



Clinical trial results:

A Randomized, Multicenter, Double-Blind, Weight-Based, Fixed-Dose, Parallel-Group, Placebo-Controlled Study of the Efficacy and Safety of Extended Release Paliperidone for the Treatment of Schizophrenia in Adolescent Subjects, 12 to 17 Years of Age

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2007-000576-16 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 30 March 2009 |

Results information

| | |
|--------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 29 May 2016 |
| First version publication date | 04 July 2015 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data setReview of data |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | R076477PSZ3001 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00518323 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Janssen-Cilag International NV |
| Sponsor organisation address | Turnhoutseweg 30, Belgium, Belgium, |
| Public contact | Turnhoutseweg 30, Belgium, 44 1494658336, Michael B Emanuel, Janssen-Cilag International NV, 44 1494658, memmanuel@gcogb.jnj.com |
| Scientific contact | Turnhoutseweg 30, Belgium, , Michael B Emanuel, Janssen-Cilag International NV, 44 1494658, memmanuel@gcogb.jnj.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-000014-PIP01-07 |
| 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? | Yes |

Notes:

Results analysis stage

| | |
|--|---------------|
| Analysis stage | Final |
| Date of interim/final analysis | 30 March 2009 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 March 2009 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy, safety, and tolerability of 3 weight-based, fixed-dose groups of paliperidone ER (to fully explore the tolerability range) as compared with placebo in adolescent subjects 12 to 17 years of age, inclusive, with schizophrenia.

Protection of trial subjects:

The safety assessments included laboratory measurements (for example, serum chemistry (including glucose), hematology, urinalysis), Investigation of weight gain and metabolic disturbances, Prolactin, ECG, Vital sign measurements, Physical examinations, Tanner staging, Pregnancy testing, Urine drug screen. The Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and Simpson Angus Rating Scale (SARS) were used to assess extrapyramidal symptoms (EPS) and dyskinesia. Adverse events and vital signs were monitored throughout the study.

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 08 August 2007 |
| 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 | India: 45 |
| Country: Number of subjects enrolled | Romania: 10 |
| Country: Number of subjects enrolled | Russian Federation: 82 |
| Country: Number of subjects enrolled | Ukraine: 34 |
| Country: Number of subjects enrolled | United States: 30 |
| Worldwide total number of subjects | 201 |
| EEA total number of subjects | 10 |

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) | 201 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Recruitment started 8 August 2007 in medical clinics located around the world. The study ended on 30 March 2009.

Pre-assignment

Screening details:

Participants who were eligible for the study had their current disallowed psychotropic medications washed out prior to assignment to treatment groups. Participants who violated inclusion criteria before assignment (eg, because they continued to take a disallowed medication) were to be removed from the study.

Period 1

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

Blinding implementation details:

Double blinding was used during the 6-week treatment period (i.e., subjects, parent(s), legal guardian(s), investigators and the sponsor remained blinded to the study drug) to reduce potential bias during data collection and evaluation of clinical endpoints.

Arms

| | |
|------------------------------|-------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Pali ER Low |

Arm description:

Paliperidone ER 1.5 mg for subjects weighing 29 kg and above

| | |
|--|----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | INVEGA prolonged release tablets |
| Investigational medicinal product code | F067 |
| Other name | Paliperidone ER |
| Pharmaceutical forms | Prolonged-release tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants were randomly assigned to 1 of the 4 following treatment groups: Oral placebo tablets, Oral paliperidone ER tablet - low dose group (1.5 milligram per day [mg/day] for all participants), Oral paliperidone ER tablet - medium dose group (3 mg/day for Participants weighing between 29 to <51 kg and 6 mg/day for Participants weighing \geq 51 kg), Oral paliperidone ER tablet - high dose group (6 mg/day for Participants weighing between 29 to <51 kg and 12 mg/day for Participants weighing \geq 51 kg).

| | |
|------------------|----------------|
| Arm title | Pali ER Medium |
|------------------|----------------|

Arm description:

