



Clinical trial results: Add-on spironolactone for the treatment of schizophrenia.

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2014-001968-35 |
| Trial protocol | DE |
| Global end of trial date | 11 August 2020 |

Results information

| | |
|-----------------------------------|---|
| Result version number | v1 (current) |
| This version publication date | 22 February 2024 |
| First version publication date | 02 February 2023 |
| Summary attachment (see zip file) | CSR-SPIRO (Ergebnisbericht_SPIROTREAT_20210815_final.pdf) |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | SPIROTREAT |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Klinikum der Universität München, vertreten durch den Vorstand |
| Sponsor organisation address | Marchioninistraße 15, München , Germany, 81377 |
| Public contact | PD Dr. rer nat. Peter Zill , Klinikum der Universität München - AöR vertreten durch den Vorstand des Bereichs Humanmedizin, 0049 89 4400 52741, Peter.Zill@med.uni-muenchen.de |
| Scientific contact | Prof. Dr. med. Alkomiet Hasan, Klinikum der Universität München - AöR vertreten durch den Vorstand des Bereichs Humanmedizin, 0049 821 4803 1001, alkomiet.hasan@med.uni-augsburg.de |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 15 August 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 11 August 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 11 August 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Primary endpoint: Improvement of working memory in n-back after 3 weeks.

Primary Objective

- To evaluate the improvement of working memory according to the n-Back performance (2-back level, relative hit rate) before and after the intervention period (V1 vs V10)

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles of Good Clinical Practice (GCP).

Each participating subject signed informed consent form and they could withdraw from the study at any time without any disadvantages and without giving reasons for this decision.

The study was regularly monitored by the Sponsor and all investigators connected to the study were GCP trained. The competent Ethics Committee and the German competent authorities approved the clinical trial.

Background therapy:

Ongoing stable antipsychotic treatment (standard of care) for at least one week.

Evidence for comparator:

n.a.

| | |
|---|---|
| Actual start date of recruitment | 08 July 2015 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy, Ethical reason, Scientific research |
| Long term follow-up duration | 2 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Germany: 84 |
| Worldwide total number of subjects | 84 |
| EEA total number of subjects | 84 |

Notes:

Subjects enrolled per age group

| | |
|--|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 | 0 |

| | |
|--|----|
| wk | |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 84 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The placebo-controlled, double blind and three-arm clinical trial was conducted in Germany at three sites. Between July 2015 and May 2020 all patients were randomised in one of the three arms. A randomization did not take place until a final check confirms that all inclusion or no exclusion criteria applied.

Pre-assignment

Screening details:

Pre-screening processes were in place, a total of 162 patients were scheduled for screening. The pre-screening and the screening phases took place in the two weeks prior to randomization. Suitable patients were approached by the investigators regarding participation in the study. No study-specific procedures took place in the pre-screening phase.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Monitor, Data analyst, Carer, Subject |

Blinding implementation details:

In every group, participants receive two identical capsules per day to maintain the blind.

Arms

| | |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Add-on 100 |

Arm description:

Add-on 100 mg spironolactone (3 weeks of double-blind intervention phase)

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Spironolactone |
| Investigational medicinal product code | C03DA01 |
| Other name | Spironolacton HEXAL, SPIRONOLACTONE, SUB10631MIG |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Group I: Spironolactone 100 mg

At day (D) 1 capsule with 50 mg spironolactone and 1 capsule with placebo, from D2 to D21 two capsules with 50 mg spironolactone (100 mg in total) per day.

| | |
|------------------|------------|
| Arm title | Add-on 200 |
|------------------|------------|

Arm description:

Add-on 200 mg spironolactone (3 weeks of double-blind intervention phase)

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Spironolactone |
| Investigational medicinal product code | C03DA01 |
| Other name | Spironolacton HEXAL, SPIRONOLACTONE, SUB10631MIG |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Group II: Spironolactone 200 mg

At D1 one capsule with 50 mg spironolactone and one capsule with placebo, at D2 two capsules with 50 mg spironolactone (100 mg in total), at D3 one capsule with 50 mg spironolactone and one capsule with 100 mg spironolactone (150 mg in total) and from D4 to D21 two capsules with 100 mg spironolactone per day (200 mg in total).

| | |
|---|---------------|
| Arm title | Add-on |
| Arm description: | |
| Add-on placebo (3 weeks of double-blind intervention phase) | |
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | Placebo |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Group III: Placebo

In group III (placebo), two capsules with placebo from D 1 to D 21.

| Number of subjects in period 1 | Add-on 100 | Add-on 200 | Add-on |
|---------------------------------------|------------|------------|--------|
| Started | 30 | 28 | 26 |
| Completed | 29 | 25 | 19 |
| Not completed | 1 | 3 | 7 |
| Not randomized, no study medication | - | - | 1 |
| Consent withdrawn by subject | - | 2 | 2 |
| Other reasons | - | 1 | 1 |
| Lost to follow-up | - | - | 1 |
| Protocol deviation | 1 | - | 2 |

Baseline characteristics

Reporting groups

| | |
|---|------------|
| Reporting group title | Add-on 100 |
| Reporting group description: | |
| Add-on 100 mg spironolactone (3 weeks of double-blind intervention phase) | |
| Reporting group title | Add-on 200 |
| Reporting group description: | |
| Add-on 200 mg spironolactone (3 weeks of double-blind intervention phase) | |
| Reporting group title | Add-on |
| Reporting group description: | |
| Add-on placebo (3 weeks of double-blind intervention phase) | |

| Reporting group values | Add-on 100 | Add-on 200 | Add-on |
|---|------------|------------|----------|
| Number of subjects | 30 | 28 | 26 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 30 | 28 | 26 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| median | 36.5 | 35.5 | 35.5 |
| full range (min-max) | 20 to 62 | 19 to 57 | 18 to 58 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 9 | 9 | 5 |
| Male | 21 | 19 | 21 |
| Course of the disease | | | |
| Course of the disease (no. continuous / no. episodic) | | | |
| Units: Subjects | | | |
| No. continuous | 14 | 7 | 9 |
| No. episodic | 16 | 21 | 17 |
| Age at first hospitalisation | | | |
| Age of first indication-related hospital stay | | | |
| Units: Years | | | |
| median | 25 | 24 | 26 |
| full range (min-max) | 17 to 56 | 17 to 44 | 16 to 48 |
| Duration of illness | | | |
| Units: months | | | |
| median | 72 | 114 | 114 |

| | | | |
|---|--------------|--------------|--------------|
| full range (min-max) | 7 to 432 | 8 to 324 | 11 to 456 |
| Number of hospitalizations | | | |
| Units: Number | | | |
| median | 3 | 2 | 3 |
| full range (min-max) | 1 to 30 | 1 to 20 | 3 to 30 |
| Duration of school education | | | |
| Units: years | | | |
| median | 10 | 12 | 11 |
| full range (min-max) | 8 to 15 | 9 to 17 | 8 to 17 |
| Duration school and Vocational Training | | | |
| Units: years | | | |
| median | 13 | 15 | 13 |
| full range (min-max) | 8 to 23 | 9 to 26 | 9 to 23 |
| Blood pressure sys | | | |
| Blood pressure systolisch at baseline | | | |
| Units: mmHg | | | |
| median | 120.0 | 124.5 | 125.5 |
| full range (min-max) | 101 to 164 | 103 to 160 | 96 to 145 |
| Blood pressure dia | | | |
| Blood pressure diastolisch at baseline | | | |
| Units: mmHg | | | |
| median | 79 | 83 | 82 |
| full range (min-max) | 62 to 103 | 62 to 102 | 57 to 96 |
| Heart Frequence | | | |
| Units: bpm | | | |
| median | 80,5 | 83 | 85,5 |
| full range (min-max) | 61 to 101 | 55 to 120 | 64 to 105 |
| Weight | | | |
| Units: kg | | | |
| median | 79.1 | 87.45 | 88 |
| full range (min-max) | 54 to 114 | 50,3 to 116 | 59 to 157 |
| Height | | | |
| Units: cm | | | |
| median | 172 | 178.5 | 179 |
| full range (min-max) | 153 to 193 | 162 to 191 | 158 to 193 |
| Body-Mass-Index | | | |
| BMI at baseline | | | |
| Units: BMI | | | |
| median | 26.5 | 26.4 | 28.1 |
| full range (min-max) | 17.9 to 40.4 | 18.4 to 38.6 | 23.2 to 44.1 |
| PANSS pos | | | |
| PANSS positive score baseline | | | |
| Units: Score | | | |
| median | 11.5 | 12 | 12 |
| full range (min-max) | 7 to 19 | 7 to 20 | 7 to 20 |
| PANSS neg | | | |
| PANSS negative score baseline | | | |
| Units: Score | | | |
| median | 14.5 | 13 | 15 |
| full range (min-max) | 7 to 24 | 8 to 25 | 8 to 22 |
| PANSS general | | | |
| PANSS general score baseline | | | |

