-0.3\) (0.06) | \(0.26\) | .819 | 0.15 | 0.04 |
| Socially Useful Activities            | \(-0.3\) (0.05) | \(-0.3\) (0.06) | \(-0.4\) (0.05) | \(0.865\) | .047 | 0.02 | 0.18 |
| Personal and Social Relationships     | \(-0.3\) (0.06) | \(-0.4\) (0.06) | \(-0.3\) (0.06) | \(0.076\) | .501 | 0.15 | 0.00 |
| Disturbing and Aggressive Behaviors   | \(0.0\) (0.05) | \(0.0\) (0.05) | \(0.0\) (0.05) | \(0.961\) | .186 | 0.00 | \(-0.07\) |
| Clinical Global Impression of Improvement\(^a\) | \(3.3\) (0.08) | \(3.4\) (0.08) | \(3.3\) (0.08) | \(0.683\) | .746 | \(-0.12\) | \(-0.02\) |
| Calgary Depression Scale for Schizophrenia | \(0.1\) (0.13) | \(-0.2\) (0.13) | \(-0.1\) (0.13) | \(0.093\) | .139 | 0.21 | 0.14 |
| Total Verbal Fluency\(^b\)            | \(2.4\) (0.64) | \(3.9\) (0.66) | \(1.7\) (0.63) | \(0.067\) | .327 | 0.21 | \(-0.10\) |
| **Responder Analysis\(^c\)**          |         |         |       |       |                        |       |       |                        |       |       |
| Number of Patients with 20% Reduction in NSFS at Week 12 | \(30/128\) (23%) | \(32/116\) (28%) | \(48/122\) (39%) | \(0.418\) | .006 | 0.05 | 0.17 |
| Number of Patients with 20% Reduction in PANSS | \(12/128\) (9%) | \(20/116\) (17%) | \(24/122\) (20%) | \(0.061\) | .021 | 0.12 | 0.15 |
| Total Score at Week 12                |         |         |       |       |                        |       |       |                        |       |       |
| Number of Patients with 7-Point Improvement in PSP Total at Week 12 | \(37/128\) (29%) | \(37/116\) (32%) | \(50/122\) (41%) | \(0.589\) | .032 | 0.03 | 0.13 |

\(^a\)Based on Cohen's \(d\).
\(^b\)Based on sum of 3 trials.
\(^c\)Effect size is based on Cohen's \(W\).
Fig. 2. PANSS Negative Symptoms Factor Score (Marder) change from baseline (MMRM) ITT population.

Note: p-values represent comparison of roluperidone dose versus placebo

Fig. 3. Personal Social Performance (PSP) total score change from baseline (MMRM) ITT population.
versus 29% on placebo; \( P \leq .032 \). Roluperidone 64 mg group was nominally statistically significantly superior to placebo on the derived PANSS emotional experience score (N2 + N4 + G16)\(^{26} \) and for the N2 + N4 reflective of avolition.

Analysis adjusted for CDSS, or SAS baseline scores did not change the study results suggesting that the observed improvement with roluperidone was independent of the depression or drug-induced extrapyramidal syndrome scores.

**Safety and Tolerability**

Treatment-emergent adverse events (TEAE) were experienced by 33% of patients who received placebo, 42% of patients who received roluperidone 32 mg, and 37% of patients who received roluperidone 64 mg. The most commonly reported TEAEs were insomnia (10% Roluperidone, 10% placebo), worsening of schizophrenia (8.0% roluperidone, 3.0% placebo), headache (5.0% roluperidone, 5.0% placebo), anxiety (4.0% roluperidone, 2.0% placebo), and agitation (3.0% roluperidone, 2.0% placebo). The remainder of reported TEAEs occurred in < 3% of the patients. The majority of TEAEs reported in all treatment groups were mild to moderate in severity with severe TEAEs reported in 17 patients (3%) overall with similar incidence in all treatment groups. There were 25 (5%) patients with serious adverse events (SAEs), 5 (3%) in the placebo group, and 20 (6%) in the roluperidone groups. There were 2 deaths during the trial in the roluperidone 32 mg dose, one patient committed suicide and another died from gastrointestinal bleeding 6 days after he withdrew consent and discontinued the trial. Neither death was considered by the investigator related to treatment. Overall, 5% of patients in the placebo group, 11% of patients in the 32 mg roluperidone group, and 9% of patients in the 64 mg roluperidone group reported TEAEs that led to the study drug being discontinued. Relapse, defined as worsening of schizophrenia symptoms was the most frequent reason for discontinuation from the trial with the highest incidence in the roluperidone 32 mg dose group (11%) and the lowest incidence in the placebo group (5%). Four patients in the roluperidone treatment groups were discontinued due to a cardiac disorder or ECG abnormality (roluperidone 32 mg: left ventricular dysfunction and T wave inversion [both events in the same patient]); roluperidone 64 mg: electrocardiogram QT prolongation (3 patients), and none in the placebo group.

