



Clinical trial results:

The switch study - efficacy of early antipsychotic switch versus maintenance in patients with schizophrenia poorly responding to two weeks of antipsychotic treatment

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2009-012031-15 |
| Trial protocol | DE RO |
| Global end of trial date | 06 February 2014 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 12 June 2021 |
| First version publication date | 12 June 2021 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 01KG0910 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01029769 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Technische Universität München, Fakultät für Medizin |
| Sponsor organisation address | Ismaninger Str. 22, München, Germany, 81675 |
| Public contact | Prof. Dr. Stefan Leucht, Klinikum rechts der Isar der TU München, Klinik für Psychiatrie, 49 4140 4249, stefan.leucht@tum.de |
| Scientific contact | Prof. Dr. Stefan Leucht, Klinikum rechts der Isar der TU München, Klinik für Psychiatrie, 49 4140 4249, stefan.leucht@tum.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 | 10 April 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 06 February 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 06 February 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the current trial is to examine the superior effectiveness of an early switch of antipsychotic treatment in patients poorly responding to two weeks of randomized treatment with either olanzapine or amisulpride. The primary endpoint is the number of patients in remission after another six weeks of treatment after either continuing on the initially started antipsychotic or having been switched to the alternative study drug.

Protection of trial subjects:

The conduct of this clinical study met the local legal and regulatory requirements. The study was conducted in accordance the ethical principles of Good Clinical Practice (GCP). Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. The study was regularly monitored by the Sponsor and all investigators connected to the study were GCP trained.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 08 February 2010 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Germany: 150 |
| Country: Number of subjects enrolled | Romania: 177 |
| Worldwide total number of subjects | 327 |
| EEA total number of subjects | 327 |

Notes:

Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 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) | 325 |
| From 65 to 84 years | 2 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Pre-screening processes were in place. Between 08.02.2010 and 06.02.2014 all patients were randomised.

Pre-assignment

Screening details:

Adult patients diagnosed with schizophrenia or schizoaffective disorder or a schizophrenic disorder examined with regard to their suitability. This was followed by the 1st double-blind randomization (olanzapine- or amisulpride-arm).

Period 1

| | |
|------------------------------|--|
| Period 1 title | Phase I |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Assessor |

Blinding implementation details:

Medication was encapsulated in capsules identical in shape, colour and taste

Arms

| | |
|-----------|-----------------------------------|
| Arm title | Phase I amisulpride or olanzapine |
|-----------|-----------------------------------|

Arm description:

Amisulpride 200-800 mg/day or olanzapine 5-20mg/day.

In phase I participants were randomised to either amisulpride (164 participants) or olanzapine (163 participants). The reason was that we wanted to rule out by the study design that any differences between switching and staying in phase II were related to the drug the participants were originally designed to in phase I. However, differences between amisulpride and olanzapine in phase I were not analysed.

| | |
|--|---|
| Arm type | Treatment before phase of interest (phase II) |
| Investigational medicinal product name | Amisulpride |
| Investigational medicinal product code | ATC Code N05AH03 |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

200-800mg/day

| | |
|--|----------------------|
| Investigational medicinal product name | Olanzapine |
| Investigational medicinal product code | ATC Code 37872.00.00 |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

5-20mg/day

| Number of subjects in period 1 | Phase I amisulpride or olanzapine |
|---------------------------------------|-----------------------------------|
| Started | 327 |
| Completed | 285 |
| Not completed | 42 |
| Consent withdrawn by subject | 18 |
| Physician decision | 2 |
| Adverse event, non-fatal | 8 |
| Lost to follow-up | 3 |
| Lack of efficacy | 4 |
| Involuntary admission | 1 |
| Protocol deviation | 6 |

Period 2

| | |
|------------------------------|--|
| Period 2 title | Phase II |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Assessor |

Blinding implementation details:

Capsules of identical shape, colour and size

Arms

| | |
|------------------------------|--------|
| Are arms mutually exclusive? | Yes |
| Arm title | Switch |

Arm description:

Non-improvers in phase I switch to the drug they were not assigned to in phase I

| | |
|--|----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Amisulpride |
| Investigational medicinal product code | ATC Code 37872.00.00 |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Per Day: 200-800 milligram(s)

| | |
|--|------------------|
| Investigational medicinal product name | Olanzapine |
| Investigational medicinal product code | ATC Code N05AH03 |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

per day: 5-20mg milligram(s)

| | |
|---|------------------------------|
| Arm title | Stay |
| Arm description: | |
| Non-improvers in phase I stay on the drug they were assigned to in phase I | |
| Arm type | Active comparator |
| Investigational medicinal product name | Amisulpride |
| Investigational medicinal product code | ATC Code 37872.00.00 |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Daily dose: 200-800 milligram(s) | |
| Investigational medicinal product name | Olanzapine |
| Investigational medicinal product code | ATC code N05AH03 |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Daily dose: 5-20 milligram(s) | |
| Arm title | Early improvers |
| Arm description: | |
| Early improvers in phase I continued to receive the same drug in phase II. Differences between early improvers and stayers/switchers were not analysed. | |
| Arm type | Follow-up of early improvers |
| Investigational medicinal product name | Amisulpride |
| Investigational medicinal product code | ATC Code 37872.00.00 |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Daily dose: 200-800 milligram(s) | |
| Investigational medicinal product name | Olanzapine |
| Investigational medicinal product code | ATC code N05AH03 |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Daily dose: 5-20 milligram(s) | |

| Number of subjects in period 2^[1] | Switch | Stay | Early improvers |
|---|--------|------|-----------------|
| Started | 70 | 72 | 140 |
| Completed | 60 | 55 | 104 |
| Not completed | 10 | 17 | 36 |
| Consent withdrawn by subject | 3 | 4 | 12 |
| Physician decision | - | 2 | - |
| Administrative | - | - | 2 |
| Adverse event, non-fatal | 2 | 1 | 3 |

| | | | |
|---------------------|---|---|---|
| suicide attempt | 1 | - | - |
| Lost to follow-up | - | 1 | 7 |
| Lack of efficacy | 2 | 6 | 5 |
| Protocol deviation | 2 | 3 | 6 |
| Randomisation error | - | - | 1 |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 3 participants were not re-randomised in phase II

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Phase I |
|-----------------------|---------|

Reporting group description:

The patients were randomised to amisulpride group or olanzapine. We present the results of both drugs combined. Differences between drugs were not analysed.

| Reporting group values | Phase I | Total | |
|--|---------|-------|--|
| Number of subjects | 327 | 327 | |
| 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) | 325 | 325 | |
| From 65-84 years | 2 | 2 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 39.5 | | |
| standard deviation | ± 11.5 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 154 | 154 | |
| Male | 173 | 173 | |

End points

End points reporting groups

| | |
|---|-----------------------------------|
| Reporting group title | Phase I amisulpride or olanzapine |
| Reporting group description: Amisulpride 200-800 mg/day or olanzapine 5-20mg/day. In phase I participants were randomised to either amisulpride (164 participants) or olanzapine (163 participants). The reason was that we wanted to rule out by the study design that any differences between switching and staying in phase II were related to the drug the participants were originally designed to in phase I. However, differences between amisulpride and olanzapine in phase I were not analysed. | |
| Reporting group title | Switch |
| Reporting group description: Non-improvers in phase I switch to the drug they were not assigned to in phase I | |
| Reporting group title | Stay |
| Reporting group description: Non-improvers in phase I stay on the drug they were assigned to in phase I | |
| Reporting group title | Early improvers |
| Reporting group description: Early improvers in phase I continued to receive the same drug in phase II. Differences between early improvers and stayers/switchers were not analysed. | |

Primary: Symptomatic remission

| | |
|--|-----------------------|
| End point title | Symptomatic remission |
| End point description: Remission according to Andreasen et al. 2005 Reference: Andreasen NC, Carpenter WT Jr, Kane JM, Lasser RA, Marder SR, Weinberger DR. Remission in schizophrenia: proposed criteria and rationale for consensus. Am J Psychiatry. 2005 Mar;162(3):441-9 | |
| End point type | Primary |
| End point timeframe: End of phase II | |

| End point values | Switch | Stay | | |
|-----------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 ^[1] | 55 ^[2] | | |
| Units: Participants | 41 | 25 | | |

Notes:

[1] - The numbers presented are the phase 2 completers

[2] - The numbers presented are the phase II completers

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Logistic regression symptomatic remission |
| Statistical analysis description: Logistic regression model with "remission" as the dependent variable and "switch" of treatment (yes/no) and PANSS-total score at visit 3 as independent variables was used. Multiple imputation (based upon 20 imputations). | |
| Comparison groups | Switch v Stay |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 ^[3] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 3.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.35 |
| upper limit | 6.72 |

Notes:

[3] - the result was 0.007

Secondary: PANSS Total Score change from Switch Randomization

| | |
|--|--|
| End point title | PANSS Total Score change from Switch Randomization |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Change from Switch Randomization to endpoint | |

| End point values | Switch | Stay | | |
|--------------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 ^[4] | 55 ^[5] | | |
| Units: PANSS units | | | | |
| arithmetic mean (standard deviation) | -22.8 (± 19.9) | -17.3 (± 15.1) | | |

Notes:

[4] - Completers

[5] - Completers

Statistical analyses

| | |
|---|--------------------------------------|
| Statistical analysis title | Mixed-model of repeated measurements |
| Comparison groups | Switch v Stay |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Median difference (final values) |
| Point estimate | -4.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.58 |
| upper limit | 0.51 |

Secondary: Positive PANSS, Change from Switch Randomization

| | |
|-----------------|--|
| End point title | Positive PANSS, Change from Switch Randomization |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Change from Switch Randomization to endpoint

| End point values | Switch | Stay | | |
|--------------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 ^[6] | 55 ^[7] | | |
| Units: PANSS points | | | | |
| arithmetic mean (standard deviation) | -6.25 (± 5.22) | -5.96 (± 5.89) | | |

Notes:

[6] - Completers

[7] - Completers

Statistical analyses

| | |
|---|--------------------------------|
| Statistical analysis title | MMRM |
| Comparison groups | Switch v Stay |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.86 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.32 |
| upper limit | 0.59 |

Secondary: Negative PANSS, Change from Switch Randomization

| | |
|-----------------|--|
| End point title | Negative PANSS, Change from Switch Randomization |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Change from Switch Randomization to endpoint

| End point values | Switch | Stay | | |
|--------------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 ^[8] | 55 ^[9] | | |
| Units: PANSS points | | | | |
| arithmetic mean (standard deviation) | -6 (± 7.15) | -3.64 (± 4.7) | | |

Notes:

[8] - Completers

[9] - Completers

Statistical analyses

No statistical analyses for this end point

Secondary: General PANSS, change from Switch Randomization

| | |
|-----------------|---|
| End point title | General PANSS, change from Switch Randomization |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Change from Switch Randomization to endpoint

| End point values | Switch | Stay | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 ^[10] | 55 ^[11] | | |
| Units: PANSS points | | | | |
| arithmetic mean (standard deviation) | -10.5 (± 9.8) | -7.75 (± 6.81) | | |

Notes:

[10] - Completers

[11] - Completers

Statistical analyses

| | |
|---|-------------------------------------|
| Statistical analysis title | Mixed-model of repeated measurement |
| Comparison groups | Switch v Stay |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.43 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.64 |
| upper limit | 0.77 |

Secondary: CGI Severity, Change from Switch Randomization

| | |
|-----------------|--|
| End point title | CGI Severity, Change from Switch Randomization |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Change from Switch Randomization to endpoint

| End point values | Switch | Stay | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 ^[12] | 55 ^[13] | | |
| Units: CGI points | | | | |
| arithmetic mean (standard deviation) | -1.42 (± 0.944) | -1.11 (± 0.956) | | |

Notes:

[12] - Completers

[13] - Completers

Statistical analyses

| | |
|---|--------------------------------|
| Statistical analysis title | MMRM |
| Comparison groups | Stay v Switch |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.34 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.64 |
| upper limit | -0.05 |

Secondary: CGI Global Improvement, Change from Switch Randomization

| | |
|-----------------|--|
| End point title | CGI Global Improvement, Change from Switch Randomization |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Change from Switch Randomization to endpoint

| End point values | Switch | Stay | | |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 | 55 ^[14] | | |
| Units: CGI points | | | | |
| arithmetic mean (standard deviation) | -1.03 (\pm 0.843) | -0.709 (\pm 1.01) | | |

Notes:

[14] - Completers

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Continuous outcomes switchers versus stayers |
| Comparison groups | Switch v Stay |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.33 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.6 |
| upper limit | -0.05 |

Secondary: Subjective Well-Being under Neuroleptics Scale (SWN), Change from Switch Randomization

| | |
|-----------------|--|
| End point title | Subjective Well-Being under Neuroleptics Scale (SWN), Change from Switch Randomization |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Change from Switch Randomization to endpoint

| End point values | Switch | Stay | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 59 ^[15] | 55 ^[16] | | |
| Units: SWN points | | | | |
| arithmetic mean (standard deviation) | 8.37 (\pm 15.3) | 5.85 (\pm 10.9) | | |

Notes:

[15] - Completers

[16] - Completers

Statistical analyses

| | |
|---|--------------------------------|
| Statistical analysis title | MMRM |
| Comparison groups | Switch v Stay |
| Number of subjects included in analysis | 114 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.52 |
| upper limit | 4.93 |

Secondary: Psychosocial Performance Scale (PSP), Change from Switch Randomization

| | |
|--|--|
| End point title | Psychosocial Performance Scale (PSP), Change from Switch Randomization |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Change from Switch Randomization to endpoint | |

| | | | | |
|--------------------------------------|--------------------|--------------------|--|--|
| End point values | Switch | Stay | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 ^[17] | 54 ^[18] | | |
| Units: PSP points | | | | |
| arithmetic mean (standard deviation) | 11.8 (± 13.6) | 10.4 (± 10.2) | | |

Notes:

[17] - Completers

[18] - Completers

Statistical analyses

| | |
|-----------------------------------|---------------|
| Statistical analysis title | MMRM |
| Comparison groups | Switch v Stay |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 114 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 3.23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.98 |
| upper limit | 8.45 |

Secondary: Drug Attitude Inventory (DAI), Change from Switch Randomisation

| | |
|--|---|
| End point title | Drug Attitude Inventory (DAI), Change from Switch Randomisation |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Change from Switch Randomization to endpoint | |

| End point values | Switch | Stay | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 58 ^[19] | 54 ^[20] | | |
| Units: DAI points | | | | |
| arithmetic mean (standard deviation) | 1.21 (± 3.98) | 1.04 (± 3.35) | | |

Notes:

[19] - Completers

[20] - Completers

Statistical analyses

| | |
|---|--------------------------------|
| Statistical analysis title | MMRM |
| Comparison groups | Switch v Stay |
| Number of subjects included in analysis | 112 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.14 |
| upper limit | 1.27 |

Secondary: Riedel-Spellmann-Musil Scale Patient (RSMP), Change from Switch Randomisation

| | |
|-----------------|---|
| End point title | Riedel-Spellmann-Musil Scale Patient (RSMP), Change from Switch Randomisation |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Change from Switch Randomization to endpoint

| End point values | Switch | Stay | | |
|--------------------------------------|-----------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 59 ^[21] | 54 ^[22] | | |
| Units: RSMP points | | | | |
| arithmetic mean (standard deviation) | -0.0847 (\pm 8.56) | 2.11 (\pm 9.5) | | |

Notes:

[21] - Completers

[22] - Completers

Statistical analyses

| | |
|---|--------------------------------|
| Statistical analysis title | MMRM |
| Comparison groups | Switch v Stay |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -2.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.16 |
| upper limit | 2.04 |

Secondary: Riedel-Spellmann-Musil Scale Observer (RSMO), Riedel-Spellmann-Musil Scale Patient (RSMP), Change from Switch Randomisation

| | |
|-----------------|---|
| End point title | Riedel-Spellmann-Musil Scale Observer (RSMO), Riedel-Spellmann-Musil Scale Patient (RSMP), Change from Switch Randomisation |
|-----------------|---|

End point description:

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Change from Switch Randomization to endpoint | |

| End point values | Switch | Stay | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 58 ^[23] | 55 ^[24] | | |
| Units: RSMO points | | | | |
| arithmetic mean (standard deviation) | 0.931 (± 4.82) | 0.509 (± 5.6) | | |

Notes:

[23] - Completers

[24] - Completers

Statistical analyses

| Statistical analysis title | MMRM |
|---|--------------------------------|
| Comparison groups | Switch v Stay |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.54 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2 |
| upper limit | 3.08 |

Secondary: Barnes Akathisia Scale, change from switch randomisation

| | |
|--|--|
| End point title | Barnes Akathisia Scale, change from switch randomisation |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Change from Switch Randomization to endpoint | |

| End point values | Switch | Stay | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 ^[25] | 55 ^[26] | | |
| Units: Barnes Akathisia Scale points | | | | |
| arithmetic mean (standard deviation) | -0.25 (± 1.79) | -0.49 (± 1.91) | | |

Notes:

[25] - Completers

[26] - Completers

Statistical analyses

| Statistical analysis title | Mixed-model of repeated measurements |
|---|--------------------------------------|
| Comparison groups | Switch v Stay |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.39 |
| upper limit | 0.69 |

Secondary: Simpson Angus Scale, change from Switch Randomization

| | |
|--|---|
| End point title | Simpson Angus Scale, change from Switch Randomization |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Change from Switch Randomization to endpoint | |

| End point values | Switch | Stay | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 ^[27] | 54 ^[28] | | |
| Units: Simpson Angus Scale points | | | | |
| arithmetic mean (standard deviation) | -0.13 (± 2.53) | 0.11 (± 3.35) | | |

Notes:

[27] - Completers

[28] - Completers

Statistical analyses

| | |
|---|-------------------------------------|
| Statistical analysis title | Mixed-model of repeated measurement |
| Comparison groups | Switch v Stay |
| Number of subjects included in analysis | 114 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.93 |
| upper limit | 1 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For the groups "switchers phase II", "stayers phase II", "early improvers phase II": from randomization for phase II to endpoint

For the group "Adverse events in phase I amisulpride and olanzapine combined": from randomization for phase I to end phase I

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 20.0 |

Reporting groups

| | |
|-----------------------|--------------------|
| Reporting group title | Switchers phase II |
|-----------------------|--------------------|

Reporting group description:

Randomised to switch in phase II and received at least one dose of study drug

| | |
|-----------------------|------------------|
| Reporting group title | Stayers phase II |
|-----------------------|------------------|

Reporting group description:

Randomised to staying on the same drug in phase II and received at least one dose of study drug

| | |
|-----------------------|--------------------------|
| Reporting group title | Early improvers phase II |
|-----------------------|--------------------------|

Reporting group description:

Improved in phase I, remained on the same study drug, and received at least one dose of study drug

| | |
|-----------------------|---|
| Reporting group title | Phase I amisulpride and olanzapine combined |
|-----------------------|---|

Reporting group description:

As the comparison of amisulpride and olanzapine is not the aim of the study, we present the adverse events that occurred in phase I for both groups combined

| Serious adverse events | Switchers phase II | Stayers phase II | Early improvers phase II |
|---|--------------------|------------------|--------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 70 (4.29%) | 4 / 72 (5.56%) | 9 / 140 (6.43%) |
| number of deaths (all causes) | 0 | 0 | 1 |
| number of deaths resulting from adverse events | 0 | 0 | 1 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 1 / 140 (0.71%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Lithium intoxication | | | |
| subjects affected / exposed | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|-----------------|
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary thrombosis | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Worsening of psychosis | | | |
| subjects affected / exposed | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 5 / 140 (3.57%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Affective worsening | | | |
| subjects affected / exposed | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 1 / 140 (0.71%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suicide attempt | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Agitation | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | 1 / 72 (1.39%) | 0 / 140 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychotic relapse | | | |
| subjects affected / exposed | 0 / 70 (0.00%) | 3 / 72 (4.17%) | 1 / 140 (0.71%) |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|--|--|
| Serious adverse events | Phase I amisulpride and olanzapine combined | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 327 (1.53%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 327 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Lithium intoxication | | | |
| subjects affected / exposed | 1 / 327 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary thrombosis | | | |
| subjects affected / exposed | 0 / 327 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Worsening of psychosis | | | |
| subjects affected / exposed | 2 / 327 (0.61%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Affective worsening | | | |
| subjects affected / exposed | 0 / 327 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Suicide attempt | | | |
| subjects affected / exposed | 0 / 327 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Agitation | | | |
| subjects affected / exposed | 0 / 327 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychotic relapse | | | |
| subjects affected / exposed | 1 / 327 (0.31%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Switchers phase II | Stayers phase II | Early improvers phase II |
|--|--------------------|------------------|--------------------------|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 31 / 70 (44.29%) | 28 / 72 (38.89%) | 63 / 140 (45.00%) |
| Vascular disorders | | | |
| Orthostatic hypotension | | | |
| subjects affected / exposed ^[1] | 0 / 70 (0.00%) | 1 / 72 (1.39%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed ^[2] | 1 / 70 (1.43%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Chills | | | |
| subjects affected / exposed ^[3] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| General physical health deterioration | | | |
| subjects affected / exposed ^[4] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed ^[5] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pyrexia | | | |
| subjects affected / exposed ^[6] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Reproductive system and breast disorders | | | |
| Galactorrhoea | | | |
| subjects affected / exposed ^[7] | 1 / 70 (1.43%) | 0 / 72 (0.00%) | 2 / 140 (1.43%) |
| occurrences (all) | 1 | 0 | 2 |
| Menstruation delayed | | | |
| subjects affected / exposed ^[8] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 1 / 140 (0.71%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|----------------------|---------------------|----------------------|
| Sexual dysfunction subjects affected / exposed ^[9] occurrences (all) | 0 / 70 (0.00%) 0 | 0 / 72 (0.00%) 0 | 1 / 140 (0.71%) 1 |
| Dysmenorrhoea subjects affected / exposed ^[10] occurrences (all) | 0 / 70 (0.00%) 0 | 0 / 72 (0.00%) 0 | 0 / 140 (0.00%) 0 |
| Gynaecomastia subjects affected / exposed ^[11] occurrences (all) | 0 / 70 (0.00%) 0 | 0 / 72 (0.00%) 0 | 0 / 140 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pharyngeal dyskinesia subjects affected / exposed ^[12] occurrences (all) | 1 / 70 (1.43%) 1 | 0 / 72 (0.00%) 0 | 0 / 140 (0.00%) 0 |
| Nasal congestion subjects affected / exposed ^[13] occurrences (all) | 0 / 70 (0.00%) 0 | 0 / 72 (0.00%) 0 | 1 / 140 (0.71%) 1 |
| Rhinorrhoea subjects affected / exposed ^[14] occurrences (all) | 0 / 70 (0.00%) 0 | 0 / 72 (0.00%) 0 | 1 / 140 (0.71%) 1 |
| Oropharyngeal pain subjects affected / exposed ^[15] occurrences (all) | 0 / 70 (0.00%) 0 | 0 / 72 (0.00%) 0 | 0 / 140 (0.00%) 0 |
| Psychiatric disorders | | | |
| Agitation subjects affected / exposed ^[16] occurrences (all) | 2 / 70 (2.86%) 2 | 0 / 72 (0.00%) 0 | 4 / 140 (2.86%) 4 |
| Anxiety subjects affected / exposed ^[17] occurrences (all) | 3 / 70 (4.29%) 3 | 1 / 72 (1.39%) 1 | 2 / 140 (1.43%) 2 |
| Insomnia subjects affected / exposed ^[18] occurrences (all) | 9 / 70 (12.86%) 9 | 2 / 72 (2.78%) 2 | 7 / 140 (5.00%) 7 |
| Irritability subjects affected / exposed ^[19] occurrences (all) | 1 / 70 (1.43%) 1 | 1 / 72 (1.39%) 1 | 0 / 140 (0.00%) 0 |
| Psychotic disorder | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed ^[20] | 0 / 70 (0.00%) | 2 / 72 (2.78%) | 5 / 140 (3.57%) |
| occurrences (all) | 0 | 2 | 5 |
| Restlessness | | | |
| subjects affected / exposed ^[21] | 1 / 70 (1.43%) | 3 / 72 (4.17%) | 3 / 140 (2.14%) |
| occurrences (all) | 1 | 3 | 3 |
| Tension | | | |
| subjects affected / exposed ^[22] | 1 / 70 (1.43%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Depression | | | |
| subjects affected / exposed ^[23] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 5 / 140 (3.57%) |
| occurrences (all) | 0 | 0 | 5 |
| Nervousness | | | |
| subjects affected / exposed ^[24] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 1 / 140 (0.71%) |
| occurrences (all) | 0 | 0 | 1 |
| Sleep disorder | | | |
| subjects affected / exposed ^[25] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 1 / 140 (0.71%) |
| occurrences (all) | 0 | 0 | 1 |
| Apathy | | | |
| subjects affected / exposed ^[26] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Catatonia | | | |
| subjects affected / exposed ^[27] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Confusional state | | | |
| subjects affected / exposed ^[28] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Disorientation | | | |
| subjects affected / exposed ^[29] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Drug use disorder | | | |
| subjects affected / exposed ^[30] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Libido increased | | | |
| subjects affected / exposed ^[31] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Panic attack | | | |

| | | | |
|--|--------------------------------------|---------------------|----------------------|
| subjects affected / exposed ^[32] occurrences (all) | 0 / 70 (0.00%) 0 | 0 / 72 (0.00%) 0 | 0 / 140 (0.00%) 0 |
| Investigations | | | |
| Electrocardiogram repolarisation abnormality | Additional description: QT prolonged | | |
| subjects affected / exposed ^[33] occurrences (all) | 0 / 70 (0.00%) 0 | 1 / 72 (1.39%) 1 | 0 / 140 (0.00%) 0 |
| Hepatic enzyme increased subjects affected / exposed ^[34] occurrences (all) | 1 / 70 (1.43%) 1 | 0 / 72 (0.00%) 0 | 1 / 140 (0.71%) 1 |
| Transaminases increased subjects affected / exposed ^[35] occurrences (all) | 1 / 70 (1.43%) 1 | 0 / 72 (0.00%) 0 | 0 / 140 (0.00%) 0 |
| Weight decreased subjects affected / exposed ^[36] occurrences (all) | 0 / 70 (0.00%) 0 | 1 / 72 (1.39%) 1 | 0 / 140 (0.00%) 0 |
| Weight increased subjects affected / exposed ^[37] occurrences (all) | 1 / 70 (1.43%) 1 | 1 / 72 (1.39%) 1 | 4 / 140 (2.86%) 4 |
| C-reactive protein increased subjects affected / exposed ^[38] occurrences (all) | 0 / 70 (0.00%) 0 | 0 / 72 (0.00%) 0 | 1 / 140 (0.71%) 1 |
| Injury, poisoning and procedural complications | | | |
| Alcohol poisoning subjects affected / exposed ^[39] occurrences (all) | 0 / 70 (0.00%) 0 | 0 / 72 (0.00%) 0 | 1 / 140 (0.71%) 1 |
| Toxicity to various agents subjects affected / exposed ^[40] occurrences (all) | 0 / 70 (0.00%) 0 | 0 / 72 (0.00%) 0 | 0 / 140 (0.00%) 0 |
| Cardiac disorders | | | |
| Hypotension subjects affected / exposed ^[41] occurrences (all) | 0 / 70 (0.00%) 0 | 1 / 72 (1.39%) 1 | 0 / 140 (0.00%) 0 |
| Myocardial infarction subjects affected / exposed ^[42] occurrences (all) | 0 / 70 (0.00%) 0 | 0 / 72 (0.00%) 0 | 0 / 140 (0.00%) 0 |
| Myocardial ischaemia | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed ^[43] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pericardial effusion | | | |
| subjects affected / exposed ^[44] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tachycardia | | | |
| subjects affected / exposed ^[45] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Dysaesthesia | | | |
| subjects affected / exposed ^[46] | 0 / 70 (0.00%) | 1 / 72 (1.39%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Extrapyramidal disorder | | | |
| subjects affected / exposed ^[47] | 2 / 70 (2.86%) | 2 / 72 (2.78%) | 0 / 140 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Headache | | | |
| subjects affected / exposed ^[48] | 4 / 70 (5.71%) | 1 / 72 (1.39%) | 6 / 140 (4.29%) |
| occurrences (all) | 4 | 1 | 6 |
| Oromandibular dystonia | | | |
| subjects affected / exposed ^[49] | 0 / 70 (0.00%) | 1 / 72 (1.39%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Paraesthesia | | | |
| subjects affected / exposed ^[50] | 1 / 70 (1.43%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Parkinson gait | | | |
| subjects affected / exposed ^[51] | 1 / 70 (1.43%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Psychomotor hyperactivity | | | |
| subjects affected / exposed ^[52] | 1 / 70 (1.43%) | 0 / 72 (0.00%) | 2 / 140 (1.43%) |
| occurrences (all) | 1 | 0 | 2 |
| Sedation | | | |
| subjects affected / exposed ^[53] | 3 / 70 (4.29%) | 2 / 72 (2.78%) | 6 / 140 (4.29%) |
| occurrences (all) | 3 | 2 | 6 |
| Somnolence | | | |
| subjects affected / exposed ^[54] | 0 / 70 (0.00%) | 1 / 72 (1.39%) | 1 / 140 (0.71%) |
| occurrences (all) | 0 | 1 | 1 |

| | | | |
|---|----------------|----------------|-----------------|
| Tremor | | | |
| subjects affected / exposed ^[55] | 4 / 70 (5.71%) | 2 / 72 (2.78%) | 8 / 140 (5.71%) |
| occurrences (all) | 4 | 2 | 8 |
| Akathisia | | | |
| subjects affected / exposed ^[56] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 7 / 140 (5.00%) |
| occurrences (all) | 0 | 0 | 7 |
| Dizziness | | | |
| subjects affected / exposed ^[57] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 2 / 140 (1.43%) |
| occurrences (all) | 0 | 0 | 2 |
| Dystonia | | | |
| subjects affected / exposed ^[58] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 1 / 140 (0.71%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypokinesia | | | |
| subjects affected / exposed ^[59] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 1 / 140 (0.71%) |
| occurrences (all) | 0 | 0 | 1 |
| Dyskinesia | | | |
| subjects affected / exposed ^[60] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Syncope | | | |
| subjects affected / exposed ^[61] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Leukocytosis | | | |
| subjects affected / exposed ^[62] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed ^[63] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eye disorders | | | |
| Vision blurred | | | |
| subjects affected / exposed ^[64] | 1 / 70 (1.43%) | 2 / 72 (2.78%) | 2 / 140 (1.43%) |
| occurrences (all) | 1 | 2 | 2 |
| accomodation disorder | | | |
| subjects affected / exposed ^[65] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dry eye | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed ^[66] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed ^[67] | 2 / 70 (2.86%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Dry mouth | | | |
| subjects affected / exposed ^[68] | 1 / 70 (1.43%) | 2 / 72 (2.78%) | 4 / 140 (2.86%) |
| occurrences (all) | 1 | 2 | 4 |
| Nausea | | | |
| subjects affected / exposed ^[69] | 0 / 70 (0.00%) | 1 / 72 (1.39%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Salivary hypersecretion | | | |
| subjects affected / exposed ^[70] | 1 / 70 (1.43%) | 0 / 72 (0.00%) | 1 / 140 (0.71%) |
| occurrences (all) | 1 | 0 | 1 |
| Vomiting | | | |
| subjects affected / exposed ^[71] | 1 / 70 (1.43%) | 1 / 72 (1.39%) | 2 / 140 (1.43%) |
| occurrences (all) | 1 | 1 | 2 |
| Abdominal discomfort | | | |
| subjects affected / exposed ^[72] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed ^[73] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed ^[74] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dysphagia | | | |
| subjects affected / exposed ^[75] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastritis | | | |
| subjects affected / exposed ^[76] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Toothache | | | |
| subjects affected / exposed ^[77] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|----------------|----------------|-----------------|
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed ^[78] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 1 / 140 (0.71%) |
| occurrences (all) | 0 | 0 | 1 |
| Alopecia | | | |
| subjects affected / exposed ^[79] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 1 / 140 (0.71%) |
| occurrences (all) | 0 | 0 | 1 |
| Rash | | | |
| subjects affected / exposed ^[80] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 1 / 140 (0.71%) |
| occurrences (all) | 0 | 0 | 1 |
| Dermal cyst | | | |
| subjects affected / exposed ^[81] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eczema | | | |
| subjects affected / exposed ^[82] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperhidrosis | | | |
| subjects affected / exposed ^[83] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Endocrine disorders | | | |
| Hyperprolactinaemia | | | |
| subjects affected / exposed ^[84] | 0 / 70 (0.00%) | 1 / 72 (1.39%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed ^[85] | 0 / 70 (0.00%) | 1 / 72 (1.39%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Muscle rigidity | | | |
| subjects affected / exposed ^[86] | 2 / 70 (2.86%) | 2 / 72 (2.78%) | 4 / 140 (2.86%) |
| occurrences (all) | 2 | 2 | 4 |
| Arthralgia | | | |
| subjects affected / exposed ^[87] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bursitis | | | |
| subjects affected / exposed ^[88] | 0 / 70 (0.00%) | 0 / 72 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---------------------|---------------------|----------------------|
| Limb discomfort subjects affected / exposed ^[89] occurrences (all) | 0 / 70 (0.00%) 0 | 0 / 72 (0.00%) 0 | 0 / 140 (0.00%) 0 |
| Torticollis subjects affected / exposed ^[90] occurrences (all) | 0 / 70 (0.00%) 0 | 0 / 72 (0.00%) 0 | 0 / 140 (0.00%) 0 |
| Infections and infestations | | | |
| Tooth infection subjects affected / exposed ^[91] occurrences (all) | 0 / 70 (0.00%) 0 | 1 / 72 (1.39%) 1 | 0 / 140 (0.00%) 0 |
| Febrile infection subjects affected / exposed ^[92] occurrences (all) | 0 / 70 (0.00%) 0 | 0 / 72 (0.00%) 0 | 1 / 140 (0.71%) 1 |
| Furuncle subjects affected / exposed ^[93] occurrences (all) | 0 / 70 (0.00%) 0 | 0 / 72 (0.00%) 0 | 1 / 140 (0.71%) 1 |
| Vaginal infection subjects affected / exposed ^[94] occurrences (all) | 0 / 70 (0.00%) 0 | 0 / 72 (0.00%) 0 | 1 / 140 (0.71%) 1 |
| Nasopharyngitis subjects affected / exposed ^[95] occurrences (all) | 0 / 70 (0.00%) 0 | 0 / 72 (0.00%) 0 | 0 / 140 (0.00%) 0 |
| Pharyngitis subjects affected / exposed ^[96] occurrences (all) | 0 / 70 (0.00%) 0 | 0 / 72 (0.00%) 0 | 0 / 140 (0.00%) 0 |
| Respiratory tract infection viral subjects affected / exposed ^[97] occurrences (all) | 0 / 70 (0.00%) 0 | 0 / 72 (0.00%) 0 | 0 / 140 (0.00%) 0 |
| Urinary tract infection subjects affected / exposed ^[98] occurrences (all) | 0 / 70 (0.00%) 0 | 0 / 72 (0.00%) 0 | 0 / 140 (0.00%) 0 |
| Viral rhinitis subjects affected / exposed ^[99] occurrences (all) | 0 / 70 (0.00%) 0 | 0 / 72 (0.00%) 0 | 0 / 140 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |

| | | | |
|--|---------------------|---------------------|----------------------|
| Increased appetite subjects affected / exposed ^[100] occurrences (all) | 0 / 70 (0.00%) 0 | 0 / 72 (0.00%) 0 | 1 / 140 (0.71%) 1 |
| Decreased appetite subjects affected / exposed ^[101] occurrences (all) | 0 / 70 (0.00%) 0 | 0 / 72 (0.00%) 0 | 0 / 140 (0.00%) 0 |
| Hypercholesterolaemia subjects affected / exposed ^[102] occurrences (all) | 0 / 70 (0.00%) 0 | 0 / 72 (0.00%) 0 | 0 / 140 (0.00%) 0 |

| Non-serious adverse events | Phase I amisulpride and olanzapine combined | | |
|---|--|--|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 100 / 327 (30.58%) | | |
| Vascular disorders Orthostatic hypotension subjects affected / exposed ^[1] occurrences (all) | 0 / 325 (0.00%) 0 | | |
| General disorders and administration site conditions Asthenia subjects affected / exposed ^[2] occurrences (all) Chills subjects affected / exposed ^[3] occurrences (all) General physical health deterioration subjects affected / exposed ^[4] occurrences (all) Oedema peripheral subjects affected / exposed ^[5] occurrences (all) Pyrexia subjects affected / exposed ^[6] occurrences (all) | 0 / 325 (0.00%) 0 1 / 325 (0.31%) 1 1 / 325 (0.31%) 1 1 / 325 (0.31%) 1 2 / 325 (0.62%) 2 | | |
| Reproductive system and breast disorders | | | |

| | | | |
|---|-----------------|--|--|
| Galactorrhoea | | | |
| subjects affected / exposed ^[7] | 0 / 325 (0.00%) | | |
| occurrences (all) | 0 | | |
| Menstruation delayed | | | |
| subjects affected / exposed ^[8] | 0 / 325 (0.00%) | | |
| occurrences (all) | 0 | | |
| Sexual dysfunction | | | |
| subjects affected / exposed ^[9] | 0 / 325 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dysmenorrhoea | | | |
| subjects affected / exposed ^[10] | 1 / 325 (0.31%) | | |
| occurrences (all) | 1 | | |
| Gynaecomastia | | | |
| subjects affected / exposed ^[11] | 1 / 325 (0.31%) | | |
| occurrences (all) | 1 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pharyngeal dyskinesia | | | |
| subjects affected / exposed ^[12] | 0 / 325 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nasal congestion | | | |
| subjects affected / exposed ^[13] | 1 / 325 (0.31%) | | |
| occurrences (all) | 1 | | |
| Rhinorrhoea | | | |
| subjects affected / exposed ^[14] | 0 / 325 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed ^[15] | 1 / 325 (0.31%) | | |
| occurrences (all) | 1 | | |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed ^[16] | 8 / 325 (2.46%) | | |
| occurrences (all) | 8 | | |
| Anxiety | | | |
| subjects affected / exposed ^[17] | 5 / 325 (1.54%) | | |
| occurrences (all) | 5 | | |
| Insomnia | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed ^[18] | 14 / 325 (4.31%) | | |
| occurrences (all) | 14 | | |
| Irritability | | | |
| subjects affected / exposed ^[19] | 0 / 325 (0.00%) | | |
| occurrences (all) | 0 | | |
| Psychotic disorder | | | |
| subjects affected / exposed ^[20] | 6 / 325 (1.85%) | | |
| occurrences (all) | 6 | | |
| Restlessness | | | |
| subjects affected / exposed ^[21] | 4 / 325 (1.23%) | | |
| occurrences (all) | 4 | | |
| Tension | | | |
| subjects affected / exposed ^[22] | 3 / 325 (0.92%) | | |
| occurrences (all) | 3 | | |
| Depression | | | |
| subjects affected / exposed ^[23] | 1 / 325 (0.31%) | | |
| occurrences (all) | 2 | | |
| Nervousness | | | |
| subjects affected / exposed ^[24] | 0 / 325 (0.00%) | | |
| occurrences (all) | 0 | | |
| Sleep disorder | | | |
| subjects affected / exposed ^[25] | 5 / 325 (1.54%) | | |
| occurrences (all) | 5 | | |
| Apathy | | | |
| subjects affected / exposed ^[26] | 1 / 325 (0.31%) | | |
| occurrences (all) | 1 | | |
| Catatonia | | | |
| subjects affected / exposed ^[27] | 1 / 325 (0.31%) | | |
| occurrences (all) | 1 | | |
| Confusional state | | | |
| subjects affected / exposed ^[28] | 1 / 325 (0.31%) | | |
| occurrences (all) | 1 | | |
| Disorientation | | | |
| subjects affected / exposed ^[29] | 1 / 325 (0.31%) | | |
| occurrences (all) | 1 | | |
| Drug use disorder | | | |

| | | | |
|--|--------------------------------------|--|--|
| subjects affected / exposed ^[30] | 1 / 325 (0.31%) | | |
| occurrences (all) | 1 | | |
| Libido increased | | | |
| subjects affected / exposed ^[31] | 1 / 325 (0.31%) | | |
| occurrences (all) | 1 | | |
| Panic attack | | | |
| subjects affected / exposed ^[32] | 1 / 325 (0.31%) | | |
| occurrences (all) | 1 | | |
| Investigations | | | |
| Electrocardiogram repolarisation abnormality | Additional description: QT prolonged | | |
| subjects affected / exposed ^[33] | 0 / 325 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed ^[34] | 0 / 325 (0.00%) | | |
| occurrences (all) | 0 | | |
| Transaminases increased | | | |
| subjects affected / exposed ^[35] | 2 / 325 (0.62%) | | |
| occurrences (all) | 2 | | |
| Weight decreased | | | |
| subjects affected / exposed ^[36] | 3 / 325 (0.92%) | | |
| occurrences (all) | 3 | | |
| Weight increased | | | |
| subjects affected / exposed ^[37] | 19 / 325 (5.85%) | | |
| occurrences (all) | 19 | | |
| C-reactive protein increased | | | |
| subjects affected / exposed ^[38] | 0 / 325 (0.00%) | | |
| occurrences (all) | 0 | | |
| Injury, poisoning and procedural complications | | | |
| Alcohol poisoning | | | |
| subjects affected / exposed ^[39] | 0 / 325 (0.00%) | | |
| occurrences (all) | 0 | | |
| Toxicity to various agents | | | |
| subjects affected / exposed ^[40] | 1 / 325 (0.31%) | | |
| occurrences (all) | 1 | | |
| Cardiac disorders | | | |

| | | | |
|---|-----------------|--|--|
| Hypotension | | | |
| subjects affected / exposed ^[41] | 3 / 325 (0.92%) | | |
| occurrences (all) | 3 | | |
| Myocardial infarction | | | |
| subjects affected / exposed ^[42] | 1 / 325 (0.31%) | | |
| occurrences (all) | 1 | | |
| Myocardial ischaemia | | | |
| subjects affected / exposed ^[43] | 1 / 325 (0.31%) | | |
| occurrences (all) | 1 | | |
| Pericardial effusion | | | |
| subjects affected / exposed ^[44] | 1 / 325 (0.31%) | | |
| occurrences (all) | 1 | | |
| Tachycardia | | | |
| subjects affected / exposed ^[45] | 2 / 325 (0.62%) | | |
| occurrences (all) | 2 | | |
| Nervous system disorders | | | |
| Dysaesthesia | | | |
| subjects affected / exposed ^[46] | 0 / 325 (0.00%) | | |
| occurrences (all) | 0 | | |
| Extrapyramidal disorder | | | |
| subjects affected / exposed ^[47] | 8 / 325 (2.46%) | | |
| occurrences (all) | 8 | | |
| Headache | | | |
| subjects affected / exposed ^[48] | 7 / 325 (2.15%) | | |
| occurrences (all) | 7 | | |
| Oromandibular dystonia | | | |
| subjects affected / exposed ^[49] | 2 / 325 (0.62%) | | |
| occurrences (all) | 2 | | |
| Paraesthesia | | | |
| subjects affected / exposed ^[50] | 0 / 325 (0.00%) | | |
| occurrences (all) | 0 | | |
| Parkinson gait | | | |
| subjects affected / exposed ^[51] | 0 / 325 (0.00%) | | |
| occurrences (all) | 0 | | |
| Psychomotor hyperactivity | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed ^[52] | 1 / 325 (0.31%) | | |
| occurrences (all) | 1 | | |
| Sedation | | | |
| subjects affected / exposed ^[53] | 15 / 325 (4.62%) | | |
| occurrences (all) | 15 | | |
| Somnolence | | | |
| subjects affected / exposed ^[54] | 3 / 325 (0.92%) | | |
| occurrences (all) | 3 | | |
| Tremor | | | |
| subjects affected / exposed ^[55] | 17 / 325 (5.23%) | | |
| occurrences (all) | 17 | | |
| Akathisia | | | |
| subjects affected / exposed ^[56] | 13 / 325 (4.00%) | | |
| occurrences (all) | 13 | | |
| Dizziness | | | |
| subjects affected / exposed ^[57] | 2 / 325 (0.62%) | | |
| occurrences (all) | 2 | | |
| Dystonia | | | |
| subjects affected / exposed ^[58] | 2 / 325 (0.62%) | | |
| occurrences (all) | 2 | | |
| Hypokinesia | | | |
| subjects affected / exposed ^[59] | 3 / 325 (0.92%) | | |
| occurrences (all) | 3 | | |
| Dyskinesia | | | |
| subjects affected / exposed ^[60] | 2 / 325 (0.62%) | | |
| occurrences (all) | 2 | | |
| Syncope | | | |
| subjects affected / exposed ^[61] | 1 / 325 (0.31%) | | |
| occurrences (all) | 1 | | |
| Blood and lymphatic system disorders | | | |
| Leukocytosis | | | |
| subjects affected / exposed ^[62] | 1 / 325 (0.31%) | | |
| occurrences (all) | 1 | | |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |

| | | | |
|--|----------------------|--|--|
| subjects affected / exposed ^[63] occurrences (all) | 1 / 325 (0.31%) 1 | | |
| Eye disorders | | | |
| Vision blurred | | | |
| subjects affected / exposed ^[64] occurrences (all) | 1 / 325 (0.31%) 1 | | |
| accomodation disorder | | | |
| subjects affected / exposed ^[65] occurrences (all) | 2 / 325 (0.62%) 2 | | |
| Dry eye | | | |
| subjects affected / exposed ^[66] occurrences (all) | 1 / 325 (0.31%) 1 | | |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed ^[67] occurrences (all) | 6 / 325 (1.85%) 6 | | |
| Dry mouth | | | |
| subjects affected / exposed ^[68] occurrences (all) | 5 / 325 (1.54%) 5 | | |
| Nausea | | | |
| subjects affected / exposed ^[69] occurrences (all) | 4 / 325 (1.23%) 4 | | |
| Salivary hypersecretion | | | |
| subjects affected / exposed ^[70] occurrences (all) | 3 / 325 (0.92%) 3 | | |
| Vomiting | | | |
| subjects affected / exposed ^[71] occurrences (all) | 1 / 325 (0.31%) 1 | | |
| Abdominal discomfort | | | |
| subjects affected / exposed ^[72] occurrences (all) | 1 / 325 (0.31%) 1 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed ^[73] occurrences (all) | 2 / 325 (0.62%) 2 | | |
| Dyspepsia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed ^[74] | 1 / 325 (0.31%) | | |
| occurrences (all) | 1 | | |
| Dysphagia | | | |
| subjects affected / exposed ^[75] | 2 / 325 (0.62%) | | |
| occurrences (all) | 2 | | |
| Gastritis | | | |
| subjects affected / exposed ^[76] | 1 / 325 (0.31%) | | |
| occurrences (all) | 1 | | |
| Toothache | | | |
| subjects affected / exposed ^[77] | 3 / 325 (0.92%) | | |
| occurrences (all) | 3 | | |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed ^[78] | 0 / 325 (0.00%) | | |
| occurrences (all) | 0 | | |
| Alopecia | | | |
| subjects affected / exposed ^[79] | 0 / 325 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rash | | | |
| subjects affected / exposed ^[80] | 0 / 325 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dermal cyst | | | |
| subjects affected / exposed ^[81] | 1 / 325 (0.31%) | | |
| occurrences (all) | 1 | | |
| Eczema | | | |
| subjects affected / exposed ^[82] | 2 / 325 (0.62%) | | |
| occurrences (all) | 2 | | |
| Hyperhidrosis | | | |
| subjects affected / exposed ^[83] | 2 / 325 (0.62%) | | |
| occurrences (all) | 2 | | |
| Endocrine disorders | | | |
| Hyperprolactinaemia | | | |
| subjects affected / exposed ^[84] | 0 / 325 (0.00%) | | |
| occurrences (all) | 0 | | |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|---|------------------|--|--|
| Back pain | | | |
| subjects affected / exposed ^[85] | 1 / 325 (0.31%) | | |
| occurrences (all) | 1 | | |
| Muscle rigidity | | | |
| subjects affected / exposed ^[86] | 10 / 325 (3.08%) | | |
| occurrences (all) | 10 | | |
| Arthralgia | | | |
| subjects affected / exposed ^[87] | 1 / 325 (0.31%) | | |
| occurrences (all) | 1 | | |
| Bursitis | | | |
| subjects affected / exposed ^[88] | 1 / 325 (0.31%) | | |
| occurrences (all) | 1 | | |
| Limb discomfort | | | |
| subjects affected / exposed ^[89] | 1 / 325 (0.31%) | | |
| occurrences (all) | 1 | | |
| Torticollis | | | |
| subjects affected / exposed ^[90] | 1 / 325 (0.31%) | | |
| occurrences (all) | 1 | | |
| Infections and infestations | | | |
| Tooth infection | | | |
| subjects affected / exposed ^[91] | 1 / 325 (0.31%) | | |
| occurrences (all) | 1 | | |
| Febrile infection | | | |
| subjects affected / exposed ^[92] | 0 / 325 (0.00%) | | |
| occurrences (all) | 0 | | |
| Furuncle | | | |
| subjects affected / exposed ^[93] | 0 / 325 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vaginal infection | | | |
| subjects affected / exposed ^[94] | 3 / 325 (0.92%) | | |
| occurrences (all) | 3 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed ^[95] | 4 / 325 (1.23%) | | |
| occurrences (all) | 4 | | |
| Pharyngitis | | | |

| | | | |
|---|----------------------|--|--|
| subjects affected / exposed ^[96] occurrences (all) | 1 / 325 (0.31%) 1 | | |
| Respiratory tract infection viral subjects affected / exposed ^[97] occurrences (all) | 1 / 325 (0.31%) 1 | | |
| Urinary tract infection subjects affected / exposed ^[98] occurrences (all) | 2 / 325 (0.62%) 2 | | |
| Viral rhinitis subjects affected / exposed ^[99] occurrences (all) | 1 / 325 (0.31%) 1 | | |
| Metabolism and nutrition disorders | | | |
| Increased appetite subjects affected / exposed ^[100] occurrences (all) | 1 / 325 (0.31%) 1 | | |
| Decreased appetite subjects affected / exposed ^[101] occurrences (all) | 1 / 325 (0.31%) 0 | | |
| Hypercholesterolaemia subjects affected / exposed ^[102] occurrences (all) | 1 / 325 (0.31%) 1 | | |

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: 2 participants did not receive study drug and were therefore excluded from the safety population

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: 2 participants did not receive study drug and were therefore excluded from the safety population

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: 2 participants did not receive study drug and were therefore excluded from the safety population

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: 2 participants did not receive study drug and were therefore excluded from the safety population

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: 2 participants did not receive study drug and were therefore excluded from the safety population

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: 2 participants did not receive study drug and were therefore excluded from the safety population

Justification: 2 participants did not receive study drug and were therefore excluded from the safety population

exposed for the reporting group. These numbers are expected to be equal.

Justification: 2 participants did not receive study drug and were therefore excluded from the safety population

[91] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: 2 participants did not receive study drug and were therefore excluded from the safety population

[92] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: 2 participants did not receive study drug and were therefore excluded from the safety population

[93] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: 2 participants did not receive study drug and were therefore excluded from the safety population

[94] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: 2 participants did not receive study drug and were therefore excluded from the safety population

[95] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: 2 participants did not receive study drug and were therefore excluded from the safety population

[96] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: 2 participants did not receive study drug and were therefore excluded from the safety population

[97] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: 2 participants did not receive study drug and were therefore excluded from the safety population

[98] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: 2 participants did not receive study drug and were therefore excluded from the safety population

[99] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: 2 participants did not receive study drug and were therefore excluded from the safety population

[100] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: 2 participants did not receive study drug and were therefore excluded from the safety population

[101] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: 2 participants did not receive study drug and were therefore excluded from the safety population

[102] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: 2 participants did not receive study drug and were therefore excluded from the safety population

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 08 March 2010 | supply of olanzapine medication by EliLilly, specification of inclusion criteria, qualification and training of study personal concerning examination with the Positive and Negative Syndrome Scale, specification of date for blood measurement, specification of randomisation and treatment allocation, specification in terms of prolactin levels, deletion of AIMS scale, amendment and specification of rescue medication |
| 07 October 2010 | dosing of olanzapine and amisulpride in the first 3 days, amendment of the exclusion criterion patients under guardianship, specification of the relevance of the pregnancy test at screening, specification about laboratory values as adverse events, specification of drug accountability, specification about destruction of study medication, prolongation of follow-up period, specification about inclusion criterion increase in level of care, specification of pre-study treatment, correction of writing error in protocol |
| 14 September 2011 | inclusion of patients with legal guardianship, specification of exclusion criterion sufficient dose of study drugs before the study, definition of a time window for visits, end of electronic documentation of study data with electronic CRF, formal changes |
| 09 November 2012 | expansion of the study to Romania, specification of pseudonymisation of Romanian participants, registration of the study in Romania, participant insurance for Romania, procedure in the case of protocol changes, change of the run time of the study, number of centers in Germany, amendment of measurement of body size in the protocol, exclusion of participants with legal guardianship in Romania |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The data of one site which violated good clinical practice in other trials were excluded.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26227799>