Paliperidone ER 3 mg (for subjects weighing between 29 kg and less than 51 kg) or 6 mg (for subjects weighing 51 kg and above)

| | |
|--|----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | INVEGA prolonged release tablets |
| Investigational medicinal product code | F067 |
| Other name | Paliperidone ER |
| Pharmaceutical forms | Prolonged-release tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants were randomly assigned to 1 of the 4 following treatment groups: Oral placebo tablets, Oral

paliperidone ER tablet - low dose group (1.5 milligram per day [mg/day] for all participants), Oral paliperidone ER tablet - medium dose group (3 mg/day for Participants weighing between 29 to <51 kg and 6 mg/day for Participants weighing ≥51 kg), Oral paliperidone ER tablet - high dose group (6 mg/day for Participants weighing between 29 to <51 kg and 12 mg/day for Participants weighing ≥51 kg).

| | |
|---|----------------------------------|
| Arm title | Pali ER High |
| Arm description: | |
| Paliperidone ER 6 mg (for subjects weighing between 29 kg and less than 51 kg) or 12 mg (for subjects weighing 51 kg and above) | |
| Arm type | Experimental |
| Investigational medicinal product name | INVEGA prolonged release tablets |
| Investigational medicinal product code | F067 |
| Other name | Paliperidone ER |
| Pharmaceutical forms | Prolonged-release tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants were randomly assigned to 1 of the 4 following treatment groups: Oral placebo tablets, Oral paliperidone ER tablet - low dose group (1.5 milligram per day [mg/day] for all participants), Oral paliperidone ER tablet - medium dose group (3 mg/day for Participants weighing between 29 to <51 kg and 6 mg/day for Participants weighing ≥51 kg), Oral paliperidone ER tablet - high dose group (6 mg/day for Participants weighing between 29 to <51 kg and 12 mg/day for Participants weighing ≥51 kg).

| | |
|---|--------------------------|
| Arm title | Placebo |
| Arm description: | |
| Matching Placebo to Paliperidone extended release tablet. | |
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Prolonged-release tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants were randomly assigned to oral placebo overencapsulated tablets.

| Number of subjects in period 1 | Pali ER Low | Pali ER Medium | Pali ER High |
|---|-------------|----------------|--------------|
| Started | 54 | 48 | 48 |
| Completed | 35 | 40 | 37 |
| Not completed | 19 | 8 | 11 |
| Adverse Event | 1 | 1 | 1 |
| Other | 3 | 1 | 1 |
| Subject Choice (Subject Withdrew Consent) | 1 | 2 | 4 |
| Lost to follow-up | - | 2 | 1 |
| Lack of efficacy | 14 | 2 | 4 |

| Number of subjects in period 1 | Placebo |
|---------------------------------------|---------|
| Started | 51 |

| | |
|---|----|
| Completed | 26 |
| Not completed | 25 |
| Adverse Event | - |
| Other | - |
| Subject Choice (Subject Withdrew Consent) | 2 |
| Lost to follow-up | 3 |
| Lack of efficacy | 20 |

Baseline characteristics

Reporting groups

| | |
|---|----------------|
| Reporting group title | Pali ER Low |
| Reporting group description: Paliperidone ER 1.5 mg for subjects weighing 29 kg and above | |
| Reporting group title | Pali ER Medium |
| Reporting group description: Paliperidone ER 3 mg (for subjects weighing between 29 kg and less than 51 kg) or 6 mg (for subjects weighing 51 kg and above) | |
| Reporting group title | Pali ER High |
| Reporting group description: Paliperidone ER 6 mg (for subjects weighing between 29 kg and less than 51 kg) or 12 mg (for subjects weighing 51 kg and above) | |
| Reporting group title | Placebo |
| Reporting group description: Matching Placebo to Paliperidone extended release tablet. | |

| Reporting group values | Pali ER Low | Pali ER Medium | Pali ER High |
|---|-------------|----------------|--------------|
| Number of subjects | 54 | 48 | 48 |
| Title for AgeCategorical Units: subjects | | | |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 54 | 48 | 48 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65 to 84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Title for AgeContinuous Units: years | | | |
| arithmetic mean | 15.1 | 15.3 | 15.5 |
| standard deviation | ± 1.5 | ± 1.6 | ± 1.6 |
| Title for Gender Units: subjects | | | |
| Female | 24 | 17 | 14 |
| Male | 30 | 31 | 34 |

| Reporting group values | Placebo | Total | |
|---|---------|-------|--|
| Number of subjects | 51 | 201 | |
| Title for AgeCategorical Units: subjects | | | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 51 | 201 | |
| Adults (18-64 years) | 0 | 0 | |
| From 65 to 84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Title for AgeContinuous Units: years | | | |
| arithmetic mean | 15.7 | | |
| standard deviation | ± 1.4 | - | |

| | | | |
|------------------|----|-----|--|
| Title for Gender | | | |
| Units: subjects | | | |
| Female | 28 | 83 | |
| Male | 23 | 118 | |