There was no notable change from baseline in weight (placebo = –0.2 ± 2.97 kg; 32 mg = 0.0 ± 3.96 kg; 64 mg = +0.1 ± 2.87 kg) or waist circumference (placebo = –1.0 ± 9.17 cm; 32 mg = –0.9 ± 7.76 cm; 64 mg = +0.8 ± 9.53 cm) in any of the 3 groups. There were no differences in the prolactin plasma variations between the 3 groups. There were no changes in vital signs, routine laboratory values, and extrapyramidal symptom ratings measured by AIMS, BARS, and SAS scores. There were no changes in suicidality expressed as S-STS scores.

**Discussion**

In this 12-week randomized, double-blind, placebo-controlled trial of symptomatically stable schizophrenia patients with moderate to severe negative symptoms, roluperidone 64 mg dose was associated with improvements in several indices of negative symptoms and social functioning. Additionally, improvement was also manifested on both experience and expression constructs of negative symptoms\(^{3} \) probably driven by roluperidone’s observed effect on motivation (avolition). These results are consistent with the results of a similarly designed roluperidone trial,\(^{20} \) which had as the primary endpoint a similar construct of PANSS negative symptoms and as secondary endpoint the Brief Negative Symptom Scale (BNSS), a measure specifically designed to assess negative symptoms of schizophrenia. Different from the previous trial in which statistical significance for the primary endpoint was reached for both 64 mg/mg and 32 mg/day\(^{20} \) this trial did not reach statistical significance on the primary endpoint. Roluperidone was well-tolerated with no adverse events that could have unmasked the drug/placebo assignment.

There are several possible reasons why two trials with almost identical patients, study designs, and comparable results may differ in terms of statistical significance. First, larger trials, which involve more study sites (61 sites in this study versus 36 in the previous study), might have increased data variability hence, reduce the likelihood to achieve statistical significance between active treatment and placebo arm.\(^{28} \) Some of the data variability can be mitigated by thorough rater training to reduce observed and reported subjective interpretations of symptoms severity.\(^{29} \) Second, a first, positive successful trial, may raise patients’ and investigators’ expectations of benefit hence, increasing the placebo effect during a second, confirmatory trial. Hence when designing a trial that follows a positive trial, the challenge is to include a sample sufficiently large to overcome the placebo effect generated by expectations yet, limit the variability associated with increasing numbers of sites. Ideally, a few well-trained and supervised sites should address this challenge.

Designs of trials targeting negative symptoms pose several challenges: (a) whether to administer the investigational drug as monotherapy or as an add-on to an antipsychotic drug; (b) what endpoint to use for the assessment of symptoms that may be sensitive to treatment effects, and (c) identifying the patient population most likely to benefit from the intervention. All 3 are challenging tasks since the presumed interaction between the pathophysiology of negative symptoms and the mechanism of action of the pharmacological intervention in question are far from elucidated.
Monotherapy vs. Add-on

Because of the prevailing practice to treat most or all schizophrenia patients continuously with antipsychotic drugs to reduce risk for exacerbation, most trials targeting specific aspects of schizophrenia such as negative symptoms or cognitive impairment employ an add-on design. However, this design introduces a potential confounder that might obscure the effect of the experimental compound. Antipsychotic drugs on one hand indirectly improve negative symptoms by reducing preoccupation with delusions and hallucinations thus enhancing social interactions, but on the other hand, interfere with dopamine-driven motivation circuits hence aggravate avolition which is a major component of the schizophrenia intrinsic negative symptoms. Therefore, by using an add-on design it is difficult to disentangle between the direct effect of the experimental drug on negative symptoms and the pseudo-effect derived from the treatment with antipsychotics that blockade the D2 receptors. To overcome this limitation it has recently been suggested that trials targeting negative symptoms should use monotherapy and placebo-controlled designs,23 which is the option taken in this trial and the previous trial.20 Furthermore, data are accumulating showing that over a third of patients do not experience exacerbation during one year of placebo administration and some might even benefit from antipsychotic drug reduction or discontinuation.30–33

Assessment Instruments

There is currently no agreement on what constitutes the best instrument to assess negative symptoms. Assessments based on raters’ observations and collateral reports have their inherent limitations29, 34 while passive digital phenotyping instruments are still under development.35 For the current trial, the NSFS and the PSP were selected as primary and key secondary endpoints as informed by the previous trial data where they appear to capture the effect of rolupereidone.

