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Name of company Organon N.V. **Name of active substance** Sublingual asenapine	**Synopsis / Tabular Format** **referring to**	

Title of the clinical trial

Long-term efficacy and safety evaluation of asenapine (10-20 mg/day) in subjects with schizophrenia or schizoaffective disorder, in a multicenter trial using olanzapine (10-20 mg/day) as a control

Clinical Trial Report on Protocol 25520

Investigators

Australia

[redacted]

Belgium

[redacted]

Czech Republic

[redacted]

France

[redacted]

Germany

[redacted]

Poland

[redacted]

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[redacted]

Russian Federation

[redacted]

South-Africa

[redacted]

Spain

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Clinical trial centers

Australia

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Belgium

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Czech Republic

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France

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Germany

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Poland

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Russian Federation

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[redacted]

South-Africa

[redacted]

Spain

[redacted]

Report/publication (ref)

Not applicable.

Studied period (years)

October, 2004 to October, 2006.

Clinical phase

IIIa

Objectives

The objectives of this trial were to evaluate the long-term safety and efficacy of asenapine in those subjects who completed triall 25517 (ACTAMESA) and who were to be continued on trial medication. Olanzapine was used as active control.

Methodology

The trial was a multi-center, olanzapine-controlled, long-term safety and efficacy trial of asenapine in those subjects who completed trial 25517 and who were to be continued on trial medication. The extension remained double-blind until the blind of trial 25517 was broken. When the blind for trial 25517 was broken, treatment continued single-blind. After investigators were informed about the discontinuation of trial 25520 the trial continued in an open-label fashion.
The trial was stopped after it had been decided to terminate trial 25520 because trial 25517 had been completed and the subject treatment codes had been broken. It should be noted that all subjects had been treated for at least one year with double-blind medication prior to termination. Since long-term data from the single-blind extension period would be difficult to interpret in combination with the double-blind data set, the trial was terminated.

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Number of subjects (total and for each treatment)

In total, 527 subjects were screened at the beginning of trial 25520: asenapine 5-10 mg bid, 350 subjects and olanzapine 10-20 mg qd, 177 subjects. Of these subjects, 440 (83.5%) were treated in trial 25520: asenapine 5-10 mg bid, 290 subjects (82.9%) and olanzapine 10-20 mg qd, 150 subjects (84.7%).

Diagnosis and criteria for inclusion

To be considered for inclusion into this trial subjects were to have completed the ACTAMESA trial and were to have provided written informed consent (or verbal witnessed informed consent for illiterate subjects in South-Africa) after the scope and nature of the extension study had been explained to them. As for the ACTAMESA trial, subjects were to be excluded from further consideration if they did not fulfil the inclusion criteria, or if they either suffered from a medical condition or required concomitant treatment that would obscure trial results or would put the patient at increased risk for treatment failure or unacceptable adverse events.

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

Asenapine, 5 mg, batch numbers: [redacted] Placebo for asenapine, batch numbers: [redacted] Dosage forms were prepared as indistinguishable sublingual tablets. Both asenapine and placebo sublingual tablets were designed to disintegrate in less than 10 seconds. For oral use.

Duration of treatment

The total duration of treatment was variable per subject as the trial continued until a decision was made to stop the trial.

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

Olanzapine, 10 mg, batch numbers: [redacted] Placebo for olanzapine, batch numbers: [redacted] Dosage forms were prepared as indistinguishable capsules. For oral use.

Criteria for evaluation

Safety: Safety was evaluated by assessing the occurrence of adverse events that occurred during the double-blind treatment period up to seven days after the last dose (30 days for serious adverse events). Safety evaluation also included laboratory tests (hematology, biochemistry and urinalysis), vital signs measurements, body weight, physical examinations and 12-lead ECGs.
Extrapyramidal symptoms (EPS): EPS were assessed using the Barnes-Akathisia Rating Scale (BARS), Simpson-Angus Rating Scale (SARS) and the Abnormal Involuntary Movement Scale (AIMS).
Efficacy: The primary efficacy rating scale was the Positive and Negative Syndrome Scale (PANSS). Secondary efficacy instruments included the three PANSS subscales (Positive, Negative, General Psychopathology) and the five PANSS Marder factors (Positive symptom, Negative symptom, Disorganized thought symptom, Hostility/Excitement symptom and Anxiety/Depression symptom). Other efficacy variables included the Clinical Global Impression of Severity of Illness (CGI-S) and Improvement (CGI-I).
Other parameters: Quality of Life was measured using the Subjective Well-being under Neuroleptics (SWN) and the Short Form health survey (SF-12). Depression was measured with the Calgary Depression Scale for Schizophrenia (CDSS). The abbreviated Level of Functioning Scale (LFS) was used to capture information on aspects of social functioning and work. Hospitalization as documented by the investigator was also recorded.

Statistical methods

Safety evaluation: Adverse events reported by the investigator were coded using the Medical Dictionary for Regulatory Activities (version 9.1). The number and proportion of subjects with adverse events, fatal and non-fatal serious adverse events and adverse events that led to discontinuation were summarized for each treatment group by MedDRA system-organ class, high level group term, preferred term, maximum severity and relationship to study drug. The number and proportion of subjects with markedly abnormal laboratory changes, markedly abnormal vital sign changes and markedly abnormal ECG changes were summarized for each treatment group based on the sponsor's pre-specified criteria. Shift analyses were performed for laboratory variables. In addition, summary statistics were calculated for the laboratory variables, vital sign measurements and body weight, as well as for the ECGs and the BARS, SARS and AIMS scores for each treatment group at each visit. All data are presented for the total period (trial 25517 and 25520 combined) and the extension period (trial 25520).

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Efficacy and other parameters: Summary statistics at each time point (including the time points of trial 25517) were calculated for all efficacy (total PANSS score, PANSS subscales, PANSS Marder factors, CGI-Severity of Illness and CGI-Clinical Global Improvement) and other parameters (SWN scores, norm-based SF-12 scores, Calgary Depression Scale scores and Health economics variables).

The following definitions were used in the statistical analysis:
Baseline: the last assessment before first IP administration in trial 25517.
Endpoint 25517: the last observed value in the in-treatment period of trial 25517. For the calculation of an endpoint, data after this in-treatment period were not used.
Endpoint 25520: the last observed value in the in-treatment period of trial 25520. For the calculation of an endpoint, data after this in-treatment period were not used.

Summary

A total of 203 asenapine-treated subjects (58.0%) and 123 olanzapine-treated subjects (69.5%) completed the trial (i.e. continued in the trial until the decision was made by the sponsor to stop the trial). No differences were evident in demographics, sociodemographics, psychiatric history and other subject characteristics between asenapine and olanzapine. A total of 114 enrolled subjects (25.9%) discontinued before the decision was made to stop trial 25520. The percentage of discontinued subjects was higher in the asenapine group (30.0%) as compared with the olanzapine group (18.0%). Subjects in the asenapine group were more likely to withdraw due to AEs (10.3% in the asenapine group versus 2.0% in the olanzapine group), lack of efficacy (2.4% versus 0.7%) and other reasons (5.2% versus 2.0%). The total number of subjects who dropped out due to insufficient therapeutic effect (i.e. the combination of subjects discontinued to lack of efficacy and the subjects discontinued due to AEs related to worsening of the disease) was 10.3% and 1.3% for the asenapine group and olanzapine group, respectively.
For 63.4% of the subjects in the asenapine group and 66.0% of the subjects in the olanzapine group the most frequently taken dose was the low dose (10 mg/day) for the total period (trial 25517 and 25520 combined). For the extension period (trial 25520), the percentages were 64.1% and 66.0%, respectively. In the asenapine group, 61.7% of the subjects had their dose increased to the high dose (20 mg/day) at some point during the total period. In the olanzapine, 58.0% had their dose increased. In the extension period, 46.2% of the asenapine-treated subjects and 44.0% of the olanzapine-treated subject had their dose increased at least once. For 61.7% of the asenapine-treated subjects and 64.0% of the olanzapine-treated subjects, the final dose taken was the low dose.
Subjects treated with asenapine show more concomitant use of hypnotics, anxiolytics, antidepressants, and anticholinergics than subjects treated with olanzapine at endpoint 25517 and subsequent time points.

Safety

The percentage of subjects who experienced one or more AEs was comparable for asenapine and olanzapine in the total period (87.6% and 88.0%, respectively). For the extension period the percentage of asenapine-treated subjects who experienced at least one AE was slightly higher than that of olanzapine-treated subjects (62.1% versus 54.7%, respectively). For the total period, the percentage of subjects who experienced one or more AEs that were drug-related according to the investigator was 67.6% in the asenapine group and 63.3% in the olanzapine group. For the extension period, this was 26.9% and 22.7%, respectively. For both the total and extension period the intensity of most AEs was mild to moderate in both treatment groups.

In total, three deaths (1.0%) were reported, all in the asenapine treatment group. One subject died due to *Cardiac failure* while on treatment, one subject died four days after last IP intake due to *Arteriosclerosis* and the third subject died 16 days after last IP intake due to unknown reasons. The relationship to the study drug was assessed as 'None' or 'Unlikely' by the investigator in all cases.

In both the total and extension period, more SAEs occurred in the asenapine-treated subjects than in the olanzapine-treated subjects (asenapine: 24.5%, total period; 18.6%, extension period; olanzapine: 10.7%, total period; 8.0%, extension period). The most frequently reported HLGT of the SAEs in subjects treated with asenapine was 'Schizophrenia and other psychotic disorders' in both the total period as in the extension period (18.3% and 14.5%, respectively). For olanzapine, these percentages were 9.3% and 6.7%.

More subjects discontinued due to an (S)AE in the asenapine group compared to the olanzapine group during the extension period (10.3% versus 2.0%). The most frequently reported AE that led to discontinuation for both treatment groups belonged to the HLGT 'Schizophrenia and other psychotic disorders' (6.6% for asenapine and 0.7% for olanzapine). These AEs were considered related to worsening of the disease. One subject (0.3%) on asenapine discontinued due to suicide attempt and none in the olanzapine group.

For the extension period, the most commonly reported AEs showing notable differences were *Schizophrenia* (asenapine 15.5%, olanzapine 4.7%), *Insomnia* (10.7% versus 7.3%), *Anxiety* (5.9% versus 10.0%) and *Nasopharyngitis* (1.7% versus 6.0%). There were no notable differences between the treatment groups for any other AEs.

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Adverse events showing notable differences between treatment groups in the total period but not in the extension period were: *Akathisia* (total period: asenapine 10.7%, olanzapine 6.0% and extension period: asenapine 2.4% and olanzapine 2.0%), *Depression* (total period: 19.3% versus 15.3%, extension period: 6.9% versus 6.0%), *Headache* (total period: 15.2% versus 11.3%, extension period: 6.2% versus 6.7%) and *Somnolence* (total period: 13.8% versus 10.0%). For this last AE the incidence in the extension period was below 2.0%.

In both treatment groups body weight increase was observed in trial 25517. During trial 25520 the mean body weight did not increase further. At Week 76, the mean change from baseline in body weight (OC) was 1.6 kg for asenapine and 5.1 kg for olanzapine. At Week 100, this was 0.9 kg and 5.9 kg, respectively.
The most frequently reported body weight related AE *Weight increased* also showed a notable difference in incidence between asenapine (27.2%) and olanzapine (38.0%) during the total period, whereas this difference was not seen during the extension period (asenapine 6.6%, olanzapine 5.3%). The incidence of markedly abnormal weight gain was lower in the asenapine group than in the olanzapine group from Week 2 onwards. The incidence of markedly abnormal body weight decrease was higher in the asenapine group than in the olanzapine group from Week 16 onwards. One subject (0.7%) in the olanzapine group discontinued trial 25520 due to weight gain versus none in the asenapine group.

For both treatment groups most of the EPS-related AEs were reported during trial 25517 (total period: asenapine 20.0%, olanzapine 10.7%; extension period: asenapine 4.5%, olanzapine 3.3%). The incidence of EPS-related AEs was similar between the asenapine and olanzapine groups in the extension period. The numerically higher frequency of EPS in asenapine-treated subjects concurred with a higher frequency of concomitant intake of anticholinergics as compared to with olanzapine-treated subjects (9.4% in the asenapine group versus 1.5% in the olanzapine group at Week 76 and 6.5% versus 0% in asenapine and olanzapine respectively, at Week 100). For both treatment groups, the most frequently reported EPS-related AE was *Akathisia* of which the incidence decreased during the extension period to 2.4% for asenapine and 2.0% for olanzapine (total period: 10.7% versus 6.0%, respectively). The SARS, BARS and AIMS showed improvement during trial 25517, and this improvement was maintained during trial 25520.

No clinically relevant effects on ECG were noted with either asenapine or olanzapine at all time points (both in trial 25517 and 25520).

In general, mean changes in laboratory variables were small in magnitude and not notably different between the treatment groups in the extension period. Compared to the hematology, biochemistry and urinalysis values at endpoint 25517, the values remained the same during trial 25520 in both treatment groups. Furthermore, the incidences of markedly abnormal clinical laboratory values and the incidences of AEs related to clinical laboratory findings were low in both treatment groups.
The notable difference in markedly abnormal values of monocytes between the two treatment groups found in the total period (asenapine 5.9%, olanzapine 2.0%) was not observed in the extension period (asenapine 1.4%, olanzapine 1.3%). For leucocyte count, an increase of 4.1% was observed in the asenapine group versus 0.7% in the olanzapine group in the total period. In the extension period, the leucocyte count showed an increase of 2.2% in the asenapine group and 0.7% in the olanzapine group. This difference between treatment groups was not considered to be clinically relevant.
During the total period, notable differences in markedly abnormal values between asenapine and olanzapine were found for ALAT (asenapine 5.5%, olanzapine 14.8%), ASAT (asenapine 1.4%, olanzapine 4.0%) and bilirubin (asenapine 0.3%, olanzapine 2.7%). However, these differences were not found in the extension period for ASAT (asenapine 0.4%, olanzapine 0.7%) or they were less pronounced than in the total period (ALAT: asenapine 2.9%, olanzapine 4.0%; bilirubin: asenapine 0.0%, olanzapine 2.0%).

The percentage of subjects having one or more markedly abnormal changes in vital signs was comparable at all time points (both in trial 25517 and 25520) for both treatment groups with consistently low percentages. The incidence of vital signs-related AEs was also low for both treatment groups.

Efficacy
Both treatment groups had similar mean total PANSS scores at baseline (asenapine 90.6 points, olanzapine 90.5 points) and showed comparable improvement during the first 52 weeks. This improvement was maintained during trial 25520 as shown by mean changes from baseline (OC) at Week 76 of -36.7 for asenapine and -36.6 for olanzapine and a maintained effect with a mean change from endpoint 25517 of 0.6 points for asenapine and -1.1 for olanzapine. At Week 124, the mean change from baseline in total PANSS score was -40.8 for asenapine and -39.5 for olanzapine and mean changes from endpoint 25517 of 1.2 points for asenapine and -1.5 points for olanzapine.
Reduction rates of ≥30% in the total PANSS score were comparable for both treatment groups throughout the course of the trial: 88.9% of the asenapine-treated subjects and 89.0% of the olanzapine-treated subjects had a reduction of ≥30% as compared to baseline (OC) in the total PANSS score at Week 76. At Week 124 these percentages were 93.9% and 92.9%, respectively.
The analysis results for the PANSS subscales and the PANSS Marder factors were consistent with those of the total PANSS score.