End points

End points reporting groups

| | |
|---|----------------|
| Reporting group title | Pali ER Low |
| Reporting group description: Paliperidone ER 1.5 mg for subjects weighing 29 kg and above | |
| Reporting group title | Pali ER Medium |
| Reporting group description: Paliperidone ER 3 mg (for subjects weighing between 29 kg and less than 51 kg) or 6 mg (for subjects weighing 51 kg and above) | |
| Reporting group title | Pali ER High |
| Reporting group description: Paliperidone ER 6 mg (for subjects weighing between 29 kg and less than 51 kg) or 12 mg (for subjects weighing 51 kg and above) | |
| Reporting group title | Placebo |
| Reporting group description: Matching Placebo to Paliperidone extended release tablet. | |

Primary: Change in the PANSS Total Score From Baseline to the Last Postrandomization Assessment in the Double-blind Period of the Study

| | |
|--|--|
| End point title | Change in the PANSS Total Score From Baseline to the Last Postrandomization Assessment in the Double-blind Period of the Study |
| End point description: The Positive and Negative Syndrome Scale (PANSS) measures the severity of psychotic symptoms of schizophrenia. Scores range from 30 to 210, where 30=best and 210=worst. The change in PANSS total score for all eligible subjects was measured from the beginning of the study to the end. The number of participants in the intent-to-treat (ITT) analysis set was used. This set includes patients who received study drug and have at least 1 efficacy measurement. The Last Observation Carried Forward method was used for imputation; ie, the last measure for subjects who ended study early was carried forward as if they completed the study. | |
| End point type | Primary |
| End point timeframe: 6 weeks | |

| End point values | Pali ER Low | Pali ER Medium | Pali ER High | Placebo |
|--------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 54 | 48 | 47 | 51 |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | -9.8 (± 16.31) | -17.3 (± 14.33) | -13.8 (± 15.74) | -7.9 (± 20.15) |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

If there were approximately 49 subjects per treatment group who had Week 6 (LOCF or end point) PANSS total measurements, the study was expected to have approximately 80% power to detect a clinically relevant difference of 13.2 points between any paliperidone ER group compared with placebo for the primary outcome measure.

| | |
|---|---|
| Comparison groups | Pali ER Low v Placebo v Pali ER Medium v Pali ER High |
| Number of subjects included in analysis | 200 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| P-value | = 0.508 ^[2] |
| Method | ANOVA |
| Parameter estimate | Median difference (final values) |
| Point estimate | -2.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.36 |
| upper limit | 4.16 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.17 |

Notes:

[1] - Used ANCOVA model with treatment(placebo, pali ER Low, pali ER Medium, and pali ER High) and country as factors and baseline value as a covariate.

[2] - The p value was associated with the closed testing procedure using Dunnett's test.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

If there were approximately 49 subjects per treatment group who had Week 6 (LOCF or end point) PANSS total measurements, the study was expected to have approximately 80% power to detect a clinically relevant difference of 13.2 points between any paliperidone ER group compared with placebo for the primary outcome measure.

| | |
|---|---|
| Comparison groups | Pali ER Medium v Placebo v Pali ER Low v Pali ER High |
| Number of subjects included in analysis | 200 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[3] |
| P-value | = 0.006 ^[4] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -10.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -16.58 |
| upper limit | -3.67 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.27 |

Notes:

[3] - Used ANCOVA model with treatment(placebo, pali ER Low, pali ER Medium, and pali ER High) and country as factors and baseline value as a covariate.

[4] - The p value was associated with the closed testing procedure using Dunnett's test.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

If there were approximately 49 subjects per treatment group who had Week 6 (LOCF or end point) PANSS total measurements, the study was expected to have approximately 80% power to detect a

clinically relevant difference of 13.2 points between any paliperidone ER group compared with placebo for the primary outcome measure.

| | |
|---|---|
| Comparison groups | Pali ER High v Placebo v Pali ER Low v Pali ER Medium |
| Number of subjects included in analysis | 200 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[5] |
| P-value | = 0.086 ^[6] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -6.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -13.07 |
| upper limit | -0.09 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.29 |

Notes:

[5] - Used ANCOVA model with treatment(placebo, pali ER Low, pali ER Medium, and pali ER High) and country as factors and baseline value as a covariate.