| | | | |
|----------------------------|----------|----------|----------|
| Units: Score | | | |
| median | 26.5 | 24 | 27 |
| full range (min-max) | 18 to 43 | 16 to 35 | 16 to 38 |
| PANSS total | | | |
| PANSS total score baseline | | | |
| Units: Score | | | |
| median | 50.5 | 51.5 | 53.5 |
| full range (min-max) | 36 to 72 | 32 to 75 | 33 to 71 |

| | | | |
|---|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 84 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | | |
| Newborns (0-27 days) | 0 | | |
| Infants and toddlers (28 days-23 months) | 0 | | |
| Children (2-11 years) | 0 | | |
| Adolescents (12-17 years) | 0 | | |
| Adults (18-64 years) | 84 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |
| Age continuous | | | |
| Units: years | | | |
| median | | | |
| full range (min-max) | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 23 | | |
| Male | 61 | | |
| Course of the disease | | | |
| Course of the disease (no. continuous / no. episodic) | | | |
| Units: Subjects | | | |
| No. continous | 30 | | |
| No. episodic | 54 | | |
| Age at first hospitalisation | | | |
| Age of first indication-related hospital stay | | | |
| Units: Years | | | |
| median | | | |
| full range (min-max) | - | | |
| Duration of illness | | | |
| Units: months | | | |
| median | | | |
| full range (min-max) | - | | |
| Number of hospitalizations | | | |
| Units: Number | | | |
| median | | | |
| full range (min-max) | - | | |
| Duration of school education | | | |
| Units: years | | | |

| | | | |
|---|---|--|--|
| median | | | |
| full range (min-max) | - | | |
| Duration school and Vocational Training | | | |
| Units: years | | | |
| median | | | |
| full range (min-max) | - | | |
| Blood pressure sys | | | |
| Blood pressure systolisch at baseline | | | |
| Units: mmHg | | | |
| median | | | |
| full range (min-max) | - | | |
| Blood pressure dia | | | |
| Blood pressure diastolisch at baseline | | | |
| Units: mmHg | | | |
| median | | | |
| full range (min-max) | - | | |
| Heart Frequency | | | |
| Units: bpm | | | |
| median | | | |
| full range (min-max) | - | | |
| Weight | | | |
| Units: kg | | | |
| median | | | |
| full range (min-max) | - | | |
| Height | | | |
| Units: cm | | | |
| median | | | |
| full range (min-max) | - | | |
| Body-Mass-Index | | | |
| BMI at baseline | | | |
| Units: BMI | | | |
| median | | | |
| full range (min-max) | - | | |
| PANSS pos | | | |
| PANSS positive score baseline | | | |
| Units: Score | | | |
| median | | | |
| full range (min-max) | - | | |
| PANSS neg | | | |
| PANSS negative score baseline | | | |
| Units: Score | | | |
| median | | | |
| full range (min-max) | - | | |
| PANSS general | | | |
| PANSS general score baseline | | | |
| Units: Score | | | |
| median | | | |
| full range (min-max) | - | | |
| PANSS total | | | |
| PANSS total score baseline | | | |
| Units: Score | | | |
| median | | | |

| | | | |
|----------------------|---|--|--|
| full range (min-max) | - | | |
|----------------------|---|--|--|

Subject analysis sets

| | |
|---|--------------------|
| Subject analysis set title | IIT |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| All randomized patients who received at least one dose of IMP | |
| Subject analysis set title | PP |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| All randomized patients who received at least one dose of IMP | |

| Reporting group values | IIT | PP | |
|---|----------|----------|--|
| Number of subjects | 84 | 73 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 84 | 73 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| median | 36 | 36 | |
| full range (min-max) | 18 to 62 | 18 to 62 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 23 | 19 | |
| Male | 61 | 54 | |
| Course of the disease | | | |
| Course of the disease (no. continuous / no. episodic) | | | |
| Units: Subjects | | | |
| No. continuous | 29 | 23 | |
| No. episodic | 54 | 49 | |
| Age at first hospitalisation | | | |
| Age of first indication-related hospital stay | | | |
| Units: Years | | | |
| median | 25 | 27 | |
| full range (min-max) | 17 to 56 | 16 to 56 | |
| Duration of illness | | | |
| Units: months | | | |
| median | 100 | 96 | |
| full range (min-max) | 7 to 456 | 7 to 456 | |

| | | | |
|---|----------------------|----------------------|--|
| Number of hospitalizations Units: Number median full range (min-max) | 2,67 1 to 30 | 2,8 1 to 30 | |
| Duration of school education Units: years median full range (min-max) | 11 8 to 17 | 11 8 to 17 | |
| Duration school and Vocational Training Units: years median full range (min-max) | 13,66 8 to 26 | 13,5 8 to 26 | |
| Blood pressure sys | | | |
| Blood pressure systolisch at baseline | | | |
| Units: mmHg median full range (min-max) | 124 101 to 164 | 124 103 to 164 | |
| Blood pressure dia | | | |
| Blood pressure diastolisch at baseline | | | |
| Units: mmHg median full range (min-max) | 81,3 57 to 103 | 81,2 62 to 103 | |
| Heart Frequence Units: bpm median full range (min-max) | 83 55 to 120 | 82 55 to 120 | |
| Weight Units: kg median full range (min-max) | 84.9 50.3 to 157 | 85 50.3 to 157 | |
| Height Units: cm median full range (min-max) | 176 153 to 193 | 175.5 157 to 193 | |
| Body-Mass-Index | | | |
| BMI at baseline | | | |
| Units: BMI median full range (min-max) | 27.0 17.9 to 40.4 | 27.5 17.9 to 44.1 | |
| PANSS pos | | | |
| PANSS positive score baseline | | | |
| Units: Score median full range (min-max) | 12 7 to 20 | 12 7 to 20 | |
| PANSS neg | | | |
| PANSS negative score baseline | | | |
| Units: Score median full range (min-max) | 15 7 to 25 | 15 7 to 25 | |
| PANSS general | | | |
| PANSS general score baseline | | | |
| Units: Score | | | |

| | | | |
|----------------------------|----------|----------|--|
| median | 26 | 26 | |
| full range (min-max) | 16 to 43 | 16 to 43 | |
| PANSS total | | | |
| PANSS total score baseline | | | |
| Units: Score | | | |
| median | 52 | 52 | |
| full range (min-max) | 32 to 75 | 32 to 75 | |

End points

End points reporting groups

| | |
|---|--------------------|
| Reporting group title | Add-on 100 |
| Reporting group description: Add-on 100 mg spironolactone (3 weeks of double-blind intervention phase) | |
| Reporting group title | Add-on 200 |
| Reporting group description: Add-on 200 mg spironolactone (3 weeks of double-blind intervention phase) | |
| Reporting group title | Add-on |
| Reporting group description: Add-on placebo (3 weeks of double-blind intervention phase) | |
| Subject analysis set title | IIT |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All randomized patients who received at least one dose of IMP | |
| Subject analysis set title | PP |
| Subject analysis set type | Per protocol |
| Subject analysis set description: All randomized patients who received at least one dose of IMP | |

Primary: Change in 2-back relative hits of n-back test on ITT

| | |
|---|--|
| End point title | Change in 2-back relative hits of n-back test on ITT |
| End point description: Analyzed with a linear mixed model with group as a fixed factor and time as a within-subject factor. The statistic analyzed for significance was the interaction between time of measurement and group. | |
| End point type | Primary |
| End point timeframe: Change between V1 and V10 | |

| End point values | Add-on 100 | Add-on 200 | Add-on | |
|--------------------------------------|-----------------|------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 30 | 28 | 26 | |
| Units: Points | | | | |
| arithmetic mean (standard deviation) | -7.96 (± 13.23) | -10.39 (± 22.86) | -2.98 (± 15.47) | |

Statistical analyses

| | |
|--|------------------------------------|
| Statistical analysis title | Interaction between time and group |
| Statistical analysis description: Analyzed with a linear mixed model with group as a fixed factor and time as a within-subject factor. The statistic analyzed for significance was the interaction between time of measurement and group. | |
| Comparison groups | Add-on 100 v Add-on 200 v Add-on |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.548 |
| Method | Mixed models analysis |