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Compared to the CGI-Severity of Illness score at endpoint 25517, the score remained the same during trial 25520 for both treatment groups. Both at Week 76 and Week 124, the mean change from endpoint 25517 in CGI-Severity of Illness score (OC) was 0.0 for asenapine. For olanzapine the mean change from endpoint 25517 in CGI-Severity of Illness score was -0.1 and -0.0 at Week 76 and 124 respectively.
As compared to endpoint 25517, no changes were observed in the CGI-Clinical Global Improvement score during trial 25520 in both treatment groups. The mean CGI-Clinical Global Improvement score (OC) in the asenapine group was 1.7 both at Week 76 and Week 124. In the olanzapine treatment group, the mean CGI-Clinical Global Improvement score was 1.7 at Week 76 and 1.5 at Week 124. The numbers of subjects falling into the category 'At least much improvement' and 'At least minimal improvement' were comparable between the two treatment groups.

Other variables
Both treatment groups had similar mean SWN total scores at baseline (asenapine 75.6 points, olanzapine 75.1 points) and showed comparable improvement in the first 52 weeks. This improvement (OC) was maintained during trial 25520. The results of the SWN subscales were comparable to the results of the SWN total score.

At baseline, the mean norm-based SF-12 PCS and MCS scores were similar for both treatment groups, i.e. 44.2 and 38.1 in the asenapine treatment group and 44.8 and 37.0 in the olanzapine treatment group, respectively. Both for asenapine and olanzapine the PCS and MCS scores increased during treatment, indicating better health. Both treatment groups showed comparable improvement in the first 52 weeks, and this was maintained during trial 25520 (OC).

At baseline, the mean CDSS score was 3.7 in the asenapine treatment group and 4.1 in the olanzapine treatment group. For both treatment groups the CDSS score decreased, trending towards improvement (OC).

Modest gains were found in trial 25517 for both treatment groups on the abbreviated Level of Functioning scale with respect to the number of subjects reporting being continuously employed, in the perceived level of competence at work, and in both the frequency and quality of relationships. This improvement was maintained during trial 25520 (OC).

The percentage of subjects who entered trial 25520 as outpatients and were hospitalized at least once during the in-treatment period was higher in the asenapine group (15.0%) compared with in the olanzapine group (10.2%). The mean total number of days of hospitalization during trial 25520 was lower for asenapine (51.1 days) compared with olanzapine (82.7 days).

In order to assess the potential impact on data and conclusions of trial 25520, introduced by the inclusion of possible unreliable data, additional analyses were conducted excluding the data form the subjects randomized at center [redacted] Comparing the results of the analyses with and without the data collected at center [redacted] allow the same interpretation regarding the effects of trial medication on primary efficacy and safety parameters.

Conclusions

Both asenapine and olanzapine were safe and well tolerated in this long-term extension trial in which subjects were treated for a total period up to two and a half years. During trial 25520 AEs related to psychiatric disorders were more frequently observed in subjects treated with asenapine, whereas increase of liver enzymes was more frequently observed in subjects treated with olanzapine. In the asenapine group three deaths were reported, which were all assessed by the investigator as not related to asenapine. In the asenapine group higher incidences of (S)AEs and discontinuations due to (S)AEs were observed compared to the olanzapine group. Apart from these findings the safety profiles of both compounds were comparable.

Asenapine showed long-term efficacy as reflected by the improvement of all efficacy parameters during trial 25517 and maintained effectiveness in trial 25520. Olanzapine also showed improvement of all efficacy parameters in trial 25517, and this was maintained during trial 25520.

Improvements were observed with asenapine with respect to the subject's personal view of their well-being and health during trial 25517 and these effects were maintained during trial 25520. Olanzapine also showed improvement in the subject's personal view of their well-being and health during trial 25517, and this was maintained during trial 25520.

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