[6] - The p value was associated with the closed testing procedure using Dunnett's test.

Secondary: Change From Baseline to End Point in Clinical Global Impression-Severity (CGI-S) Scale

| | |
|-----------------|--|
| End point title | Change From Baseline to End Point in Clinical Global Impression-Severity (CGI-S) Scale |
|-----------------|--|

End point description:

The CGI-S rating scale was used to assess the severity of a subject's overall clinical condition. Scores range from 1 to 7, where 1=best and 7=worst. The number of participants in the intent-to-treat (ITT) analysis set was used. This set includes patients who received study drug and have at least 1 efficacy measurement. The Last Observation Carried Forward method was used for imputation; ie, the last measure for subjects who ended study early was carried forward as if they completed the study.

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

End point timeframe:

6 weeks

| End point values | Pali ER Low | Pali ER Medium | Pali ER High | Placebo |
|-------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 54 | 48 | 47 | 51 |
| Units: units on a scale | | | | |
| median (full range (min-max)) | 0 (-3 to 1) | -1 (-3 to 0) | -1 (-3 to 1) | 0 (-3 to 1) |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Analysis of the change in the CGI-S score at end point was performed using an analysis of covariance model on the ranks of the change in score at end point with treatment (placebo, pali ER Low, pali ER Medium, and pali ER High) and country as factors, and (non-ranked) baseline CGI-S score as a

covariate.

| | |
|---|---|
| Comparison groups | Pali ER Low v Placebo v Pali ER High v Pali ER Medium |
| Number of subjects included in analysis | 200 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.968 ^[7] |
| Method | ANCOVA |

Notes:

[7] - Comparison with placebo was without multiplicity adjustment.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

Analysis of the change in the CGI-S score at end point was performed using an analysis of covariance model on the ranks of the change in score at end point with treatment (placebo, pali ER Low, pali ER Medium, and pali ER High) and country as factors, and (non-ranked) baseline CGI-S score as a covariate.

| | |
|---|---|
| Comparison groups | Pali ER Medium v Placebo v Pali ER High v Pali ER Low |
| Number of subjects included in analysis | 200 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[8] |
| Method | ANCOVA |

Notes:

[8] - Comparison with placebo was without multiplicity adjustment.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

Analysis of the change in the CGI-S score at end point was performed using an analysis of covariance model on the ranks of the change in score at end point with treatment (placebo, pali ER Low, pali ER Medium, and pali ER High) and country as factors, and (non-ranked) baseline CGI-S score as a covariate.

| | |
|---|---|
| Comparison groups | Pali ER High v Placebo v Pali ER Low v Pali ER Medium |
| Number of subjects included in analysis | 200 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.021 ^[9] |
| Method | ANCOVA |

Notes:

[9] - Comparison with placebo was without multiplicity adjustment.

Secondary: Change From Baseline to End Point in Children's Global Assessment (CGAS) Score

| | |
|-----------------|--|
| End point title | Change From Baseline to End Point in Children's Global Assessment (CGAS) Score |
|-----------------|--|

End point description:

The CGAS score assesses psychological, social, and school functioning for children 6 to 17 years of age. Scores range from 1 to 100, where 100=best and 1=worst. The number of participants in the intent-to-treat (ITT) analysis set was used. This set includes patients who received study drug and have at least 1 efficacy measurement. The Last Observation Carried Forward method was used for imputation; ie, the last measure for subjects who ended study early was carried forward as if they completed the study.

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

End point timeframe:

6 weeks

| End point values | Pali ER Low | Pali ER Medium | Pali ER High | Placebo |
|--------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 54 | 48 | 47 | 51 |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | 4.4 (± 10.72) | 13.1 (± 12.07) | 8.6 (± 11.18) | 5 (± 13.82) |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Pali ER Low v Placebo v Pali ER Medium v Pali ER High |
| Number of subjects included in analysis | 200 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[10] |
| P-value | = 0.846 ^[11] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.54 |
| upper limit | 3.73 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.1 |

Notes:

[10] - Used ANCOVA model with treatment (placebo, pali ER Low, pali ER Medium, and pali ER High) and country as factors and baseline value as a covariate.