Secondary: Change in 2-back relative hits of n-back test on PP

| | |
|---|---|
| End point title | Change in 2-back relative hits of n-back test on PP |
| End point description: Analyzed with a linear mixed model with group as a fixed factor and time as a within-subject factor. The statistic analyzed for significance was the interaction between time of measurement and group. | |
| End point type | Secondary |
| End point timeframe: Change between V1 and V10 | |

| End point values | Add-on 100 | Add-on 200 | Add-on | |
|--------------------------------------|-------------------|-------------------|-------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 26 ^[1] | 26 ^[2] | 21 ^[3] | |
| Units: Points | | | | |
| arithmetic mean (standard deviation) | -6.84 (± 12.98) | -10.33 (± 23.7) | -3.4 (± 16.74) | |

Notes:

[1] - Per protocol set

[2] - Per protocol set

[3] - Per protocol set

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Interaction between time and group on PP |
| Statistical analysis description: Analyzed with a linear mixed model with group as a fixed factor and time as a within-subject factor on the per protocol set. The statistic analyzed for significance was the interaction between time of measurement and group. | |
| Comparison groups | Add-on 100 v Add-on 200 v Add-on |
| Number of subjects included in analysis | 73 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.869 |
| Method | Mixed models analysis |

Secondary: Change in 1-back relative hits of n-back test on ITT

| | |
|---|--|
| End point title | Change in 1-back relative hits of n-back test on ITT |
| End point description: Analyzed with a linear mixed model with group as a fixed factor and time as a within-subject factor. The statistic analyzed for significance was the interaction between time of measurement and group. | |

| | |
|---------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Change between V1 and V10 | |

| End point values | Add-on 100 | Add-on 200 | Add-on | |
|--------------------------------------|----------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 30 | 28 | 26 | |
| Units: points | | | | |
| arithmetic mean (standard deviation) | -6.41 (\pm 17.07) | -8.93 (\pm 24.87) | -5.68 (\pm 15.76) | |

Statistical analyses

| | |
|---|------------------------------------|
| Statistical analysis title | Interaction between time and group |
| Statistical analysis description: | |
| Analyzed with a linear mixed model with group as a fixed factor and time as a within-subject factor. The statistic analyzed for significance was the interaction between time of measurement and group. | |
| Comparison groups | Add-on 100 v Add-on 200 v Add-on |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.586 |
| Method | Mixed models analysis |

Secondary: Change in 0-back relative hits of n-back test on ITT

| | |
|---|--|
| End point title | Change in 0-back relative hits of n-back test on ITT |
| End point description: | |
| Analyzed with a linear mixed model with group as a fixed factor and time as a within-subject factor. The statistic analyzed for significance was the interaction between time of measurement and group. | |
| End point type | Secondary |
| End point timeframe: | |
| Change between V1 and V10 | |

| End point values | Add-on 100 | Add-on 200 | Add-on | |
|--------------------------------------|---------------------|---------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 30 | 28 | 26 | |
| Units: points | | | | |
| arithmetic mean (standard deviation) | -4.64 (\pm 16.1) | 1.23 (\pm 13.55) | -4.65 (\pm 16.33) | |

Statistical analyses

| | |
|--|------------------------------------|
| Statistical analysis title | Interaction between time and group |
| Statistical analysis description: Analyzed with a linear mixed model with group as a fixed factor and time as a within-subject factor. The statistic analyzed for significance was the interaction between time of measurement and group. | |
| Comparison groups | Add-on 100 v Add-on 200 v Add-on |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.967 |
| Method | Mixed models analysis |

Secondary: VLMT 5th trial

| | |
|---|----------------|
| End point title | VLMT 5th trial |
| End point description: | |
| End point type | Secondary |
| End point timeframe: Change between V1 and V10 | |

| | | | | |
|--------------------------------------|-----------------|-----------------|-----------------|--|
| End point values | Add-on 100 | Add-on 200 | Add-on | |
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 30 | 28 | 26 | |
| Units: points | | | | |
| arithmetic mean (standard deviation) | -0.17 (± 1.46) | 0.3 (± 1.92) | -0.38 (± 2.33) | |

Statistical analyses

| | |
|--|------------------------------------|
| Statistical analysis title | Interaction between time and group |
| Statistical analysis description: Analyzed with a linear mixed model with group as a fixed factor and time as a within-subject factor. The statistic analyzed for significance was the interaction between time of measurement and group. | |
| Comparison groups | Add-on 100 v Add-on 200 v Add-on |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.368 |
| Method | Mixed models analysis |

Secondary: VLMT 7th trial

| | |
|---------------------------|----------------|
| End point title | VLMT 7th trial |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Change between V1 and V10 | |

| End point values | Add-on 100 | Add-on 200 | Add-on | |
|--------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 30 | 28 | 26 | |
| Units: points | | | | |
| arithmetic mean (standard deviation) | 0.1 (± 2.63) | 0.27 (± 2.63) | -0.1 (± 2.7) | |

Statistical analyses

| | |
|---|------------------------------------|
| Statistical analysis title | Interaction between time and group |
| Statistical analysis description: | |
| Analyzed with a linear mixed model with group as a fixed factor and time as a within-subject factor. The statistic analyzed for significance was the interaction between time of measurement and group. | |
| Comparison groups | Add-on 100 v Add-on 200 v Add-on |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.687 |
| Method | Mixed models analysis |

Secondary: VLMT recognition V1

| | |
|------------------------|---------------------|
| End point title | VLMT recognition V1 |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Measured at Visit 1 | |

| End point values | Add-on 100 | Add-on 200 | Add-on | |
|--------------------------------------|-----------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 30 | 28 | 25 | |
| Units: points | | | | |
| arithmetic mean (standard deviation) | 37.93 (\pm 12.000) | 12.39 (\pm 3.337) | 10.68 (\pm 4.394) | |

Statistical analyses

| Statistical analysis title | VLMT recognition at V1 |
|--|----------------------------------|
| Statistical analysis description: Kruskal-Wallis Test | |
| Comparison groups | Add-on 100 v Add-on 200 v Add-on |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.173 |
| Method | Kruskal-wallis |

Secondary: VLMT recognition V10

| End point title | VLMT recognition V10 |
|---|----------------------|
| End point description: | |
| End point type | Secondary |
| End point timeframe: Measured at Visit 10. | |

| End point values | Add-on 100 | Add-on 200 | Add-on | |
|--------------------------------------|-----------------------|----------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 29 | 27 | 21 | |
| Units: points | | | | |
| arithmetic mean (standard deviation) | 28.38 (\pm 10.304) | 10.63 (\pm 5.443) | 9.86 (\pm 5.053) | |

Statistical analyses

| | |
|--|----------------------------------|
| Statistical analysis title | VLMT recognition at V10 |
| Statistical analysis description: Kruskal-Wallis Test | |
| Comparison groups | Add-on 100 v Add-on 200 v Add-on |
| Number of subjects included in analysis | 77 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.627 |
| Method | Kruskal-wallis |

Secondary: TMT A

| | |
|---|-----------|
| End point title | TMT A |
| End point description: | |
| End point type | Secondary |
| End point timeframe: Change between V1 and V10 | |

| End point values | Add-on 100 | Add-on 200 | Add-on | |
|--------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 30 | 28 | 26 | |
| Units: second | | | | |
| arithmetic mean (standard deviation) | 6.6 (± 10.12) | 6.04 (± 10.96) | 2.77 (± 8.8) | |

Statistical analyses

| | |
|--|------------------------------------|
| Statistical analysis title | Interaction between time and group |
| Statistical analysis description: Analyzed with a linear mixed model with group as a fixed factor and time as a within-subject factor. The statistic analyzed for significance was the interaction between time of measurement and group. | |
| Comparison groups | Add-on 100 v Add-on 200 v Add-on |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.443 |
| Method | Mixed models analysis |

Secondary: TMT B

| | |
|------------------------|-------|
| End point title | TMT B |
| End point description: | |

| | |
|---------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Change between V1 and V10 | |

| End point values | Add-on 100 | Add-on 200 | Add-on | |
|--------------------------------------|--------------------|----------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 30 | 28 | 26 | |
| Units: second | | | | |
| arithmetic mean (standard deviation) | 6.3 (\pm 42.56) | 11.19 (\pm 30.01) | 4.45 (\pm 32.57) | |

Statistical analyses

| | |
|---|------------------------------------|
| Statistical analysis title | Interaction between time and group |
| Statistical analysis description: | |
| Analyzed with a linear mixed model with group as a fixed factor and time as a within-subject factor. The statistic analyzed for significance was the interaction between time of measurement and group. | |
| Comparison groups | Add-on 100 v Add-on 200 v Add-on |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.378 |
| Method | Mixed models analysis |