Patient Population

In designing the inclusion criteria for this trial the investigator intended to target a patient population that on one hand is sufficiently large to make the results clinically relevant and on the other hand to restrict it to patients who can maintain symptoms stability without continuous maintenance treatment with antipsychotic drugs. Historically, trials targeting negative symptoms have included patients who have relatively severe negative symptoms but do not exceed a pre-established threshold on positive symptoms. However, by defining overly stringent inclusion criteria a large proportion of schizophrenia patients would be excluded from trials, since many of the patients have substantial—albeit stable—positive symptoms, making the results less clinically relevant, and less generalizable.36 Therefore, the trial presented here did not require an upper limit on the subscore of positive symptoms. On the other hand, we tried to select a group of patients who can maintain symptoms stability without maintenance treatment with antipsychotics. These are patients who for at least 6 months immediately prior to the trial: (1) manifested moderate to severe negative symptoms, (2) manifested no substantial variation in psychotic symptoms, (3) have a low level of symptoms related to agitation, poor impulse control, hostility, suspiciousness, and uncooperativeness, (4) were not actively using illegal drugs 5) have not manifested behaviors which put the patient or those around them at risk. This patient group which constitutes over 60% of the outpatient schizophrenia population37 has already been described in the literature.38, 39, 40 Interestingly the drop-out rate from the trial due to exacerbation of positive symptoms was very low during the 12 weeks double-blind part of the trial as well as during 9 months of open-label trial (data not shown) consistent with the hypothesis that this patient population can maintain symptoms stability on Rolupereidone monotherapy.

Choice of Adjustment of Multiplicity and of Data Set

Perhaps the most challenging aspect of this trial and the conclusions that can be drawn are related to the prespecification of the truncated Hochberg method for controlling the Type I error rate at the 2-sided 0.050 alpha level within the family of primary and the key secondary hypotheses. The investigators’ choice was informed by the results of the previous trial20 where both doses of rolupereidone were statistically superior to placebo in using the same multiplicity adjustment. If a more traditional adjustment method such as the step-down approach had been selected, the study results would have shown statistical significance on both the primary endpoint and the key secondary endpoint for the 64 mg rolupereidone dose.

The quality of the data was analyzed with the help of logic checks on site, during the rating and, centrally with the help of artificial intelligence. This analysis revealed that at 1/61 participating sites, a site that recruited 17/513 patients reported implausible behavioral (schizophrenia symptoms) and physiological (blood pressure data). All 17 subjects had the same CGI-S score between Baseline and any of the visits during the 12-week study duration as well as extreme clustering of blood pressure without the expected physiologically variability within and between subjects. Of note, throughout the 12-week double-blind study duration, the site reported only 1 TEAE across all 17 subjects which is not impossible, but very unusual in double-blind placebo-controlled schizophrenia studies. The decision to exclude these 17 patients and create the equivalent of an m-ITT analysis set was taken before the database was locked and the treatment codes unblinded. Nevertheless, the results section reports both ITT and m-ITT.
Limitations

Among the limitations of this trial are the short washout period and the possibility that some of the improvement in NSFS might be attributed to the withdrawal of antipsychotics and decrease in secondary negative symptoms. However, the randomization should have mitigated such effects. Also, some of the statistically significant advantages of roluperdine are derived from posthoc analysis. Nevertheless, the advantages of the active drug versus placebo are consistent within-trial and between the two trials.

In summary, the results of this trial are consistent with the results of a previous similar trial suggesting that roluperdine might benefit negative symptoms and social functioning in schizophrenic patients with stable negative and positive symptoms. Supporting the validity of the results of this and the previous trial is the fact that roluperdine is indistinguishable from placebo by subjective or observable adverse effects, hence drug/placebo unmasking is not possible.

Because aspects of negative symptoms manifest in 19 distinct DSM-5 categories and in adolescents suspected of prodromal and spectrum schizophrenia, future trials targeting negative symptoms or aspects of negative symptoms such as avolition across DSM categories or along the research domain criteria principles will be conducted.

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