[11] - Comparison with placebo was without multiplicity adjustment.

| | |
|---|---|
| Statistical analysis title | Statistical Analysis 2 |
| Comparison groups | Pali ER Medium v Placebo v Pali ER Low v Pali ER High |
| Number of subjects included in analysis | 200 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[12] |
| P-value | < 0.001 ^[13] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 8.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 4.28 |
| upper limit | 12.82 |

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.17 |

Notes:

[12] - Used ANCOVA model with treatment(placebo, pali ER Low, pali ER Medium, and pali ER High) and country as factors and baseline value as a covariate.

[13] - Comparison with placebo was without multiplicity adjustment.

| | |
|---|---|
| Statistical analysis title | Statistical Analysis 3 |
| Comparison groups | Pali ER High v Placebo v Pali ER Low v Pali ER Medium |
| Number of subjects included in analysis | 200 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[14] |
| P-value | = 0.067 ^[15] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.28 |
| upper limit | 8.33 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.18 |

Notes:

[14] - Used ANCOVA model with treatment(placebo, pali ER Low, pali ER Medium, and pali ER High) and country as factors and baseline value as a covariate.

[15] - Comparison with placebo was without multiplicity adjustment.

Secondary: Change From Baseline to End Point in Sleep Visual Analog Scale (VAS) for Quality of Sleep.

| | |
|-----------------|--|
| End point title | Change From Baseline to End Point in Sleep Visual Analog Scale (VAS) for Quality of Sleep. |
|-----------------|--|

End point description:

The sleep VAS for sleep quality is a scale for measuring the quality of sleep experienced by a patient. Scores range from 0 to 100, where 100=best and 0=worst. The number of participants in the intent-to-treat (ITT) analysis set was used. This set includes patients who received study drug and have at least 1 efficacy measurement. The Last Observation Carried Forward method was used for imputation; ie, the last measure for subjects who ended study early was carried forward as if they completed the study.

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

End point timeframe:

6 weeks

| End point values | Pali ER Low | Pali ER Medium | Pali ER High | Placebo |
|--------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 54 | 48 | 47 | 50 |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | 6.6 (± 24.57) | 16 (± 27.06) | 14.4 (± 22.72) | -0.3 (± 34.21) |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | Pali ER Low v Placebo v Pali ER Medium v Pali ER High |
| Number of subjects included in analysis | 199 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[16] |
| P-value | = 0.058 ^[17] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 8.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.29 |
| upper limit | 16.56 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.27 |

Notes:

[16] - Used ANCOVA model with treatment(placebo, pali ER Low, pali ER Medium, and pali ER High) and country as factors and baseline value as a covariate.

[17] - Comparison with placebo was without multiplicity adjustment.

| Statistical analysis title | Statistical Analysis 2 |
|---|---|
| Comparison groups | Pali ER Medium v Placebo v Pali ER Low v Pali ER High |
| Number of subjects included in analysis | 199 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[18] |
| P-value | < 0.001 ^[19] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 16.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 8.08 |
| upper limit | 25.43 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.4 |

Notes:

[18] - Used ANCOVA model with treatment(placebo, pali ER Low, pali ER Medium, and pali ER High) and country as factors and baseline value as a covariate.

[19] - Comparison with placebo was without multiplicity adjustment.

| Statistical analysis title | Statistical Analysis 3 |
|---|---|
| Comparison groups | Pali ER High v Placebo v Pali ER Low v Pali ER Medium |
| Number of subjects included in analysis | 199 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[20] |
| P-value | = 0.003 ^[21] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 13.5 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 4.76 |
| upper limit | 22.23 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.43 |

Notes:

[20] - Used ANCOVA model with treatment(placebo, pali ER Low, pali ER Medium, and pali ER High) and country as factors and baseline value as a covariate.

[21] - Comparison with placebo was without multiplicity adjustment.

Secondary: Change From Baseline to End Point in Sleep VAS for Daytime Drowsiness

| | |
|-----------------|---|
| End point title | Change From Baseline to End Point in Sleep VAS for Daytime Drowsiness |
|-----------------|---|

End point description:

The sleep VAS for daytime drowsiness is a scale for measuring the drowsiness experienced by a patient. Scores range from 0 to 100, where 100=best and 0=worst. The number of participants in the intent-to-treat (ITT) analysis set was used. This set includes patients who received study drug and have at least 1 efficacy measurement. The Last Observation Carried Forward method was used for imputation; ie, the last measure for subjects who ended study early was carried forward as if they completed the study.