Secondary: TMT B-A

| | |
|---------------------------|-----------|
| End point title | TMT B-A |
| End point description: | |
| | |
| End point type | Secondary |
| End point timeframe: | |
| Change between V1 and V10 | |

| End point values | Add-on 100 | Add-on 200 | Add-on | |
|--------------------------------------|---------------------|---------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 30 | 28 | 26 | |
| Units: second | | | | |
| arithmetic mean (standard deviation) | -0.3 (\pm 45.62) | 5.15 (\pm 28.33) | 1.68 (\pm 30.96) | |

Statistical analyses

| | |
|--|------------------------------------|
| Statistical analysis title | Interaction between time and group |
| Statistical analysis description: Analyzed with a linear mixed model with group as a fixed factor and time as a within-subject factor. The statistic analyzed for significance was the interaction between time of measurement and group. | |
| Comparison groups | Add-on 100 v Add-on 200 v Add-on |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.191 |
| Method | Mixed models analysis |

Secondary: d2 total signs

| | |
|---|----------------|
| End point title | d2 total signs |
| End point description: | |
| End point type | Secondary |
| End point timeframe: Change between V1 and V10 | |

| | | | | |
|--------------------------------------|-----------------------|-----------------------|-----------------------|--|
| End point values | Add-on 100 | Add-on 200 | Add-on | |
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 30 | 28 | 26 | |
| Units: points | | | | |
| arithmetic mean (standard deviation) | -14.36 (\pm 43.57) | -29.22 (\pm 39.93) | -33.95 (\pm 50.83) | |

Statistical analyses

| | |
|--|------------------------------------|
| Statistical analysis title | Interaction between time and group |
| Statistical analysis description: Analyzed with a linear mixed model with group as a fixed factor and time as a within-subject factor. The statistic analyzed for significance was the interaction between time of measurement and group. | |
| Comparison groups | Add-on 100 v Add-on 200 v Add-on |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.174 |
| Method | Mixed models analysis |

Secondary: d2 failures

| | |
|---------------------------|-------------|
| End point title | d2 failures |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Change between V1 and V10 | |

| End point values | Add-on 100 | Add-on 200 | Add-on | |
|--------------------------------------|---------------------|---------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 30 | 28 | 26 | |
| Units: points | | | | |
| arithmetic mean (standard deviation) | 5.11 (\pm 10.92) | 4.52 (\pm 15.55) | 2.38 (\pm 18.47) | |

Statistical analyses

| | |
|---|------------------------------------|
| Statistical analysis title | Interaction between time and group |
| Statistical analysis description: | |
| Analyzed with a linear mixed model with group as a fixed factor and time as a within-subject factor. The statistic analyzed for significance was the interaction between time of measurement and group. | |
| Comparison groups | Add-on 100 v Add-on 200 v Add-on |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.969 |
| Method | Mixed models analysis |

Secondary: d2 concentration score

| | |
|---------------------------|------------------------|
| End point title | d2 concentration score |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Change between V1 and V10 | |

| End point values | Add-on 100 | Add-on 200 | Add-on | |
|--------------------------------------|-----------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 30 | 28 | 26 | |
| Units: points | | | | |
| arithmetic mean (standard deviation) | -12.57 (\pm 15.94) | -18.52 (\pm 16.1) | -6.86 (\pm 64.17) | |

Statistical analyses

| | |
|--|------------------------------------|
| Statistical analysis title | Interaction between time and group |
| Statistical analysis description: Analyzed with a linear mixed model with group as a fixed factor and time as a within-subject factor. The statistic analyzed for significance was the interaction between time of measurement and group. | |
| Comparison groups | Add-on 100 v Add-on 200 v Add-on |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.649 |
| Method | Mixed models analysis |

Secondary: GAF

| | |
|---|-----------|
| End point title | GAF |
| End point description: | |
| End point type | Secondary |
| End point timeframe: Change between V1 and V10 | |

| End point values | Add-on 100 | Add-on 200 | Add-on | |
|--------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 30 | 28 | 26 | |
| Units: points | | | | |
| arithmetic mean (standard deviation) | -6.7 (± 7.42) | -1.52 (± 5.6) | -2.23 (± 7.26) | |

Statistical analyses

| | |
|--|------------------------------------|
| Statistical analysis title | Interaction between time and group |
| Statistical analysis description: Analyzed with a linear mixed model with group as a fixed factor and time as a within-subject factor. The statistic analyzed for significance was the interaction between time of measurement and group. | |
| Comparison groups | Add-on 100 v Add-on 200 v Add-on |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.005 |
| Method | Mixed models analysis |

Secondary: CDSS at V1

| | |
|------------------------|------------|
| End point title | CDSS at V1 |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Measured at Visit 1 | |

| End point values | Add-on 100 | Add-on 200 | Add-on | |
|--------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 28 | 28 | 26 | |
| Units: points | | | | |
| arithmetic mean (standard deviation) | 3.82 (± 3.300) | 2.07 (± 3.066) | 2.81 (± 2.191) | |

Statistical analyses

| | |
|---|----------------------------------|
| Statistical analysis title | CDSS at V1 |
| Statistical analysis description: | |
| Kruskal-Wallis test | |
| Comparison groups | Add-on 100 v Add-on 200 v Add-on |
| Number of subjects included in analysis | 82 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.024 |
| Method | Kruskal-wallis |

Secondary: SDSS at V10

| | |
|------------------------|-------------|
| End point title | SDSS at V10 |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Measured at Visit 10 | |

| End point values | Add-on 100 | Add-on 200 | Add-on | |
|--------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 30 | 27 | 22 | |
| Units: points | | | | |
| arithmetic mean (standard deviation) | 3.10 (± 2.869) | 2.15 (± 2.797) | 3.68 (± 4.674) | |

Statistical analyses

| Statistical analysis title | CDSS at V10 |
|---|----------------------------------|
| Statistical analysis description: | |
| Kruskal-Wallis test | |
| Comparison groups | Add-on 100 v Add-on 200 v Add-on |
| Number of subjects included in analysis | 79 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.305 |
| Method | Kruskal-wallis |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During the follow-up period (starts after V11), hospitalization to a psychiatric hospital due to schizophrenia was a priori defined not to be considered a SAE.

Adverse event reporting additional description:

Adverse events (AE), severe adverse events (SAE) and Suspected Unexpected Serious Adverse Reactions (SUSAR) were to be documented following established definitions and legal requirements. The intensity of AEs was defined according to the Common Terminology Criteria for Adverse Events (CTCAE Version 4.03).

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 23.1 |

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Overall study |
|-----------------------|---------------|

Reporting group description:

The safety set consisted of all patients who entered the trial and was used for conducting all safety analyses.

| Serious adverse events | Overall study | | |
|---|----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 84 (2.38%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Nervous system disorders | | | |
| Psychotic disorder | | | |
| subjects affected / exposed | 2 / 84 (2.38%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Overall study | | |
|---|------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 39 / 84 (46.43%) | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 5 / 84 (5.95%) | | |
| occurrences (all) | 5 | | |

| | | | |
|--|------------------------|--|--|
| Dizziness subjects affected / exposed occurrences (all) | 5 / 84 (5.95%) 5 | | |
| Tremor subjects affected / exposed occurrences (all) | 4 / 84 (4.76%) 5 | | |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) | 10 / 84 (11.90%) 10 | | |
| Psychiatric disorders Psychotic disorder subjects affected / exposed occurrences (all) | 6 / 84 (7.14%) 6 | | |
| Metabolism and nutrition disorders Hyperkalaemia subjects affected / exposed occurrences (all) | 10 / 84 (11.90%) 13 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 30 September 2015 | The following major changes were included in AM 2: extension of inclusion criterion 3 (not only patients with monotherapy, but with two antipsychotics allowed) and clearer definition of inclusion criterion 5 and exclusion criterion 8. |
| 11 October 2016 | The following major changes were included in AM 3: additional inclusion of women allowed (not pregnant, contraception according to CTFG guideline), clearer definition of excluded antipsychotics. |
| 18 April 2017 | The following major changes were included in AM 4: Additional site Regensburg, clarification of the negative wording of an exclusion criterion, extension of study period. |
| 25 June 2018 | The following major changes were included in AM 6: change in IMP Manufacturer and add-on to patient information to reflect new regulation on data protection. |
| 31 October 2019 | The following major changes were included in AM 7: adapted description in power planning and statistical analysis and improved specification of secondary endpoints. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/32072071>