Clinical trial results:
A Randomized Double-Blind, Placebo-Controlled Clinical Trial of Efficacy and Safety of Atomoxetine up to 12 weeks in Newly Diagnosed Children and Adolescents Outpatients with Attention-Deficit/Hyperactivity Disorder (ADHD)

Summary

EudraCT number	2004-004088-31
Trial protocol	ES
Global end of trial date	06 February 2008

Results information

Result version number	v1 (current)
This version publication date	04 July 2016
First version publication date	02 August 2015

Trial information

Trial identification

Sponsor protocol code	B4Z-XM-LYDM

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00191945
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 8836, Trial Alias: B4Z-XM-LYDM

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, 1 877-CTLilly,
Scientific contact	Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 877-285-4559,

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	06 February 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 February 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Double blinded clinical trial placebo controlled in 153 children (planned enrollment) with recent diagnosis of ADHD. Patients will be randomized to atomoxetine or placebo arm (2:1). The double blinded period will last 12 weeks and the treatment open phase will last up to 1 year, and atomoxetine treatment will be administered.

A gatekeeper strategy will be employed for sequentially testing the secondary objectives.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (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	09 May 2005
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	Spain: 151
Worldwide total number of subjects	151
EEA total number of subjects	151

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)	113
Adolescents (12-17 years)	38
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:

158 patients enrolled during the Screening Period (Visits 1 and 2), but 7 did not receive study drug and are not included in the 151 patients randomized in the Double-Blind Period.

Period 1

Period 1 title	Double-Blind Acute Treatment
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Atomoxetine

Arm description:

Double-Blind Acute Period: 0.5 milligram/kilogram (mg/kg) /day every day, by mouth for 2 weeks, 1.2 - 1.4 mg/kg/day every day, by mouth for 10 weeks

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

Dosage and administration details:

0.5 mg/kg/day every day, by mouth for 2 weeks, 1.2 - 1.4 mg/kg/day every day, by mouth for 10 weeks

Arm title	Placebo

Arm description:

Double-Blind Acute Period: every day, by mouth for 12 weeks,then possibility to switch to atomoxetine at 0.5 mg/kg/day every day, by mouth for 1 week

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Double-Blind Acute Period: every day, by mouth for 12 weeks,then possibility to switch to atomoxetine at 0.5 mg/kg/day every day, by mouth for 1 week

Investigational medicinal product name	Atomoxetine Hydrochloride
Investigational medicinal product code	
Other name	LY139603, Strattera
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

atomoxetine at 0.5 mg/kg/day every day, by mouth for 1 week

Number of subjects in period 1	Atomoxetine	Placebo
Started	100	51
Completed	94	48
Not completed	6	3
Physician decision	-	2
Non Protocol Compliance	3	-
Lost to follow-up	-	1
Parent's Decision	3	-

Period 2	
Period 2 title	Open-Label Treatment Extension
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	Atomoxetine

Arm description:

1.2 - 1.4 mg/kg/day every day, by mouth for up to 1 year

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

Dosage and administration details:

1.2 - 1.4 mg/kg/day every day, by mouth for up to 1 year

Arm title	Placebo

Arm description:

1.2 - 1.4 mg/kg/day every day, by mouth for up to 1 year

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

Dosage and administration details:

1.2 - 1.4 mg/kg/day every day, by mouth for up to 1 year

Number of subjects in period 2	Atomoxetine	Placebo
Started	94	48
Completed	94	48

Baseline characteristics

Reporting groups	
Reporting group title	Atomoxetine
Reporting group description:	
Double-Blind Acute Period: 0.5 milligram/kilogram (mg/kg) /day every day, by mouth for 2 weeks, 1.2 - 1.4 mg/kg/day every day, by mouth for 10 weeks	
Reporting group title	Placebo
Reporting group description:	
Double-Blind Acute Period: every day, by mouth for 12 weeks,then possibility to switch to atomoxetine at 0.5 mg/kg/day every day, by mouth for 1 week	

Reporting group values	Atomoxetine	Placebo	Total
Number of subjects	100	51	151
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	10.3	10.3	
standard deviation	± 2.48	± 2.43	-
Gender categorical Units: Subjects			
Female	21	10	31
Male	79	41	120
Region of Enrollment Units: Subjects			
Spain	100	51	151
Attention-Deficit/Hyperactivity Disorder Subtype Units: Subjects			
Inattentive	30	19	49
Hyperactive	5	1	6
Combined (Hyperactive-Inattentive)	64	30	94
Not Assessed	1	1	2
Race/Ethnicity Units: Subjects			
Caucasian	98	47	145
African	0	1	1
Hispanic	2	3	5
Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version:Investigator-Administered			
Measures the 18 symptoms contained in the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, Text Revision (DSM-IV-TR) diagnosis of Attention-Deficit/Hyperactivity Disorder. Individual item scores range from 0 (none/never or rarely) to 3 (severe/very often). Total scores range from 0 to 54.			
Units: units on a scale			
arithmetic mean	39.1	39.5	
standard deviation	± 9	± 9	-
Systolic Blood Pressure			

Units: millimeters of mercury (mmHg)			
arithmetic mean	101.2	100.5	
standard deviation	± 10.01	± 10.01	-
Body Weight			
Units: kilograms			
arithmetic mean	37.9	37.4	
standard deviation	± 11.86	± 12.18	-
Diastolic Blood Pressure			
Units: mmHg			
arithmetic mean	57.9	58	
standard deviation	± 7.15	± 7.68	-

End points

End points reporting groups

Reporting group title	Atomoxetine
Reporting group description:	
Double-Blind Acute Period: 0.5 milligram/kilogram (mg/kg) /day every day, by mouth for 2 weeks, 1.2 - 1.4 mg/kg/day every day, by mouth for 10 weeks	
Reporting group title	Placebo
Reporting group description:	
Double-Blind Acute Period: every day, by mouth for 12 weeks,then possibility to switch to atomoxetine at 0.5 mg/kg/day every day, by mouth for 1 week	
Reporting group title	Atomoxetine
Reporting group description:	
1.2 - 1.4 mg/kg/day every day, by mouth for up to 1 year	

Reporting group title	Placebo
Reporting group description:	
1.2 - 1.4 mg/kg/day every day, by mouth for up to 1 year	
Subject analysis set title	Outcome Measure 1 Atomoxetine
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Intention to Treat analysis. Single item missing scores were imputed with the mean score of the remaining items when computing subscale and total scores.	
Subject analysis set title	Outcome Measure 1 Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Intention to Treat analysis. Single item missing scores were imputed with the mean score of the remaining items when computing subscale and total scores.	
Subject analysis set title	Outcome Measure 2 Atomoxetine
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Intention to Treat analysis. Single item missing scores were imputed with the mean score of the remaining items when computing subscale and total scores.	
Subject analysis set title	Outcome Measure 2 Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Intention to Treat analysis. Single item missing scores were imputed with the mean score of the remaining items when computing subscale and total scores.	
Subject analysis set title	Outcome Measure 3 Atomoxetine
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Intention to Treat analysis. Single item missing scores were imputed with the mean score of the remaining items when computing subscale and total scores.	
Subject analysis set title	Outcome Measure 3 Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Intention to Treat analysis. Single item missing scores were imputed with the mean score of the remaining items when computing subscale and total scores.	
Subject analysis set title	Outcome Measure 4 Atomoxetine
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Intention to Treat analysis. Single item missing scores were imputed with the mean score of the	

remaining items when computing subscale and total scores.

Subject analysis set title	Outcome Measure 4 Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention to Treat analysis. Single item missing scores were imputed with the mean score of the remaining items when computing subscale and total scores.

Subject analysis set title	Outcome Measure 5 Atomoxetine
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention to Treat analysis. Single item missing scores were imputed with the mean score of the remaining items when computing subscale and total scores.

Subject analysis set title	Outcome Measure 5 Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention to Treat analysis. Single item missing scores were imputed with the mean score of the remaining items when computing subscale and total scores.

Subject analysis set title	Outcome Measure 6 Atomoxetine
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention to Treat analysis. Single item missing scores were imputed with the mean score of the remaining items when computing subscale and total scores.

Subject analysis set title	Outcome Measure 6 Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention to Treat analysis. Single item missing scores were imputed with the mean score of the remaining items when computing subscale and total scores.

Subject analysis set title	Outcome Measure 7 Atomoxetine
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention to Treat analysis. Last observation carried forward.

Subject analysis set title	Outcome Measure 8 Atomoxetine
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention to Treat analysis. Last observation carried forward.

Subject analysis set title	Outcome Measure 8 Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention to Treat analysis. Last observation carried forward.

Subject analysis set title	Outcome Measure 9 Atomoxetine
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention to Treat analysis. Last observation carried forward.

Subject analysis set title	Outcome Measure 9 Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention to Treat analysis. Last observation carried forward.

Subject analysis set title	Outcome Measure 10 Atomoxetine
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention to Treat analysis. All randomized participants who took at least one dose of study drug.

Subject analysis set title	Outcome Measure 10 Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention to Treat analysis. All randomized participants who took at least one dose of study drug.

Subject analysis set title	Outcome Measure 11 Atomoxetine
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention to Treat analysis. Last observation carried forward.

Subject analysis set title	Outcome Measure 12 Atomoxetine
Subject analysis set type	Full analysis

Subject analysis set description:

All randomized participants.

Subject analysis set title	Outcome Measure 12 Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

All randomized participants.

Subject analysis set title	Outcome Measure 13 Atomoxetine
Subject analysis set type	Full analysis

Subject analysis set description:

All randomized participants.

Subject analysis set title	Outcome Measure 13 Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

All randomized participants.

Subject analysis set title	Outcome Measure 14 Atomoxetine
Subject analysis set type	Full analysis

Subject analysis set description:

All randomized participants.

Subject analysis set title	Outcome Measure 14 Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

All randomized participants.

Subject analysis set title	Outcome Measure 15 Atomoxetine
Subject analysis set type	Full analysis

Subject analysis set description:

All randomized participants.

Subject analysis set title	Outcome Measure 15 Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

All randomized participants.

Primary: Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version:Investigator Administered and Scored (ADHDRS-IV-Parent:Inv) Total Score at 12 Week Endpoint

End point title	Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version:Investigator Administered and Scored (ADHDRS-IV-Parent:Inv) Total Score at 12 Week Endpoint

End point description:

Measures the 18 symptoms contained in the DSM-IV diagnosis of Attention-Deficit/Hyperactivity Disorder. Individual item scores range from 0 (none/never or rarely) to 3 (severe/very often). Total Scores range from 0 to 54.

End point type	Primary

End point timeframe:

Week 12

End point values	Outcome Measure 1 Atomoxetine	Outcome Measure 1 Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	99	50		
Units: units on a scale				
arithmetic mean (standard deviation)	26.3 (± 12.7)	34.8 (± 12.3)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for Outcome Measure 1

Statistical analysis description:

Other relevant estimation information: Least Squares Mean difference at week 12 (Atomoxetine minus Placebo)

Comparison groups	Outcome Measure 1 Atomoxetine v Outcome Measure 1 Placebo
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-7.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11
upper limit	-4.8
Variability estimate	Standard error of the mean
Dispersion value	1.6

Notes:

[1] - Mixed Model Repeated Measures analysis method: treatment, study site, visit, treatment-by-visit interaction, baseline. Least Squares Mean difference at week 12 (Atomoxetine minus Placebo)

Secondary: Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version:Investigator Administered and Scored (ADHDRS-IV-Parent:Inv) Total Score at 9 Weeks

End point title	Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version:Investigator Administered and Scored (ADHDRS-IV-Parent:Inv) Total Score at 9 Weeks

End point description:

Measures the 18 symptoms contained in the DSM-IV diagnosis of Attention-Deficit/Hyperactivity Disorder. Individual item scores range from 0 (none/never or rarely) to 3 (severe/very often). Total scores range from 0 to 54.

End point type	Secondary

End point timeframe:

Week 9

End point values	Outcome Measure 2 Atomoxetine	Outcome Measure 2 Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	99	50		
Units: units on a scale				
arithmetic mean (standard deviation)	27.3 (± 12.3)	34.4 (± 12)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for Outcome Measure 2

Statistical analysis description:

A gatekeeper strategy was employed for sequentially testing the secondary hypotheses using a REML-based Mixed-Model Repeated Measures (MMRM) technique as defined for the primary efficacy analyses. If primary hypothesis is significant at 0.05 (2-sided), first secondary hypothesis will be tested at Visit 6 from MMRM. If comparison is significant, subsequent secondary hypotheses will be tested in sequence until first null hypothesis fails to be rejected.

Comparison groups	Outcome Measure 2 Atomoxetine v Outcome Measure 2 Placebo
Number of subjects included in analysis	149
Analysis specification	Post-hoc
Analysis type	superiority[2]
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.5
upper limit	-3.6
Variability estimate	Standard error of the mean
Dispersion value	1.5

Notes:

[2] - Mixed Model Repeated Measures analysis method: treatment, study site, visit, treatment-by-visit interaction, baseline.

Secondary: Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version:Investigator Administered and Scored (ADHDRS-IV-Parent:Inv) Total Score at 6 Weeks

End point title	Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version:Investigator Administered and Scored (ADHDRS-IV-Parent:Inv) Total Score at 6 Weeks

End point description:

Measures the 18 symptoms contained in the DSM-IV diagnosis of Attention-Deficit/Hyperactivity Disorder. Individual item scores range from 0 (none/never or rarely) to 3 (severe/very often). Total scores range from 0 to 54.

End point type	Secondary

End point timeframe:

Week 6

End point values	Outcome Measure 3 Atomoxetine	Outcome Measure 3 Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	99	50		
Units: units on a scale				
arithmetic mean (standard deviation)	28.7 (± 12.9)	34.4 (± 12)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for Outcome Measure 3

Statistical analysis description:

A gatekeeper strategy was employed for sequentially testing the secondary hypotheses using a REML-based Mixed-Model Repeated Measures (MMRM) technique as defined for the primary efficacy analyses. If primary hypothesis is significant at 0.05 (2-sided), first secondary hypothesis will be tested at Visit 6 from MMRM. If comparison is significant, subsequent secondary hypotheses will be tested in sequence until first null hypothesis fails to be rejected.

Comparison groups	Outcome Measure 3 Atomoxetine v Outcome Measure 3 Placebo
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0009
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-5.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.2
upper limit	-2.2
Variability estimate	Standard error of the mean
Dispersion value	1.5

Notes:

[3] - Mixed Model Repeated Measures analysis method: treatment, study site, visit, treatment-by-visit interaction, baseline.

Secondary: Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version:Investigator Administered and Scored (ADHDRS-IV-Parent:Inv) Total Score at 4 Weeks

End point title	Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version:Investigator Administered and Scored (ADHDRS-IV-Parent:Inv) Total Score at 4 Weeks

End point description:

Measures the 18 symptoms contained in the DSM-IV diagnosis of Attention-Deficit/Hyperactivity Disorder. Individual item scores range from 0 (none/never or rarely) to 3 (severe/very often). Total scores range from 0 to 54.

End point type	Secondary

End point timeframe:

Week 4

End point values	Outcome Measure 4 Atomoxetine	Outcome Measure 4 Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	99	50		
Units: units on a scale				
arithmetic mean (standard deviation)	31.2 (± 12)	35.5 (± 12)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Ouctome Measure 4

Statistical analysis description:

A gatekeeper strategy was employed for sequentially testing the secondary hypotheses using a REML-based Mixed-Model Repeated Measures (MMRM) technique as defined for the primary efficacy analyses. If primary hypothesis is significant at 0.05 (2-sided), first secondary hypothesis will be tested at Visit 6 from MMRM. If comparison is significant, subsequent secondary hypotheses will be tested in sequence until first null hypothesis fails to be rejected.

Comparison groups	Outcome Measure 4 Atomoxetine v Outcome Measure 4 Placebo
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.0033
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-3.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.4
upper limit	-1.3
Variability estimate	Standard error of the mean
Dispersion value	1.3

Notes:

[4] - Mixed Model Repeated Measures analysis method: treatment, study site, visit, treatment-by-visit interaction, baseline.

Secondary: Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version:Investigator Administered and Scored (ADHDRS-IV-Parent:Inv) Total Score Change From Week 6 to Week 12

End point title	Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version:Investigator Administered and Scored (ADHDRS-IV-Parent:Inv) Total Score Change From Week 6 to Week 12

End point description:

Measures the 18 symptoms contained in the DSM-IV diagnosis of Attention-Deficit/Hyperactivity Disorder. Individual item scores range from 0 (none/never or rarely) to 3 (severe/very often). Total

scores range from 0 to 54.

End point type	Secondary

End point timeframe:

week 6 and week 12

End point values	Outcome Measure 5 Atomoxetine	Outcome Measure 5 Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	99	50		
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 6	28.7 (± 12.9)	34.4 (± 12)		
Week 12	26.3 (± 12.7)	34.8 (± 12.3)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for Outcome Measure 5

Statistical analysis description:

A gatekeeper strategy was employed for sequentially testing the secondary hypotheses using a REML-based Mixed-Model Repeated Measures (MMRM) technique as defined for the primary efficacy analyses. If primary hypothesis is significant at 0.05 (2-sided), first secondary hypothesis will be tested at Visit 6 from MMRM. If comparison is significant, subsequent secondary hypotheses will be tested in sequence until first null hypothesis fails to be rejected.

Comparison groups	Outcome Measure 5 Atomoxetine v Outcome Measure 5 Placebo
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.013 [6]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.9
upper limit	-0.6
Variability estimate	Standard error of the mean
Dispersion value	1.1

Notes:

[5] - Mixed Model Repeated Measures analysis method: treatment, study site, visit, treatment-by-visit interaction, baseline.
[6] - P-value is for the difference between groups in the change from 12 weeks minus 6 weeks.

Secondary: Clinical Global Impressions- Attention-Deficit/Hyperactivity Disorder-Severity Changes From Baseline to Visit 7 (12 Weeks)

End point title	Clinical Global Impressions- Attention-Deficit/Hyperactivity Disorder-Severity Changes From Baseline to Visit 7 (12 Weeks)

End point description:	
Measures severity of the patient's overall severity of ADHD symptoms (1=normal, not at all ill; 7=among the most extremely ill patients).	
End point type	Secondary
End point timeframe:	
Baseline and 12 weeks	

End point values	Outcome Measure 6 Atomoxetine	Outcome Measure 6 Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	99	50		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	5.06 (± 0.93)	5.04 (± 0.83)		
Week 12	3.89 (± 1.15)	4.5 (± 0.91)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impressions- Attention-Deficit/Hyperactivity Disorder-Severity Change From Baseline to Endpoint (Visit 18) of the Open-Label Extension (107 Weeks)

End point title	Clinical Global Impressions- Attention-Deficit/Hyperactivity Disorder-Severity Change From Baseline to Endpoint (Visit 18) of the Open-Label Extension (107 Weeks)
End point description:	
Measures severity of the patient's overall severity of ADHD symptoms (1=normal, not at all ill; 7=among the most extremely ill patients).	
End point type	Secondary
End point timeframe:	
Baseline and Open-Label Endpoint (107 weeks)	

End point values	Outcome Measure 7 Atomoxetine			
Subject group type	Subject analysis set			
Number of subjects analysed	140			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	5.1 (± 0.92)			
Week 107	3.2 (± 1.28)			

Statistical analyses

No statistical analyses for this end point

Secondary: Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S) Total Score Changes From Baseline to Endpoint (Week 12)

End point title	Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S) Total Score Changes From Baseline to Endpoint (Week 12)

End point description:

The CPRS-R:S has 27 items to be completed by the parent to assess behavioral problems related to ADHD. Individual item scores range from 0 (not at all true/never/seldom: lowest impairment) to 3 (very much true/very often/very frequent: highest impairment). The total score is calculated as the sum of all items. Total scores range from 0 to 81.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Outcome Measure 8 Atomoxetine	Outcome Measure 8 Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	99	50		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	54.6 (± 12.6)	54.7 (± 13.6)		
Week 12	37.8 (± 18.7)	48.5 (± 17.4)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for Outcome Measure 8
Comparison groups	Outcome Measure 8 Placebo v Outcome Measure 8 Atomoxetine
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-10.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.1
upper limit	-6.2
Variability estimate	Standard error of the mean
Dispersion value	2.3

Notes:

[7] - mixed model repeated measures analyis: treatment, visit, patient, and CPRS-R: S Total score at baseline as covariate, with treatment*visit interaction.

P-value is for the difference between groups in the change from 12 weeks minus baseline.

Secondary: Child Health and Illness Profile (CHIP) Change From Baseline to Endpoint (12 Weeks)

End point title	Child Health and Illness Profile (CHIP) Change From Baseline to Endpoint (12 Weeks)

End point description:

Parent-rated assessment of a child's health status and level of functioning. It consists of 76 items. The majority of items assess frequency of activities or feelings using a five-point response format (for example, 'how good is your child at making friends?' 1=never, 5=always). Standard scores (t-value) were established, with all domains and subdomains having a mean score of 50 and standard deviation of 10. Standard scores are expressed in standard deviation units. T-score=[(Score-4.2382)*10/0.32835]+50. Higher scores mean improvement.

End point type	Secondary

End point timeframe:

Baseline to 12 weeks

End point values	Outcome Measure 9 Atomoxetine	Outcome Measure 9 Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	99	50		
Units: standard deviation units				
arithmetic mean (standard deviation)				
Parent: Satisfaction Baseline	38 (± 14.9)	39 (± 14.7)		
Parent: Comfort Baseline	42.8 (± 12.5)	44.4 (± 11.7)		
Parent: Resilience Baseline	42.1 (± 11.2)	41.8 (± 11.6)		
Parent: Risk Avoidance Baseline	31.7 (± 15.8)	34.1 (± 15.9)		
Parent: Achievement Baseline	33.2 (± 9.5)	33.1 (± 10.8)		
Parent: Satisfaction 12 Weeks	40.4 (± 12.5)	40 (± 13.8)		
Parent: Comfort 12 Weeks	44.6 (± 11.4)	44.1 (± 11.5)		
Parent: Resilience 12 Weeks	45.3 (± 11)	42.2 (± 10.8)		
Parent: Risk Avoidance 12 Weeks	40.5 (± 14.8)	35.9 (± 13.9)		
Parent: Achievement 12 Weeks	38 (± 10)	34.4 (± 10.3)		
Child/Adolescent: Satisfaction Baseline	49.2 (± 9.2)	50 (± 12.6)		
Child/Adolescent: Comfort Baseline	49.9 (± 9.6)	50.6 (± 7.9)		
Child/Adolescent: Resilience Baseline	52 (± 10.8)	52 (± 11.6)		
Child/Adolescent: Risk Avoidance Baseline	47.6 (± 10.4)	49.1 (± 11.3)		
Child/Adolescent: Achievement Baseline	42.1 (± 10.3)	44.6 (± 10.8)		
Child/Adolescent: Satisfaction 12 Weeks	50.6 (± 9.2)	52.3 (± 11.1)		
Child/Adolescent: Comfort 12 Weeks	52.7 (± 8.2)	51.9 (± 7.7)		
Child/Adolescent: Resilience 12 Weeks	52.4 (± 9.5)	52.2 (± 9.4)		
Child/Adolescent: Risk Avoidance 12 Weeks	51.9 (± 8.7)	49.7 (± 11.7)		
Child/Adolescent: Achievement 12 Weeks	45.5 (± 10.2)	45.7 (± 11.5)		

Statistical analyses

Statistical analysis title	Statistical Analysis 2 for Outcome Measure 9

Statistical analysis description:

ANCOVA model: Dependent variable=standardized mean scores of domain at Visit 7 minus scores at Visit 1; Factors=Treatment, Investigator, Rater; Covariate=standardized mean scores of domain at Visit 1. Both treatment by rater and treatment by covariate interaction terms included in model.

Comparison groups	Outcome Measure 9 Atomoxetine v Outcome Measure 9 Placebo
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.243 [8]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	1.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.35
upper limit	5.29

Notes:

[8] - P-value for Parent: Comfort difference (Atomoxetine - Placebo) in the change from 12 weeks minus baseline.

Statistical analysis title	Statistical Analysis 1 for Outcome Measure 9

Statistical analysis description:

ANCOVA model: Dependent variable=standardized mean scores of domain at Visit 7 minus scores at Visit 1; Factors=Treatment, Investigator, Rater; Covariate=standardized mean scores of domain at Visit 1. Both treatment by rater and treatment by covariate interaction terms included in model.

Comparison groups	Outcome Measure 9 Atomoxetine v Outcome Measure 9 Placebo
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.81 [9]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.39
upper limit	4.33

Notes:

[9] - P-value for Parent: Satisfaction difference (Atomoxetine - Placebo) in the change from 12 weeks minus baseline.

Statistical analysis title	Statistical Analysis 3 for Outcome Measure 9

Statistical analysis description:

ANCOVA model: Dependent variable=standardized mean scores of domain at Visit 7 minus scores at Visit 1; Factors=Treatment, Investigator, Rater; Covariate=standardized mean scores of domain at Visit 1. Both treatment by rater and treatment by covariate interaction terms included in model.

Comparison groups	Outcome Measure 9 Atomoxetine v Outcome Measure 9 Placebo

Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.419 [10]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	1.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.26
upper limit	5.39

Notes:

[10] - P-value for Parent: Resilience difference (Atomoxetine - Placebo) in the change from 12 weeks minus baseline.

Statistical analysis title	Statistical Analysis 4 for Outcome Measure 9
Comparison groups	Outcome Measure 9 Atomoxetine v Outcome Measure 9 Placebo
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [11]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	8.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.27
upper limit	12.55

Notes:

[11] - P-value for Parent:Risk Avoidance difference (Atomoxetine - Placebo) in the change from 12 weeks minus baseline.

Statistical analysis title	Statistical Analysis 5 for Outcome Measure 9

Statistical analysis description:

ANCOVA model: Dependent variable=standardized mean scores of domain at Visit 7 minus scores at Visit 1; Factors=Treatment, Investigator, Rater; Covariate=standardized mean scores of domain at Visit 1. Both treatment by rater and treatment by covariate interaction terms included in model.

Comparison groups	Outcome Measure 9 Atomoxetine v Outcome Measure 9 Placebo
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.042 [12]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	3.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.13
upper limit	6.65

Notes:

[12] - P-value for Parent:Achievement difference (Atomoxetine - Placebo) in the change from 12 weeks minus baseline.

Statistical analysis title	Statistical Analysis 6 for Outcome Measure 9

Statistical analysis description:

ANCOVA model: Dependent variable=standardized mean scores of domain at Visit 7 minus scores at Visit 1; Factors=Treatment, Investigator, Rater; Covariate=standardized mean scores of domain at Visit 1. Both treatment by rater and treatment by covariate interaction terms included in model.

Comparison groups	Outcome Measure 9 Atomoxetine v Outcome Measure 9 Placebo
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.323 [13]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.06
upper limit	1.35

Notes:

[13] - P-value for Child/Adolescent:Satisfaction difference (Atomoxetine - Placebo) in the change from 12 weeks minus baseline.

Statistical analysis title	Statistical Analysis 7 for Outcome Measure 9

Statistical analysis description:

ANCOVA model: Dependent variable=standardized mean scores of domain at Visit 7 minus scores at Visit 1; Factors=Treatment, Investigator, Rater; Covariate=standardized mean scores of domain at Visit 1. Both treatment by rater and treatment by covariate interaction terms included in model.

Comparison groups	Outcome Measure 9 Atomoxetine v Outcome Measure 9 Placebo
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.452 [14]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.49
upper limit	3.34

Notes:

[14] - P-value for Child/Adolescent:Comfort difference (Atomoxetine - Placebo) in the change from 12 weeks minus baseline.

Statistical analysis title	Statistical Analysis 8 for Outcome Measure 9

Statistical analysis description:

ANCOVA model: Dependent variable=standardized mean scores of domain at Visit 7 minus scores at Visit 1; Factors=Treatment, Investigator, Rater; Covariate=standardized mean scores of domain at Visit 1. Both treatment by rater and treatment by covariate interaction terms included in model.

Comparison groups	Outcome Measure 9 Atomoxetine v Outcome Measure 9 Placebo
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.91 [15]
Method	ANCOVA
Parameter estimate	Median difference (net)
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.59
upper limit	2.9

Notes:

[15] - P-value for Child/Adolescent:Resilience difference (Atomoxetine - Placebo) in the change from 12 weeks minus baseline.

Statistical analysis title	Statistical Analysis 9 for Outcome Measure 9

Statistical analysis description:

ANCOVA model: Dependent variable=standardized mean scores of domain at Visit 7 minus scores at Visit 1; Factors=Treatment, Investigator, Rater; Covariate=standardized mean scores of domain at Visit 1. Both treatment by rater and treatment by covariate interaction terms included in model.

Comparison groups	Outcome Measure 9 Atomoxetine v Outcome Measure 9 Placebo
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006 [16]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	3.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.04
upper limit	6.08

Notes:

[16] - P-value for Child/Adolescent:Risk Avoidance difference (Atomoxetine - Placebo) in the change from 12 weeks minus baseline.

Statistical analysis title	Statistical Analysis 10 for Outcome Measure 9

Statistical analysis description:

ANCOVA model: Dependent variable=standardized mean scores of domain at Visit 7 minus scores at Visit 1; Factors=Treatment, Investigator, Rater; Covariate=standardized mean scores of domain at Visit 1. Both treatment by rater and treatment by covariate interaction terms included in model.

Comparison groups	Outcome Measure 9 Atomoxetine v Outcome Measure 9 Placebo
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.541 [17]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.99

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.21
upper limit	4.19

Notes:

[17] - P-value for Child/Adolescent:Achievement difference (Atomoxetine - Placebo) in the change from 12 weeks minus baseline.

Secondary: Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version (K-SADS-PL)

End point title	Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version (K-SADS-PL)

End point description:

The K-SADS-PL is a semi-structured interview schedule for assessing psychiatric disorders in children and adolescents. It is used to assess the status of 32 DSM-IV child and adolescent psychiatric diagnosis.

End point type	Secondary

End point timeframe:

Baseline

End point values	Outcome Measure 10 Atomoxetine	Outcome Measure 10 Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	99	50		
Units: participants				
number (not applicable)				
Participants with any Comorbidity	46	22		
Participants with Oppositional Defiant Disorder	28	10		
Participants with Tic Disorder	16	9		
Participants with Affective Disorders	3	2		
Participants with Anxiety Disorders	13	6		
Participants with Conduct Disorder	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version:Investigator Administered and Scored (ADHDRS-IV-Parent:Inv) at 107 Weeks (Open-Label Extension)

End point title	Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version:Investigator Administered and Scored (ADHDRS-IV-Parent:Inv) at 107 Weeks (Open-Label Extension)

End point description:

Measures the 18 symptoms contained in the DSM-IV diagnosis of Attention-Deficit/Hyperactivity Disorder. Individual item scores range from 0 (none/never or rarely) to 3 (severe/very often). Total scores range from 0 to 54.

End point type	Secondary

End point timeframe:

Week 107

End point values	Outcome Measure 11 Atomoxetine			
Subject group type	Subject analysis set			
Number of subjects analysed	140			
Units: units on a scale				
arithmetic mean (standard deviation)	21.4 (± 12.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Vital Signs - Systolic Blood Pressure

End point title	Vital Signs - Systolic Blood Pressure

End point description:

No text entered

End point type	Secondary

End point timeframe:

Baseline and 12 weeks

End point values	Outcome Measure 12 Atomoxetine	Outcome Measure 12 Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	100	51		
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline	98.7 (± 13)	102.2 (± 11.4)		
12 Weeks	102.9 (± 10.2)	101.2 (± 11.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Vital Signs - Diastolic Blood Pressure

End point title	Vital Signs - Diastolic Blood Pressure

End point description:

No text entered

End point type	Secondary

End point timeframe:
Baseline and 12 weeks

End point values	Outcome Measure 13 Atomoxetine	Outcome Measure 13 Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	100	51		
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline	56.4 (± 9)	58.2 (± 7.2)		
12 Weeks	59.3 (± 7.1)	57.5 (± 8.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Vital Signs - Pulse

End point title	Vital Signs - Pulse

End point description:
No text entered

End point type	Secondary

End point timeframe:
Baseline and 12 weeks

End point values	Outcome Measure 14 Atomoxetine	Outcome Measure 14 Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	100	51		
Units: beats per minute				
arithmetic mean (standard deviation)				
Baseline	75.8 (± 9.8)	77 (± 9.3)		
12 Weeks	84.5 (± 12.5)	79 (± 9.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Vital Signs - Weight

End point title	Vital Signs - Weight

End point description:	
No text entered	
End point type	Secondary
End point timeframe:	
Baseline and 12 weeks	

End point values	Outcome Measure 15 Atomoxetine	Outcome Measure 15 Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	100	51		
Units: kilograms				
arithmetic mean (standard deviation)				
Baseline	38 (± 12)	37.5 (± 12.3)		
12 Weeks	37 (± 11.5)	38.9 (± 12.8)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Entire Study

Adverse event reporting additional description:

B4Z-XM-LYDM

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups

Reporting group title	Atomoxetine

Reporting group description: -

Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Atomoxetine	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 100 (2.00%)	2 / 51 (3.92%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
overdose			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	1 / 100 (1.00%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	0 / 100 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
headache			
alternative dictionary used: MedDRA 11.0			

subjects affected / exposed	1 / 100 (1.00%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
nausea			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	1 / 100 (1.00%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
vomiting			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	1 / 100 (1.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
asthma			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	0 / 100 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
appendicitis			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	1 / 100 (1.00%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Atomoxetine	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	89 / 100 (89.00%)	44 / 51 (86.27%)	
Cardiac disorders			

tachycardia			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	5 / 100 (5.00%)	3 / 51 (5.88%)	
occurrences (all)	5	3	
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	12 / 100 (12.00%)	7 / 51 (13.73%)	
occurrences (all)	14	7	
headache			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	44 / 100 (44.00%)	19 / 51 (37.25%)	
occurrences (all)	60	25	
somnolence			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	28 / 100 (28.00%)	10 / 51 (19.61%)	
occurrences (all)	33	10	
General disorders and administration site conditions			
fatigue			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	13 / 100 (13.00%)	9 / 51 (17.65%)	
occurrences (all)	17	10	
irritability			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	16 / 100 (16.00%)	7 / 51 (13.73%)	
occurrences (all)	20	8	
pyrexia			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	14 / 100 (14.00%)	6 / 51 (11.76%)	
occurrences (all)	16	7	
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	23 / 100 (23.00%)	12 / 51 (23.53%)	
occurrences (all)	32	17	

abdominal pain upper			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	7 / 100 (7.00%)	3 / 51 (5.88%)	
occurrences (all)	8	3	
constipation			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	7 / 100 (7.00%)	0 / 51 (0.00%)	
occurrences (all)	7	0	
diarrhoea			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	9 / 100 (9.00%)	7 / 51 (13.73%)	
occurrences (all)	12	7	
nausea			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	8 / 100 (8.00%)	6 / 51 (11.76%)	
occurrences (all)	10	7	
vomiting			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	25 / 100 (25.00%)	13 / 51 (25.49%)	
occurrences (all)	42	21	
Respiratory, thoracic and mediastinal disorders			
cough			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	8 / 100 (8.00%)	3 / 51 (5.88%)	
occurrences (all)	9	4	
pharyngolaryngeal pain			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	7 / 100 (7.00%)	5 / 51 (9.80%)	
occurrences (all)	7	7	
Skin and subcutaneous tissue disorders			
rash			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	2 / 100 (2.00%)	3 / 51 (5.88%)	
occurrences (all)	3	3	
Psychiatric disorders			

initial insomnia			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	5 / 100 (5.00%)	4 / 51 (7.84%)	
occurrences (all)	6	4	
tic			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	6 / 100 (6.00%)	2 / 51 (3.92%)	
occurrences (all)	8	4	
Infections and infestations			
ear infection			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	2 / 100 (2.00%)	7 / 51 (13.73%)	
occurrences (all)	2	10	
gastroenteritis			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	8 / 100 (8.00%)	2 / 51 (3.92%)	
occurrences (all)	13	3	
influenza			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	6 / 100 (6.00%)	2 / 51 (3.92%)	
occurrences (all)	6	2	
nasopharyngitis			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	33 / 100 (33.00%)	12 / 51 (23.53%)	
occurrences (all)	54	18	
tonsillitis			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	13 / 100 (13.00%)	4 / 51 (7.84%)	
occurrences (all)	14	10	
Metabolism and nutrition disorders			
anorexia			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	6 / 100 (6.00%)	3 / 51 (5.88%)	
occurrences (all)	6	3	
decreased appetite			

alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	36 / 100 (36.00%)	18 / 51 (35.29%)	
occurrences (all)	39	21	

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

None reported