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

End point timeframe:

6 weeks

| End point values | Pali ER Low | Pali ER Medium | Pali ER High | Placebo |
|--------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 54 | 48 | 47 | 50 |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | -6.2 (± 24.69) | -7.2 (± 25.22) | 1 (± 29.55) | -2.8 (± 30.27) |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Placebo v Pali ER Medium v Pali ER Low v Pali ER High |
| Number of subjects included in analysis | 199 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[22] |
| P-value | = 0.237 ^[23] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -4.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -13.11 |
| upper limit | 3.26 |

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.15 |

Notes:

[22] - Used ANCOVA model with treatment(placebo, pali ER Low, pali ER Medium, and pali ER High) and country as factors and baseline value as a covariate.

[23] - Comparison with placebo was without multiplicity adjustment.

| | |
|---|---|
| Statistical analysis title | Statistical Analysis 2 |
| Comparison groups | Pali ER Medium v Placebo v Pali ER Low v Pali ER High |
| Number of subjects included in analysis | 199 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[24] |
| P-value | = 0.119 ^[25] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -6.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -15.15 |
| upper limit | 1.74 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.28 |

Notes:

[24] - Used ANCOVA model with treatment(placebo, pali ER Low, pali ER Medium, and pali ER High) and country as factors and baseline value as a covariate.

[25] - Comparison with placebo was without multiplicity adjustment.

| | |
|---|---|
| Statistical analysis title | Statistical Analysis 3 |
| Comparison groups | Pali ER High v Placebo v Pali ER Low v Pali ER Medium |
| Number of subjects included in analysis | 199 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.574 ^[26] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -2.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11 |
| upper limit | 6.11 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.34 |

Notes:

[26] - Used ANCOVA model with treatment(placebo, pali ER Low, pali ER Medium, and pali ER High) and country as factors and baseline value as a covariate.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Pali ER Low |
|-----------------------|-------------|

Reporting group description:

Paliperidone ER 1.5 mg for subjects weighing 29 kg and above

| | |
|-----------------------|----------------|
| Reporting group title | Pali ER Medium |
|-----------------------|----------------|

Reporting group description:

Paliperidone ER 3 mg (for subjects weighing between 29 kg and less than 51 kg) or 6 mg (for subjects weighing 51 kg and above)

| | |
|-----------------------|--------------|
| Reporting group title | Pali ER High |
|-----------------------|--------------|

Reporting group description:

Paliperidone ER 6 mg (for subjects weighing between 29 kg and less than 51 kg) or 12 mg (for subjects weighing 51 kg and above)

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

No text entered.

| Serious adverse events | Pali ER Low | Pali ER Medium | Pali ER High |
|---|----------------|----------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 54 (3.70%) | 1 / 48 (2.08%) | 1 / 48 (2.08%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Gastrointestinal disorders | | | |
| Mallory-Weiss Syndrome | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 1 / 48 (2.08%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 1 / 54 (1.85%) | 0 / 48 (0.00%) | 0 / 48 (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 |
| Psychotic Disorder | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 48 (0.00%) | 0 / 48 (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 |
| Schizophrenia | | | |
| subjects affected / exposed | 1 / 54 (1.85%) | 0 / 48 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Placebo | | |
|---|----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | | | |
| Gastrointestinal disorders | | | |
| Mallory-Weiss Syndrome | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychotic Disorder | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Schizophrenia | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Pali ER Low | Pali ER Medium | Pali ER High |
|--|--|---|---|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 19 / 54 (35.19%) | 20 / 48 (41.67%) | 33 / 48 (68.75%) |
| Investigations Weight Increased subjects affected / exposed occurrences (all) | 4 / 54 (7.41%) 4 | 2 / 48 (4.17%) 2 | 1 / 48 (2.08%) 1 |
| Cardiac disorders Tachycardia alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 2 / 48 (4.17%) 2 | 4 / 48 (8.33%) 5 |
| Nervous system disorders Cogwheel Rigidity subjects affected / exposed occurrences (all) Akathisia subjects affected / exposed occurrences (all) Dystonia subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Somnolence subjects affected / exposed occurrences (all) Tremor subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 2 / 54 (3.70%) 2 1 / 54 (1.85%) 2 5 / 54 (9.26%) 5 3 / 54 (5.56%) 3 1 / 54 (1.85%) 1 | 0 / 48 (0.00%) 0 4 / 48 (8.33%) 4 1 / 48 (2.08%) 1 3 / 48 (6.25%) 3 7 / 48 (14.58%) 8 4 / 48 (8.33%) 7 | 4 / 48 (8.33%) 7 8 / 48 (16.67%) 8 4 / 48 (8.33%) 9 5 / 48 (10.42%) 6 10 / 48 (20.83%) 12 4 / 48 (8.33%) 4 |
| Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Vomiting | 0 / 54 (0.00%) 0 | 0 / 48 (0.00%) 0 | 4 / 48 (8.33%) 6 |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 3 / 48 (6.25%) 3 | 4 / 48 (8.33%) 6 |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 3 / 54 (5.56%) | 1 / 48 (2.08%) | 0 / 48 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| Anxiety | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 48 (0.00%) | 4 / 48 (8.33%) |
| occurrences (all) | 0 | 0 | 4 |
| Insomnia | | | |
| subjects affected / exposed | 5 / 54 (9.26%) | 3 / 48 (6.25%) | 6 / 48 (12.50%) |
| occurrences (all) | 10 | 3 | 8 |
| Schizophrenia | | | |
| subjects affected / exposed | 5 / 54 (9.26%) | 0 / 48 (0.00%) | 2 / 48 (4.17%) |
| occurrences (all) | 5 | 0 | 2 |
| Metabolism and nutrition disorders | | | |
| Decreased Appetite | | | |
| subjects affected / exposed | 1 / 54 (1.85%) | 0 / 48 (0.00%) | 1 / 48 (2.08%) |
| occurrences (all) | 1 | 0 | 1 |

| | | | |
|---|------------------|--|--|
| Non-serious adverse events | Placebo | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 24 / 51 (47.06%) | | |
| Investigations | | | |
| Weight Increased | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | | |
| occurrences (all) | 0 | | |
| Cardiac disorders | | | |
| Tachycardia | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nervous system disorders | | | |
| Cogwheel Rigidity | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | | |
| occurrences (all) | 0 | | |
| Akathisia | | | |

| | | | |
|------------------------------------|------------------|--|--|
| subjects affected / exposed | 0 / 51 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dystonia | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | | |
| occurrences (all) | 0 | | |
| Headache | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | | |
| occurrences (all) | 2 | | |
| Somnolence | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | | |
| occurrences (all) | 1 | | |
| Tremor | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 6 / 51 (11.76%) | | |
| occurrences (all) | 7 | | |
| Vomiting | | | |
| subjects affected / exposed | 5 / 51 (9.80%) | | |
| occurrences (all) | 6 | | |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | | |
| occurrences (all) | 2 | | |
| Anxiety | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | | |
| occurrences (all) | 2 | | |
| Insomnia | | | |
| subjects affected / exposed | 11 / 51 (21.57%) | | |
| occurrences (all) | 16 | | |
| Schizophrenia | | | |
| subjects affected / exposed | 4 / 51 (7.84%) | | |
| occurrences (all) | 4 | | |
| Metabolism and nutrition disorders | | | |

| | | | |
|--|---------------------|--|--|
| Decreased Appetite subjects affected / exposed occurrences (all) | 3 / 51 (5.88%) 3 | | |
|--|---------------------|--|--|

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------|---|
| 15 May 2007 | This amendment was done to balance a number of important study design concerns as follows: 1) Lower weight subjects may have nearly double the drug exposure compared with higher weight subjects. Therefore, a regimen for lower weight subjects was milligram per kilogram (mg/kg) with half of the dose strength; 2) a regulatory agency objective requires that the entire dose range be explored. The current design used doses of ranging from 1.5 mg to 12 mg of paliperidone ER and the design allowed testing of the lowest possible dose of 1.5 mg; 3) Each paliperidone ER dose group covered nonoverlapping mg/kg values and thus allowed for a clear interpretation of each paliperidone ER group. The combinations of 3mg and 6 mg for the paliperidone ER medium dose group and that of 6mg and 12mg for the paliperidone ER high dose group wer interpreted as mg/kg over a range of mg/kg values as captured by the mg/kg of those subjects randomly assigned to those categories. |

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.

No information about longer-term (ie, >6 weeks) efficacy and safety in adolescents or in young (<12 years) children with schizophrenia. Results with doses less than 1.5 mg or more than 12 mg cannot be extrapolated from the data.

Notes: