



Clinical trial results:

Assessing the Effect of Missing Doses (Off-Days) of Daily Medication in Patients Stable on Pharmacotherapy for ADHD Receiving Atomoxetine or OROS Methylphenidate: A Parallel Matched Group Clinical Study (On/Off Study)

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2009-011426-33 |
| Trial protocol | ES NL SE |
| Global end of trial date | 03 May 2011 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 10 June 2018 |
| First version publication date | 10 June 2018 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | B4Z-EW-LYEN |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|---------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01127646 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Trial Number: 13070 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Eli Lilly and Company |
| Sponsor organisation address | Lilly Corporate Center, Indianapolis, IN, United States, 46285 |
| Public contact | Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 877CTLilly, |
| Scientific contact | Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 8772854559, |

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? | Yes |

Notes:

Results analysis stage

| | |
|--|-------------|
| Analysis stage | Final |
| Date of interim/final analysis | 03 May 2011 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|-------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 03 May 2011 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main purpose of the study is to help to understand the effect on children and adolescents who are stable on treatment with atomoxetine or osmotic-release oral system (OROS) methylphenidate for attention-deficit/hyperactivity disorder (ADHD) of not taking the medication for a maximum of 6 days over a 28-day study treatment period.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 22 June 2010 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|----------------|
| Country: Number of subjects enrolled | Netherlands: 1 |
| Country: Number of subjects enrolled | Spain: 20 |
| Country: Number of subjects enrolled | Sweden: 2 |
| Worldwide total number of subjects | 23 |
| EEA total number of subjects | 23 |

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) | 14 |
| Adolescents (12-17 years) | 9 |
| Adults (18-64 years) | 0 |

| | |
|---------------------|---|
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Not Applicable

Period 1

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

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|-------------|
| Arm title | Atomoxetine |
|------------------|-------------|

Arm description:

Participants received 25-80 milligrams (mg) of atomoxetine orally, once daily for 4 weeks (on/off period), except for the off-days, where participants received 1 or 2 oral once daily placebo doses per week, with 6 nonconsecutive, double-blinded placebo doses in total over the 4-week on/off period.

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | Atomoxetine |
| Investigational medicinal product code | LY139603 |
| Other name | Strattera |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received 25-80 milligrams (mg) of atomoxetine orally, once daily for 4 weeks (on/off period), except for the off-days, where participants received 1 or 2 oral once daily placebo doses per week, with 6 nonconsecutive, double-blinded placebo doses in total over the 4-week on/off period.

| | |
|------------------|--|
| Arm title | Osmotic-Release Oral System (OROS) Methylphenidate |
|------------------|--|

Arm description:

Participants received 18-54 mg of OROS methylphenidate orally, once daily for 4 weeks (on/off period), except for the off-days, where participants received 1 or 2 oral once daily placebo doses per week, with 6 nonconsecutive, double-blinded placebo doses in total over the 4-week on/off period.

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | Osmotic-Release Oral System (OROS) Methylphenidate |
| Investigational medicinal product code | |
| Other name | Concerta |
| Pharmaceutical forms | Prolonged-release tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received 18-54 mg of OROS methylphenidate orally, once daily for 4 weeks (on/off period), except for the off-days, where participants received 1 or 2 oral once daily placebo doses per week, with 6 nonconsecutive, double-blinded placebo doses in total over the 4-week on/off period.

| Number of subjects in period 1 | Atomoxetine | Osmotic-Release Oral System (OROS) Methylphenidate |
|--------------------------------|-------------|--|
| | | |
| Started | 15 | 8 |
| Completed | 14 | 7 |
| Not completed | 1 | 1 |
| Entry Criteria Not Met | 1 | - |
| Protocol deviation | - | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Atomoxetine |
|-----------------------|-------------|

Reporting group description:

Participants received 25-80 milligrams (mg) of atomoxetine orally, once daily for 4 weeks (on/off period), except for the off-days, where participants received 1 or 2 oral once daily placebo doses per week, with 6 nonconsecutive, double-blinded placebo doses in total over the 4-week on/off period.

| | |
|-----------------------|--|
| Reporting group title | Osmotic-Release Oral System (OROS) Methylphenidate |
|-----------------------|--|

Reporting group description:

Participants received 18-54 mg of OROS methylphenidate orally, once daily for 4 weeks (on/off period), except for the off-days, where participants received 1 or 2 oral once daily placebo doses per week, with 6 nonconsecutive, double-blinded placebo doses in total over the 4-week on/off period.

| Reporting group values | Atomoxetine | Osmotic-Release Oral System (OROS) Methylphenidate | Total |
|------------------------------------|-------------|--|-------|
| Number of subjects | 15 | 8 | 23 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|----------------|----------------|----|
| Age Continuous Units: years arithmetic mean standard deviation | 10.8 ± 2.65 | 10.9 ± 2.80 | - |
| Gender, Male/Female Units: Participants | | | |
| Female | 3 | 2 | 5 |
| Male | 12 | 6 | 18 |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 1 | 1 |
| Asian | 0 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 0 |
| White | 15 | 7 | 22 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Region of Enrollment Units: Subjects | | | |
| Netherlands | 1 | 0 | 1 |
| Spain | 12 | 8 | 20 |
| Sweden | 2 | 0 | 2 |
| Attention-Deficit/Hyperactivity Disorder (ADHD) Subtype: Current Episode Units: Subjects | | | |
| Combined | 7 | 4 | 11 |
| Hyperactive/Impulsive | 0 | 1 | 1 |
| Inattentive | 1 | 0 | 1 |
| Subtype not present | 6 | 3 | 9 |

| | | | |
|---|---|---|----|
| Missing | 1 | 0 | 1 |
| Attention-Deficit/Hyperactivity Disorder (ADHD) Subtype: Lifetime Episode | | | |
| Lifetime episode refers to the most severe episode in the past. | | | |
| Units: Subjects | | | |
| Combined | 8 | 7 | 15 |
| Hyperactive/Impulsive | 0 | 1 | 1 |
| Inattentive | 5 | 0 | 5 |
| Subtype not present | 1 | 0 | 1 |
| Missing | 1 | 0 | 1 |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | Atomoxetine |
| Reporting group description: Participants received 25-80 milligrams (mg) of atomoxetine orally, once daily for 4 weeks (on/off period), except for the off-days, where participants received 1 or 2 oral once daily placebo doses per week, with 6 nonconsecutive, double-blinded placebo doses in total over the 4-week on/off period. | |
| Reporting group title | Osmotic-Release Oral System (OROS) Methylphenidate |
| Reporting group description: Participants received 18-54 mg of OROS methylphenidate orally, once daily for 4 weeks (on/off period), except for the off-days, where participants received 1 or 2 oral once daily placebo doses per week, with 6 nonconsecutive, double-blinded placebo doses in total over the 4-week on/off period. | |

Primary: Daily Parent Report of Evening and Morning Behavior-Revised (DPREMB-R) Scale Mean Total Score (On-Days versus Off-Days) During the 4-Week Treatment Period

| | |
|--|---|
| End point title | Daily Parent Report of Evening and Morning Behavior-Revised (DPREMB-R) Scale Mean Total Score (On-Days versus Off-Days) During the 4-Week Treatment Period ^[1] |
| End point description: Parent-completed 11-item questionnaire; measures difficulty level of and 8 common evening behaviors (such as, sit through dinner) and 3 common morning behaviors (such as, get out of bed). Each item is scored on a 4-point Likert scale ranging from 0 (no difficulty) to 3 (a lot of difficulty). Total score (evening+morning) range is 0 to 33. Higher scores indicate greater difficulty in evening and morning behavior. DPREMB-R total score between days without missing doses (on-days) and days with missing doses (off-days) was not analyzed due to the insufficient sample size. Analysis Population Description: No participants had data analyzed due to the termination of the trial and the insufficient sample size. | |
| End point type | Primary |
| End point timeframe: Baseline through 4 weeks | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Zero participants were analyzed due to trial termination. Therefore, no inferential statistics were planned or conducted for this endpoint.

| End point values | Atomoxetine | Osmotic-Release Oral System (OROS) Methylphenidate | | |
|-----------------------------|------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[2] | 0 ^[3] | | |
| Units: Not Applicable (NA) | | | | |

Notes:

[2] - Zero participants were analyzed due to trial termination.

[3] - Zero participants were analyzed due to trial termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Global Impression of Perceived Difficulties (GIPD) Scale-Patient Version Total Score and Individual Items (On-Days Versus Off-Days) During the 4-Week Treatment Period

| | |
|-----------------|--|
| End point title | Global Impression of Perceived Difficulties (GIPD) Scale-Patient Version Total Score and Individual Items (On-Days Versus Off-Days) During the 4-Week Treatment Period |
|-----------------|--|

End point description:

Assesses attention-deficit/hyperactivity disorder (ADHD)-related difficulties (overall difficulties perceived in morning, during school, during homework, in evening, over entire day and night). Participant rates difficulties during past week on 7-point scale (1=normal, not difficult at all; 7=extremely difficult) for each of 5 items. Total score=sum of all subscores (items); range: 5 to 35. Higher scores=greater impairment. GIPD-Pat total score and item scores between days without missing doses (on-days) and days with missing doses (off-days) were not analyzed due to insufficient sample size.
Analysis Population Description: No data displayed because Outcome Measure has zero total participants analyzed.

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

End point timeframe:

Baseline through 4 weeks

| End point values | Atomoxetine | Osmotic-Release Oral System (OROS) Methylphenidate | | |
|-----------------------------|------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[4] | 0 ^[5] | | |
| Units: Not Applicable (NA) | | | | |

Notes:

[4] - Zero participants were analyzed due to trial termination.

[5] - Zero participants were analyzed due to trial termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Conners' Global Index-Teacher Rating Scale Total Score (On-Days Versus Off-Days) During the 4-Week Treatment Period

| | |
|-----------------|---|
| End point title | Conners' Global Index-Teacher Rating Scale Total Score (On-Days Versus Off-Days) During the 4-Week Treatment Period |
|-----------------|---|

End point description:

The teacher version of Conners' Global Index consists of 10 items with each item being scored on a 4-point scale ranging from 0 (not true at all, or never/seldom) to 3 (very much true, or very often/very frequent). The total score ranges from 0 to 30. Higher scores indicate greater impairment. The Conner's Global Index-Teacher Rating Scale total score between days without missing doses (on-days) and days with missing doses (off-days) was not analyzed due to the insufficient sample size.
Analysis Population Description: No participants had data analyzed due to the termination of the trial and the insufficient sample size.

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

End point timeframe:

Baseline through 4 weeks

| End point values | Atomoxetine | Osmotic-Release Oral System (OROS) Methylphenidate | | |
|-----------------------------|------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[6] | 0 ^[7] | | |
| Units: Not Applicable (NA) | | | | |

Notes:

[6] - Zero participants were analyzed due to trial termination.

[7] - Zero participants were analyzed due to trial termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Global Impression of Perceived Difficulties Scale-Patient Version (GIPD-Pat) Scale Total Score and Individual Items during the 4-Week Treatment Period

| | |
|-----------------|--|
| End point title | Global Impression of Perceived Difficulties Scale-Patient Version (GIPD-Pat) Scale Total Score and Individual Items during the 4-Week Treatment Period |
|-----------------|--|

End point description:

Assesses attention-deficit/hyperactivity disorder (ADHD)-related difficulties (overall difficulties perceived in morning, during school, during homework, in evening, over entire day and night). Difficulties during past week are rated by participant on a 7-point scale (1=normal, not difficult at all; 7=extremely difficult) for each of 5 items. Total score=sum of all subscores (items); range: 5 to 35. Higher scores=greater impairment. Mean GIPD-Pat total score and individual item scores for days with missing doses (off-days) between both groups were not analyzed due to insufficient sample size.

Analysis Population Description: No participants had data analyzed due to the termination of the trial and the insufficient sample size.

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

End point timeframe:

Baseline through 4 weeks

| End point values | Atomoxetine | Osmotic-Release Oral System (OROS) Methylphenidate | | |
|-----------------------------|------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[8] | 0 ^[9] | | |
| Units: Not Applicable (NA) | | | | |

Notes:

[8] - Zero participants were analyzed due to trial termination.

[9] - Zero participants were analyzed due to trial termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Attention-Deficit/Hyperactivity Disorder Rating Scale-Parent Version: Investigator Administered and Scored (ADHD-RS-IV Parent:Inv) Total Score and Subscores at Weeks 2, 3, and 4

| | |
|---|---|
| End point title | Attention-Deficit/Hyperactivity Disorder Rating Scale-Parent Version: Investigator Administered and Scored (ADHD-RS-IV Parent:Inv) Total Score and Subscores at Weeks 2, 3, and 4 |
| End point description: Assesses 18 Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, Text Revision (DSM-IV-TR) ADHD diagnosis symptoms/severity in past week. Each item: 0 (none/never, rarely) to 3 (severe/very often). Total score ranges from 0 to 54. Higher total scores indicate greater illness severity. This outcome measure was not analyzed due to the insufficient sample size. Analysis Population Description: No participants had data analyzed due to the termination of the trial and the insufficient sample size. | |
| End point type | Secondary |
| End point timeframe: Weeks 2, 3, and 4 | |

| End point values | Atomoxetine | Osmotic-Release Oral System (OROS) Methylphenidate | | |
|-----------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[10] | 0 ^[11] | | |
| Units: Not Applicable (NA) | | | | |

Notes:

[10] - Zero participants were analyzed due to trial termination.

[11] - Zero participants were analyzed due to trial termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression-Attention Deficit/Hyperactivity Disorder-Severity Scale (CGI-ADHD-S) at Weeks 2, 3, and 4

| | |
|---|--|
| End point title | Clinical Global Impression-Attention Deficit/Hyperactivity Disorder-Severity Scale (CGI-ADHD-S) at Weeks 2, 3, and 4 |
| End point description: This instrument is a single-item expert rating of the severity of the participant's attention-deficit/hyperactivity disorder (ADHD) symptoms in relation to the assessor's total experience of participants with ADHD. Severity is rated on a 7-point scale (1=normal, not ill at all; 7=among the most extremely ill participants). Higher scores represent greater illness severity. This outcome measure was not analyzed due to the insufficient sample size. Analysis Population Description: No data displayed because Outcome Measure has zero total participants analyzed. | |
| End point type | Secondary |
| End point timeframe: Weeks 2, 3, and 4 | |

| | | | | |
|-----------------------------|-------------------|--|--|--|
| End point values | Atomoxetine | Osmotic-Release Oral System (OROS) Methylphenidate | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[12] | 0 ^[13] | | |
| Units: Not Applicable (NA) | | | | |

Notes:

[12] - Zero participants were analyzed due to trial termination.

[13] - Zero participants were analyzed due to trial termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Emotion Expression Scale for Children (EESC)-Parent Rated Total Score up to Week 5

| | |
|-----------------|--|
| End point title | Emotion Expression Scale for Children (EESC)-Parent Rated Total Score up to Week 5 |
|-----------------|--|

End point description:

29-item parent-reported measure used to monitor effect of attention-deficit/hyperactivity disorder (ADHD) medication; examines 3 aspects of emotion expression: positive emotions, emotional flatness, and emotional lability. Each item rated on 5-point Likert scale (1="not at all true" to 5="very much true"). Positive emotional subscale items reversed scored (6-row score). Total score=transformed positive emotion + emotional flatness+ emotional lability subscales. Total scores range: 29 to 145. Higher scores=emotional impairment. This outcome measure not analyzed due to insufficient sample size.

Analysis Population Description: No participants had data analyzed due to the termination of the trial and the insufficient sample size.

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

End point timeframe:

Up to Week 5

| | | | | |
|-----------------------------|-------------------|--|--|--|
| End point values | Atomoxetine | Osmotic-Release Oral System (OROS) Methylphenidate | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[14] | 0 ^[15] | | |
| Units: Not Applicable (NA) | | | | |

Notes:

[14] - Zero participants were analyzed due to trial termination.

[15] - Zero participants were analyzed due to trial termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Daily Parent Report of Evening and Morning Behavior-Revised (DPREMB-R) Scale Subscores (On-Days Versus Off-Days) During the 4-Week Treatment Period

| | |
|-----------------|---|
| End point title | Daily Parent Report of Evening and Morning Behavior-Revised |
|-----------------|---|

End point description:

Parent-completed 11-item questionnaire; measures difficulty level of 8 common evening behaviors (such as, sit through dinner) and 3 common morning behaviors (such as, get out of bed) from 0 (no difficulty) to 3 (a lot of difficulty). Evening behavior total score range is 0 to 24. Morning behavior total score range is 0 to 9. Higher scores indicate greater difficulty in evening and morning behavior. DPREMB-R subscores between days without missing doses (on-days) and days with missing doses (off-days) not analyzed due to insufficient sample size.

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

End point timeframe:

Baseline through 4 weeks

| End point values | Atomoxetine | Osmotic-Release Oral System (OROS) Methylphenidate | | |
|-----------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[16] | 0 ^[17] | | |
| Units: Not Applicable (NA) | | | | |

Notes:

[16] - Zero participants were analyzed due to trial termination.

[17] - Zero participants were analyzed due to trial termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Outcomes Questions (On-Days Versus Off-Days) During the 4-Week Treatment Period

| | |
|-----------------|---|
| End point title | Patient Outcomes Questions (On-Days Versus Off-Days) During the 4-Week Treatment Period |
|-----------------|---|

End point description:

6-item questionnaire from attention-deficit/hyperactivity disorder (ADHD) advocacy group evaluates treatment outcomes ADHD participant's perspective. Parent completed on each day of on/off period. Each item ranged from 1 ("I totally agree") to 5 ("I totally disagree"). Items 1 and 2 pertain to sleeping and eating; high scores=better outcome. Items 3-6 pertain to behavior; high scores=worse outcome. The mean scores for analysis would have been created for each question across the days of each of the on and off phases; however, mean scores were not analyzed due to insufficient sample size. Analysis Population Description: No participants had data analyzed due to the termination of the trial and the insufficient sample size.

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

End point timeframe:

Baseline through 4 weeks

| End point values | Atomoxetine | Osmotic-Release Oral System (OROS) Methylphenidate | | |
|-----------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[18] | 0 ^[19] | | |
| Units: Not Applicable (NA) | | | | |

Notes:

[18] - Zero participants were analyzed due to trial termination.

[19] - Zero participants were analyzed due to trial termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Daily Parent Report of Evening and Morning Behavior-Revised (DPREMB-R) Scale Total Score and Subscores During the 4-Week Treatment Period

| | |
|-----------------|---|
| End point title | Daily Parent Report of Evening and Morning Behavior-Revised (DPREMB-R) Scale Total Score and Subscores During the 4-Week Treatment Period |
|-----------------|---|

End point description:

Parent-completed 11-item questionnaire; measures difficulty level of 3 common morning behaviors (such as, get out of bed) and 8 common evening behaviors (such as, sit through dinner) from 0 (no difficulty) to 3 (a lot of difficulty). Evening behavior total score range is 0 to 24. Morning behavior total score range is 0 to 9. Total score (evening+morning) range is 0 to 33. Higher scores indicate greater difficulty in evening and morning behavior. Mean DPREMB-R total score and subscores for days with missing doses (off-days) between both groups were not analyzed due to insufficient sample size. Analysis Population Description: No participants had data analyzed due to the termination of the trial and the insufficient sample size.

| | |
|--------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline through 4 weeks | |

| End point values | Atomoxetine | Osmotic-Release Oral System (OROS) Methylphenidate | | |
|-----------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[20] | 0 ^[21] | | |
| Units: Not Applicable (NA) | | | | |

Notes:

[20] - Zero participants were analyzed due to trial termination.

[21] - Zero participants were analyzed due to trial termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Conners' Global Index-Teacher Rating Scale Total Score During the 4-Week Treatment Period

| | |
|-----------------|---|
| End point title | Conners' Global Index-Teacher Rating Scale Total Score During |
|-----------------|---|

End point description:

The teacher version of Conners' Global Index consists of 10 items with each item being scored on a 4-point scale ranging from 0 (not true at all, or never/seldom) to 3 (very much true, or very often/very frequent). The total score ranges from 0 to 30. Higher scores indicate greater impairment. The Conners' Global Index-Teacher Rating Scale total score for days with missing doses (off-days) between both groups were not analyzed due to insufficient sample size.

Analysis Population Description: No participants had data analyzed due to the termination of the trial and the insufficient sample size.

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

| |
|----------------------|
| End point timeframe: |
|----------------------|

| |
|--------------------------|
| Baseline through 4 weeks |
|--------------------------|

| End point values | Atomoxetine | Osmotic-Release Oral System (OROS) Methylphenidate | | |
|-----------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[22] | 0 ^[23] | | |
| Units: Not Applicable (NA) | | | | |

Notes:

[22] - Zero participants were analyzed due to trial termination.

[23] - Zero participants were analyzed due to trial termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Global Impression of Perceived Difficulties Investigator Version (GIPD-Inv) Total Score and Subscores At Weeks 2, 3, and 4

| | |
|-----------------|--|
| End point title | Global Impression of Perceived Difficulties Investigator Version (GIPD-Inv) Total Score and Subscores At Weeks 2, 3, and 4 |
|-----------------|--|

End point description:

Assesses attention-deficit/hyperactivity disorder (ADHD)-related difficulties (overall difficulties perceived in morning, during school, during homework, in evening, and over entire day and night). Difficulties during past week are rated by investigator on a 7-point scale (1=normal, not difficult at all; 7=extremely difficult) for each of 5 items. Total score=sum of all subscores (items) and ranges from 5 to 35. Higher scores indicate greater impairment. This outcome measure was not analyzed due to the insufficient sample size.

Analysis Population Description: No participants had data analyzed due to the termination of the trial and the insufficient sample size.

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

| |
|----------------------|
| End point timeframe: |
|----------------------|

| |
|-------------------|
| Weeks 2, 3, and 4 |
|-------------------|

| End point values | Atomoxetine | Osmotic-Release Oral System (OROS) Methylphenidate | | |
|-----------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[24] | 0 ^[25] | | |
| Units: Not Applicable (NA) | | | | |

Notes:

[24] - Zero participants were analyzed due to trial termination.

[25] - Zero participants were analyzed due to trial termination.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from Baseline in Heart Rate up to 5 Weeks

| | |
|-----------------|--|
| End point title | Change from Baseline in Heart Rate up to 5 Weeks |
|-----------------|--|

End point description:

Analysis Population Description: Safety population: all participants who entered the study and took at least 1 dose of study medication.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline, up to 5 weeks

| End point values | Atomoxetine | Osmotic-Release Oral System (OROS) Methylphenidate | | |
|--------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 | 8 | | |
| Units: beats per minute (bpm) | | | | |
| arithmetic mean (standard deviation) | -1.2 (± 7.65) | 2.5 (± 12.74) | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from Baseline in Systolic and Diastolic Blood Pressure up to 5 Weeks

| | |
|-----------------|---|
| End point title | Change from Baseline in Systolic and Diastolic Blood Pressure up to 5 Weeks |
|-----------------|---|

End point description:

Analysis Population Description: Safety population: all participants who entered the study and took at least 1 dose of study medication.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:
Baseline, up to 5 weeks

| End point values | Atomoxetine | Osmotic- Release Oral System (OROS) Methylphenidat e | | |
|---------------------------------------|-----------------|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 14 | 7 | | |
| Units: millimeters of mercury (mm Hg) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Diastolic Blood Pressure | 1.9 (± 6.14) | -1.5 (± 4.67) | | |
| Systolic Blood Pressure | -0.1 (± 9.00) | -3.7 (± 3.75) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event data were collected for the entire study period, which included the following: 3-14 day screening period, a run-in period of up to 7 days, a 4-week on/off period, and a 1-5 day run-out period for a maximum of 54 days.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 14.0 |

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Osmotic-Release Oral System (OROS) Methylphenidate |
|-----------------------|--|

Reporting group description:

Participants received 18-54 mg of OROS methylphenidate orally, once daily during the run-in period for up to 7 days. The run-in period was followed by the 4-week on/off period in which participants received 18-54 mg of OROS methylphenidate orally, once daily for 4 weeks, except for the off-days, where participants received 1 or 2 oral once daily placebo doses per week, with 6 nonconsecutive, double-blinded placebo doses in total over the 4-week on/off period. The on/off period was followed by a run-out period in which participants received 18-54 mg of OROS methylphenidate orally, once daily for 1-5 days.

| | |
|-----------------------|-------------|
| Reporting group title | Atomoxetine |
|-----------------------|-------------|

Reporting group description:

Participants received 25-80 milligrams (mg) of atomoxetine orally, once daily during the run-in period for up to 7 days. The run-in period was followed by the 4-week on/off period in which participants received 25-80 mg of atomoxetine orally, once daily for 4 weeks, except for the off-days, where participants received 1 or 2 oral once daily placebo doses per week, with 6 nonconsecutive, double-blinded placebo doses in total over the 4-week on/off period. The on/off period was followed by a run-out period in which participants received 25-80 mg of atomoxetine orally, once daily for 1-5 days.

| Serious adverse events | Osmotic-Release Oral System (OROS) Methylphenidate | Atomoxetine | |
|---|--|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 15 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |

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

| Non-serious adverse events | Osmotic-Release Oral System (OROS) Methylphenidate | Atomoxetine | |
|---|--|-----------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 4 / 8 (50.00%) | 7 / 15 (46.67%) | |
| Nervous system disorders | | | |

| | | | |
|---|---------------------|----------------------|--|
| Disturbance in attention alternative dictionary used: MedDRA 14.0 subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 0 / 15 (0.00%) 0 | |
| Dizziness alternative dictionary used: MedDRA 14.0 subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 2 / 15 (13.33%) 2 | |
| Headache alternative dictionary used: MedDRA 14.0 subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 2 / 15 (13.33%) 8 | |
| Somnolence alternative dictionary used: MedDRA 14.0 subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 1 / 15 (6.67%) 3 | |
| General disorders and administration site conditions Fatigue alternative dictionary used: MedDRA 14.0 subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 1 / 15 (6.67%) 2 | |
| Pyrexia alternative dictionary used: MedDRA 14.0 subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 1 / 15 (6.67%) 1 | |
| Gastrointestinal disorders Abdominal pain alternative dictionary used: MedDRA 14.0 subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 1 / 15 (6.67%) 6 | |
| Abdominal pain upper alternative dictionary used: MedDRA 14.0 subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 1 / 15 (6.67%) 1 | |
| Nausea | | | |

| | | | |
|---|---|---|--|
| <p>alternative dictionary used: MedDRA 14.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>0 / 8 (0.00%)</p> <p>0</p> | <p>2 / 15 (13.33%)</p> <p>3</p> | |
| <p>Toothache</p> <p>alternative dictionary used: MedDRA 14.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>0 / 8 (0.00%)</p> <p>0</p> | <p>1 / 15 (6.67%)</p> <p>1</p> | |
| <p>Vomiting</p> <p>alternative dictionary used: MedDRA 14.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>0 / 8 (0.00%)</p> <p>0</p> | <p>2 / 15 (13.33%)</p> <p>10</p> | |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Oropharyngeal pain</p> <p>alternative dictionary used: MedDRA 14.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>0 / 8 (0.00%)</p> <p>0</p> | <p>1 / 15 (6.67%)</p> <p>1</p> | |
| <p>Psychiatric disorders</p> <p>Affect lability</p> <p>alternative dictionary used: MedDRA 14.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Impulsive behaviour</p> <p>alternative dictionary used: MedDRA 14.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Insomnia</p> <p>alternative dictionary used: MedDRA 14.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nervousness</p> <p>alternative dictionary used: MedDRA 14.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>0 / 8 (0.00%)</p> <p>0</p> <p>2 / 8 (25.00%)</p> <p>2</p> <p>1 / 8 (12.50%)</p> <p>1</p> <p>0 / 8 (0.00%)</p> <p>0</p> | <p>1 / 15 (6.67%)</p> <p>1</p> <p>0 / 15 (0.00%)</p> <p>0</p> <p>0 / 15 (0.00%)</p> <p>0</p> <p>1 / 15 (6.67%)</p> <p>1</p> | |
| <p>Musculoskeletal and connective tissue disorders</p> | | | |

| | | | |
|---|---------------------|---------------------|--|
| Pain in extremity alternative dictionary used: MedDRA 14.0 subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 0 / 15 (0.00%) 0 | |
| Infections and infestations Herpes zoster alternative dictionary used: MedDRA 14.0 subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 1 / 15 (6.67%) 1 | |
| Metabolism and nutrition disorders Decreased appetite alternative dictionary used: MedDRA 14.0 subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 1 / 15 (6.67%) 2 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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.

| |
|---|
| This study (Study LYEN) was terminated after enrolling 23 participants due to lack of availability of study participants to accommodate the study design. |
|---|

Notes: