Clinical trial results:
Double-Blind, Randomized, Placebo-Controlled, Crossover Study Evaluating the Academic, Behavioral and Cognitive Effects of CONCERTA® on Older Children with ADHD. The ABC Study.

Summary

EudraCT number	2015-001042-28
Trial protocol	Outside EU/EEA
Global end of trial date	26 June 2009

Results information

Result version number	v2 (current)
This version publication date	10 July 2016
First version publication date	06 August 2015
Version creation reason	• Correction of full data set Review of data

Trial information

Trial identification

Sponsor protocol code	CONCERTA-ATT-4080

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00799487
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ortho-McNeil Janssen Scientific Affairs LLC
Sponsor organisation address	Archimedesweg 29, Leiden, Netherlands, 2333CM
Public contact	Clinical Registry Group-JB BV, Ortho-McNeil Janssen Scientific Affairs LLC, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group-JB BV, Ortho-McNeil Janssen Scientific Affairs LLC, ClinicalTrialsEU@its.jnj.com

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	26 June 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 June 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this trial is to determine if the study medication, CONCERTA (methylphenidate HCl), is safe and effective in improving academic performance and behavior in children with Attention Deficit Hyperactivity Disorder (ADHD) when compared to placebo.

Protection of trial subjects:

The safety assessments included the monitoring of adverse events (AEs), performing laboratory tests, measurement of vital signs, electrocardiogram (ECG) and performing physical examinations throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 December 2008
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	United States: 89
Worldwide total number of subjects	89
EEA total number of subjects	0

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)	79
Adolescents (12-17 years)	10
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:

A total of 89 participants were enrolled in the Open-Label Dose Adjustment Period and received at least 1 dose of study drug.

Period 1

Period 1 title	Dose Adjustment Period
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Concerta

Arm description:

Participants received Concerta in a dose of 18 milligram/day (mg/day) once daily orally. Concerta dose was increased as 18 mg/day every 3 to 7 days until an optimal individualized dose was achieved, up to a maximum dose of 54 mg/day.

Arm type	Experimental
Investigational medicinal product name	Concerta
Investigational medicinal product code	
Other name	Methylphenidate hydrochloride
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Concerta capsule was administered in a dose of 18-54 (milligram per day) mg/day.

Number of subjects in period 1	Concerta
Started	89
Completed	68
Not completed	21
Consent withdrawn by subject	3
Adverse event, non-fatal	2
Not meet the optimal dose criteria	8
Withdrew for “other” reasons	5
Lost to follow-up	1
Withdrawn at the discretion of the investigator	2

Period 2

Period 2 title	Double-Blind Assessment Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	No
Arm title	Placebo/Concerta

Arm description:

Children randomized to receive Placebo at lab school day 1 and Concerta lab school day 2

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

Dosage and administration details:

Placebo matching with Concerta was administered.

Investigational medicinal product name	Concerta
Investigational medicinal product code	
Other name	Methylphenidate hydrochloride
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Concerta capsule was administered in a dose of 18-54 mg/day.

Arm title	Concerta/Placebo

Arm description:

Children randomized to receive Concerta at lab school day 1 and Placebo at lab school day 2

Arm type	Experimental
Investigational medicinal product name	Concerta
Investigational medicinal product code	
Other name	Methylphenidate hydrochloride
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Concerta capsule was administered in a dose of 18-54 mg/day.

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

Dosage and administration details:

Placebo matching with Concerta was administered.

Number of subjects in period 2	Placebo/Concerta	Concerta/Placebo
Started	34	34
Completed	33	32
Not completed	1	2
Other	1	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Concerta
Reporting group description:	
Participants received Concerta in a dose of 18 milligram/day (mg/day) once daily orally. Concerta dose was increased as 18 mg/day every 3 to 7 days until an optimal individualized dose was achieved, up to a maximum dose of 54 mg/day.	

Reporting group values	Concerta	Total	
Number of subjects	89	89	
Title for AgeCategorical Units: subjects			
Children (2-11 years)	80	80	
Adolescents (12-17 years)	9	9	
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	10.2		
standard deviation	± 1.03	-	
Title for Gender Units: subjects			
Female	29	29	
Male	60	60	

End points

End points reporting groups

Reporting group title	Concerta
Reporting group description:	
Participants received Concerta in a dose of 18 milligram/day (mg/day) once daily orally. Concerta dose was increased as 18 mg/day every 3 to 7 days until an optimal individualized dose was achieved, up to a maximum dose of 54 mg/day.	
Reporting group title	Placebo/Concerta
Reporting group description:	
Children randomized to receive Placebo at lab school day 1 and Concerta lab school day 2	
Reporting group title	Concerta/Placebo
Reporting group description:	
Children randomized to receive Concerta at lab school day 1 and Placebo at lab school day 2	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Participants randomized to receive Placebo at lab school day 1 or lab school day 2	
Subject analysis set title	Concerta
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Participants randomized to receive Concerta at lab school day 1 or lab school day 2	

Primary: Hour 4 Permanent Product Math Test Attempted Score (PERMP-Attempted)

End point title	Hour 4 Permanent Product Math Test Attempted Score (PERMP-Attempted)
End point description:	
PERMP (range: 0, 400) is a measure of academic productivity. These seatwork math tasks provide an objective measure of attention and accuracy in calculations. The level of difficulty is established on a screening math pretest. The subsequent laboratory school day assessments employed a series of 10-minute math tests (5 pages of 80 math problem each for a total of 400 problems available). Children were graded on the number of attempted problems. A higher number of problems attempted was indicative of greater attention to detail (higher score is preferable.)	
End point type	Primary
End point timeframe:	
Hour 4 of the Double-Blind Assessment Period Lab School Day	

End point values	Placebo	Concerta		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	67		
Units: Problems attempted				
arithmetic mean (standard deviation)	88 (± 39.79)	116.1 (± 38.99)		

Statistical analyses

Statistical analysis title	Placebo vs. Concerta
Comparison groups	Placebo v Concerta
Number of subjects included in analysis	131
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-27.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.4
upper limit	-20.2

Primary: Hour 4 Permanent Product Math Test Correct Score (PERMP-Correct)	
End point title	Hour 4 Permanent Product Math Test Correct Score (PERMP-Correct)
End point description:	
PERMP (range: 0, 400) is a measure of academic productivity. These seatwork math tasks provide an objective measure of attention and accuracy in calculations. The level of difficulty is established on a screening math pretest. The subsequent laboratory school day assessments employed a series of 10-minute math tests (5 pages of 80 math problem each for a total of 400 problems available). Children were graded on the number of correct problems. A higher number of problems correct, of those attempted, was indicative of greater accuracy.	
End point type	Primary
End point timeframe:	
Hour 4 of the Lab School Day During the Double-Blind Assessment Period	

End point values	Placebo	Concerta		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	67		
Units: Problems correct				
arithmetic mean (standard deviation)	84 (± 39.93)	112.8 (± 39.6)		

Statistical analyses

Statistical analysis title	Placebo vs. Concerta
Comparison groups	Concerta v Placebo

Number of subjects included in analysis	131
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-35.1
upper limit	-20.8

Secondary: Hour 4 Swanson, Kotkin, Alger, M-Flynn and Pelham Scale for Deportment (SKAMP-Deportment)

End point title	Hour 4 Swanson, Kotkin, Alger, M-Flynn and Pelham Scale for Deportment (SKAMP-Deportment)

End point description:

The SKAMP scale measures the manifestations of ADHD using an independent observer (teacher) rating of children impairment in classroom behavior. The SKAMP-Deportment (SKAMP-D) (range: 0,36) is a sum of ratings on 6 deportment items (interacting with other children, interacting with adults, remaining quiet, staying seated, complying with the teacher's directions, and following the classroom rules). Each item was rated on a 7-point impairment scale (0=normal, 6=maximum impairment), with higher scores indicating more severe symptoms.

End point type	Secondary

End point timeframe:

Hour 4 of the Lab School Day During the Double-Blind Assessment Period

End point values	Placebo	Concerta		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	67		
Units: Units on a scale				
arithmetic mean (standard deviation)	8 (± 6.54)	3.1 (± 3.65)		

Statistical analyses

Statistical analysis title	Placebo vs. Concerta
Comparison groups	Placebo v Concerta
Number of subjects included in analysis	131
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	5

Confidence interval	
level	95 %
sides	2-sided
lower limit	3.4
upper limit	6.6

Secondary: Hour 4 Swanson, Kotkin, Alger, M-Flynn and Pelham Scale for Attention (SKAMP-Attention)

End point title	Hour 4 Swanson, Kotkin, Alger, M-Flynn and Pelham Scale for Attention (SKAMP-Attention)

End point description:

The SKAMP scale measures the manifestations of ADHD using an independent observer (teacher) rating of children impairment in classroom behavior. The SKAMP-Attention (SKAMP-A) (range: 0, 42) is a sum of the ratings on 7 attention items (getting started, sticking with tasks, attending to an activity, making activity transitions, completing assigned tasks, performing work accurately, and being neat and careful while writing or drawing). Each item was rated on a 7-point impairment scale (0=normal, 6=maximum impairment), with higher scores indicating more severe symptoms.

End point type	Secondary

End point timeframe:

Hour 4 of the Lab School Day During the Double-Blind Assessment Period

End point values	Placebo	Concerta		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	67		
Units: Units on a scale				
arithmetic mean (standard deviation)	10.1 (± 5.51)	5.6 (± 3.69)		

Statistical analyses

Statistical analysis title	Placebo vs. Concerta
Comparison groups	Placebo v Concerta
Number of subjects included in analysis	131
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.2
upper limit	5.8

Secondary: Hour 4 Swanson, Kotkin, Alger, M-Flynn and Pelham Scale for Composite (SKAMP-Composite)

End point title	Hour 4 Swanson, Kotkin, Alger, M-Flynn and Pelham Scale for Composite (SKAMP-Composite)

End point description:

The SKAMP scale measures the manifestations of ADHD using an independent observer (teacher) rating of child impairment in classroom behavior. A composite score (range: 0, 78) for the SKAMP variable (13 items total) was obtained by summing the SKAMP-D and SKAMP-A subscale scores. A lower score was preferable, as a higher score represented greater behavioral impairment.

End point type	Secondary

End point timeframe:

Hour 4 of the Lab School Day During the Double-Blind Assessment Period

End point values	Placebo	Concerta		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	67		
Units: Units on a scale				
arithmetic mean (standard deviation)	18.1 (± 10.61)	8.7 (± 6.1)		

Statistical analyses

Statistical analysis title	Placebo vs. Concerta
Comparison groups	Concerta v Placebo
Number of subjects included in analysis	131
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	9.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.9
upper limit	12

Secondary: Hour 5.5 Test of Variables of Attention (TOVA) ADHD Score

End point title	Hour 5.5 Test of Variables of Attention (TOVA) ADHD Score

End point description:

The TOVA is a computerized, visual continuous performance test which provides measures of attention. The stimulus, presented for 100 milliseconds (ms) at the rate of 30 per minute, is a computer-presented square containing a square hole near the top (target) or bottom (non-target) edge. The first half of the

TOVA requires that the child sustain attention while the second half requires inhibition of response to a non-target (observed range: -15.2, 5.2). An ADHD score of less than -1.80 is suggestive of ADHD.

End point type	Secondary

End point timeframe:

Hour 5.5 of the Lab School Day During the Double-Blind Assessment Period.

End point values	Placebo	Concerta		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	67		
Units: Units on a scale				
arithmetic mean (standard deviation)	-4.19 (± 3.563)	-0.68 (± 3.672)		

Statistical analyses

Statistical analysis title	Placebo vs. Concerta
Comparison groups	Concerta v Placebo
Number of subjects included in analysis	131
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-3.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.27
upper limit	-2.74

Secondary: Hour 5.5 Test of Variables of Attention (TOVA) Reaction Time (Msec)

End point title	Hour 5.5 Test of Variables of Attention (TOVA) Reaction Time (Msec)

End point description:

The TOVA is a computerized, visual continuous performance test which provides measures of attention. The stimulus, presented for 100 milliseconds (ms) at the rate of 30 per minute, is a computer-presented square containing a square hole near the top (target) or bottom (non-target) edge. The first half of the TOVA requires that the child sustain attention while the second half requires inhibition of response to a non-target. Mean response latency in msecs (observed range: -75.4, 129.5). Higher score indicates faster reaction time.

End point type	Secondary

End point timeframe:

Hour 5.5 of the Lab School Day During the Double-Blind Assessment Period

End point values	Placebo	Concerta		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	67		
Units: Milliseconds (msecs)				
arithmetic mean (standard deviation)	75.23 (± 26.74)	93.21 (± 32.619)		

Statistical analyses

Statistical analysis title	Placebo vs. Concerta
Comparison groups	Placebo v Concerta
Number of subjects included in analysis	131
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-17.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.72
upper limit	-11.45

Secondary: Hour 5.5 Test of Variables of Attention(TOVA) Reaction Time Variability (Standard Deviation in Milliseconds (Msecs))

End point title	Hour 5.5 Test of Variables of Attention(TOVA) Reaction Time Variability (Standard Deviation in Milliseconds (Msecs))

End point description:

The TOVA is a computerized, visual continuous performance test which provides measures of attention. The stimulus, presented for 100 milliseconds (ms) at the rate of 30 per minute, is a computer-presented square containing a square hole near the top (target) or bottom (non-target) edge. The first half of the TOVA requires that the child sustain attention while the second half requires inhibition of response to a non-target. SD of response times (msecs) (observed range: -177.6, 132.9). Higher score indicates less variability.

End point type	Secondary

End point timeframe:

Hour 5.5 of the Lab School Day During the Double-Blind Assessment Period

End point values	Placebo	Concerta		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	67		
Units: milliseconds				
arithmetic mean (standard deviation)	56.58 (± 54.478)	87.22 (± 45.643)		

Statistical analyses

Statistical analysis title	Placebo vs. Concerta
Comparison groups	Placebo v Concerta
Number of subjects included in analysis	131
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-30.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-39.29
upper limit	-21.37

Secondary: Hour 5.5 Wide Range Assessment of Memory and Learning (WRAML-2) Finger Windows Backwards

End point title	Hour 5.5 Wide Range Assessment of Memory and Learning (WRAML-2) Finger Windows Backwards

End point description:

WRAML-2 (range: 0, 28) is designed to evaluate a child's ability to learn and to memorize information, consists of 9 subtests from which 4 summary indexes can be calculated: verbal memory index, visual memory index, learning index, and general memory index. During this test the investigator pointed to a longer and longer series of windows on a card at the rate of 1 location per second, and then the child was asked to reproduce the sequence exactly in reverse order. One point was given for each correctly recalled sequence, and the test was discontinued after 3 consecutive errors.

End point type	Secondary

End point timeframe:

Hour 5.5 of the Lab School Day During the Double-Blind Assessment Period

End point values	Placebo	Concerta		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	67		
Units: Correct Sequences				
arithmetic mean (standard deviation)	9.8 (± 4.95)	10.9 (± 4.5)		

Statistical analyses

Statistical analysis title	Placebo vs. Concerta
Comparison groups	Concerta v Placebo
Number of subjects included in analysis	131
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.0297
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.15
upper limit	-0.12

Secondary: Hour 5.5 Wide Range Assessment of Memory and Learning (WRAML-2) Finger Windows Forwards

End point title	Hour 5.5 Wide Range Assessment of Memory and Learning (WRAML-2) Finger Windows Forwards

End point description:

WRAML-2 (range: 0, 28) is designed to evaluate a child's ability to learn and to memorize information, consists of 9 subtests from which 4 summary indexes can be calculated: verbal memory index, visual memory index, learning index, and general memory index. During this test the investigator pointed to a longer and longer series of windows on a card at the rate of 1 location per second, and then the child was asked to reproduce the sequence exactly. One point was given for each correctly recalled sequence, and the test was discontinued after 3 consecutive errors.

End point type	Secondary

End point timeframe:

Hour 5.5 of the Lab School Day During the Double-Blind Assessment Period

End point values	Placebo	Concerta		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	67		
Units: Correct Sequences				
arithmetic mean (standard deviation)	12.3 (± 4.94)	13.2 (± 4.85)		

Statistical analyses

Statistical analysis title	Placebo vs. Concerta
Comparison groups	Placebo v Concerta
Number of subjects included in analysis	131
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.0955
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.84
upper limit	0.15

Secondary: Hour 5.5 Test of Variables of Attention (TOVA) Commissions

End point title	Hour 5.5 Test of Variables of Attention (TOVA) Commissions

End point description:

The TOVA is a computerized, visual continuous performance test which provides measures of attention. The stimulus, presented for 100 milliseconds (ms) at the rate of 30 per minute, is a computer-presented square containing a square hole near the top (target) or bottom (non-target) edge. The first half of the TOVA requires that the child sustain attention while the second half requires inhibition of response to a non-target. Responses to non-targets. Higher score is preferable (observed range: -82.4, 128.9).

End point type	Secondary

End point timeframe:

Hour 5.5 of the Lab School Day During the Double-Blind Assessment Period

End point values	Placebo	Concerta		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	67		
Units: Responses to non-targets				
arithmetic mean (standard deviation)	78.35 (± 47.39)	90.54 (± 36.132)		

Statistical analyses

Statistical analysis title	Placebo vs. Concerta
Comparison groups	Concerta v Placebo

Number of subjects included in analysis	131
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.0002
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-14.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.52
upper limit	-7.23

Secondary: Hour 5.5 Wechsler Intelligence Scale for Children - 3rd ed. (WISC-III-PI) Digit Span Backwards

End point title	Hour 5.5 Wechsler Intelligence Scale for Children - 3rd ed. (WISC-III-PI) Digit Span Backwards

End point description:

Each child individually was given a sequence of numbers with the sequence becoming progressively longer. The child was then asked to repeat the digits in the same sequence, either forwards or backwards. Each sequence length was attempted twice. The test was complete after failure on both trials of any sequence length. One point was awarded if the participant passed only 1 trial of a sequence length. Zero points were given if the participant failed both trials. The maximum raw scores were 16 forwards and 14 backwards. A higher score was indicative of better recall and attention (range: 0, 14).

End point type	Secondary

End point timeframe:

Hour 5.5 of the Lab School Day During the Double-Blind Assessment Period

End point values	Placebo	Concerta		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	67		
Units: Correct Sequences				
arithmetic mean (standard deviation)	4.8 (± 1.85)	5.1 (± 1.87)		

Statistical analyses

Statistical analysis title	Placebo vs. Concerta
Comparison groups	Placebo v Concerta
Number of subjects included in analysis	131
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.2335
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.26

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.17

Secondary: Hour 8.75 Gray Silent Reading Test (GSRT)

End point title	Hour 8.75 Gray Silent Reading Test (GSRT)

End point description:

Gray Silent Reading Test (GSRT) is a reliable, validated measure of reading comprehension administered in the group setting during the first half hour of the homework session (observed range: 0, 141). A higher score is preferable as it means more questions were answered correctly.

End point type	Secondary

End point timeframe:

Hour 8.75 of the Lab School Day During the Double-Blind Assessment Period

End point values	Placebo	Concerta		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	67		
Units: Units on a scale				
arithmetic mean (standard deviation)	89.1 (± 19.44)	92.1 (± 19.03)		

Statistical analyses

Statistical analysis title	Placebo vs. Concerta
Comparison groups	Placebo v Concerta
Number of subjects included in analysis	131
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.2321
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-2.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.67
upper limit	1.65

Secondary: Hour 7.5 Test of Handwriting Skills (Revised) (THS-R)

End point title	Hour 7.5 Test of Handwriting Skills (Revised) (THS-R)

End point description:

The THS-R is a standardized, untimed assessment designed to evaluate neurosensory integration manifested in manuscript and cursive writing. The test includes the 10 subtests: writing from memory the upper- and lower-case letters of the alphabet in order, writing from dictation the upper and lower-case letters of the alphabet out of order, single digit-numbers out of order, selected words, and copying selected letters, words, and sentences. Each subtest was scored from zero (poorly formed letters) to 3 (perfectly formed letters). A higher score was preferable (observed range: 0, 118).

End point type	Secondary

End point timeframe:

Hour 7.5 of the Lab School Day During the Double-Blind Assessment Period

End point values	Placebo	Concerta		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	67		
Units: Units on a scale				
arithmetic mean (standard deviation)	79.1 (± 13.86)	82.7 (± 13.34)		

Statistical analyses

Statistical analysis title	Placebo vs. Concerta
Comparison groups	Placebo v Concerta
Number of subjects included in analysis	131
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.0015
Method	Mixed models analysis
Parameter estimate	LS Mean Differenc
Point estimate	-3.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.64
upper limit	-1.4

Secondary: Hour 3.5 Dynamic Indicators of Basic Early Literacy Skills (DIBELS)

End point title	Hour 3.5 Dynamic Indicators of Basic Early Literacy Skills (DIBELS)

End point description:

The DIBELS (observed range: 0, 212), used to assess reading fluency, consists of standardized, individually administered measures of early literacy development. These short (1 minute) fluency measures were developed based upon essential early literacy domains to assess development of phonological awareness, alphabetic understanding, and automaticity and fluency. Only the paragraph fluency component of an age/grade-appropriate DIBELS was used. Children read 3 stories and completed the forms. A higher score was preferable and indicated a greater number of words read correctly in the time allowed.

End point type	Secondary

End point timeframe:

Hour 3.5 of the Lab School Day During the Double-Blind Assessment Period

End point values	Placebo	Concerta		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	67		
Units: Units on a scale				
arithmetic mean (standard deviation)	110.8 (± 39.21)	117.8 (± 39.38)		

Statistical analyses

Statistical analysis title	Placebo vs. Concerta
Comparison groups	Placebo v Concerta
Number of subjects included in analysis	131
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.0101
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-5.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.43
upper limit	-1.33

Secondary: Hour 5.5 Wechsler Intelligence Scale for Children - 3rd ed. (WISC-III-PI) Digit Span Forwards

End point title	Hour 5.5 Wechsler Intelligence Scale for Children - 3rd ed. (WISC-III-PI) Digit Span Forwards

End point description:

Each child individually was given a sequence of numbers with the sequence becoming progressively longer. The child was then asked to repeat the digits in the same sequence, either forwards or backwards. Each sequence length was attempted twice. The test was complete after failure on both trials of any sequence length. One point was awarded if the participant passed only 1 trial of a sequence length. Zero points were given if the participant failed both trials. The maximum raw scores were 16 forwards and 14 backwards. A higher score was indicative of better recall and attention (range: 0, 16).

End point type	Secondary

End point timeframe:

Hour 5.5 of the Lab School Day During the Double-Blind Assessment Period

End point values	Placebo	Concerta		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	67		
Units: Correct Sequences				
arithmetic mean (standard deviation)	8.4 (± 1.6)	8.5 (± 1.56)		

Statistical analyses

Statistical analysis title	Placebo vs. Concerta
Comparison groups	Concerta v Placebo
Number of subjects included in analysis	131
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.6642
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.53
upper limit	0.34

Secondary: Hour 5.5 Test of Variables of Attention (TOVA) Omissions

End point title	Hour 5.5 Test of Variables of Attention (TOVA) Omissions

End point description:

The TOVA is a computerized, visual continuous performance test which provides measures of attention. The stimulus, presented for 100 milliseconds (ms) at the rate of 30 per minute, is a computer-presented square containing a square hole near the top (target) or bottom (non-target) edge. The first half of the TOVA requires that the child sustain attention while the second half requires inhibition of response to a non-target. Number of targets missed. Higher score is preferable (observed range: -419.4, 108.9).

End point type	Secondary

End point timeframe:

Hour 5.5 of the Lab School Day During the Double-Blind Assessment Period

End point values	Placebo	Concerta		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	67		
Units: Targets missed				
arithmetic mean (standard deviation)	36.34 (± 103.888)	71.49 (± 82.508)		

Statistical analyses

Statistical analysis title	Placebo vs. Concerta
Comparison groups	Concerta v Placebo
Number of subjects included in analysis	131
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.004
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-35.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-58.89
upper limit	-11.71

Secondary: Hour 3.0 Grammar Task

End point title	Hour 3.0 Grammar Task

End point description:

This task, presented once during a laboratory school day, was designed to index "attention to detail" by determining how many grammatical mistakes each child could identify and circle in a brief paragraph. The errors were not difficult to identify and were designed to show attention to task, not comprehension. A higher number of errors identified, of those possible, was indicative of better attention - identification of grammatical errors (range: 0, 1 represents correct responses divided by the number of possible responses).

End point type	Secondary

End point timeframe:

Hour 3.0 of the Lab School Day During the Double-Blind Assessment Period

End point values	Placebo	Concerta		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	67		
Units: Units on a scale				
arithmetic mean (standard deviation)	0.252 (± 0.1894)	0.34 (± 0.2195)		

Statistical analyses

Statistical analysis title	Placebo vs. Concerta
Comparison groups	Placebo v Concerta

Number of subjects included in analysis	131
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.0012
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	-0.03

Secondary: Hour 8.75 Packet Activity - Short Story With Questions for Comprehension

End point title	Hour 8.75 Packet Activity - Short Story With Questions for Comprehension

End point description:

Packet Activities: Assessment of ability to organize, listen to instructions, initiate task, complete task, and distractibility, by completing a word search, reading a short story for comprehension on a multiple choice test, reading a longer story for comprehension on a true/false test, decoding a mystery sentence, and completing various vocabulary assessments (word choice, homophones; base/root words, alphabetic order)(range: 0, 1 represents correct responses divided by the number of possible responses).

End point type	Secondary

End point timeframe:

Hour 8.75 of the Lab School Day During the Double-Blind Assessment Period

End point values	Placebo	Concerta		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	67		
Units: Units on a scale				
arithmetic mean (standard deviation)	0.619 (± 0.2435)	0.699 (± 0.2239)		

Statistical analyses

Statistical analysis title	Placebo vs. Concerta
Comparison groups	Concerta v Placebo
Number of subjects included in analysis	131
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.0051
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.07

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	-0.02

Secondary: Hour 8.75 Packet Activity - Identiy Root Word

End point title	Hour 8.75 Packet Activity - Identiy Root Word

End point description:

Packet Activities: Assessment of ability to organize, listen to instructions, initiate task, complete task, and distractibility, by completing a word search, reading a short story for comprehension on a multiple choice test, reading a longer story for comprehension on a true/false test, decoding a mystery sentence, and completing various vocabulary assessments (word choice, homophones; base/root words, alphabetic order) (range: 0, 1 represents correct responses divided by the number of possible responses).

End point type	Secondary

End point timeframe:

Hour 8.75 of the Lab School Day During the Double-Blind Assessment Period

End point values	Placebo	Concerta		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	67		
Units: Units on a scale				
arithmetic mean (standard deviation)	0.58 (± 0.3478)	0.638 (± 0.323)		

Statistical analyses

Statistical analysis title	Placebo vs. Concerta
Comparison groups	Concerta v Placebo
Number of subjects included in analysis	131
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.1768
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	0.02

Secondary: Hour 8.75 Packet Activity - Alphabetize List of Words

End point title	Hour 8.75 Packet Activity - Alphabetize List of Words

End point description:

Packet Activities: Assessment of ability to organize, listen to instructions, initiate task, complete task, and distractibility, by completing a word search, reading a short story for comprehension on a multiple choice test, reading a longer story for comprehension on a true/false test, decoding a mystery sentence, and completing various vocabulary assessments (word choice, homophones; base/root words, alphabetic order) (range: 0, 1 represents correct responses divided by the number of possible responses).

End point type	Secondary

End point timeframe:

Hour 8.75 of the Lab School Day During the Double-Blind Assessment Period

End point values	Placebo	Concerta		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	67		
Units: Units on a scale				
arithmetic mean (standard deviation)	0.638 (± 0.3269)	0.66 (± 0.3396)		

Statistical analyses

Statistical analysis title	Placebo vs. Concerta
Comparison groups	Concerta v Placebo
Number of subjects included in analysis	131
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.4245
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0.04

Secondary: Hour 8.75 Packet Activity - Identify Multiple Meanings for Words

End point title	Hour 8.75 Packet Activity - Identify Multiple Meanings for Words

End point description:

Packet Activities: Assessment of ability to organize, listen to instructions, initiate task, complete task, and distractibility, by completing a word search, reading a short story for comprehension on a multiple choice test, reading a longer story for comprehension on a true/false test, decoding a mystery sentence, and completing various vocabulary assessments (word choice, homophones; base/root words, alphabetic order) (range: 0, 1 represents correct responses divided by the number of possible responses).

End point type	Secondary

End point timeframe:

Hour 8.75 of the Lab School Day During the Double-Blind Assessment Period

End point values	Placebo	Concerta		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	67		
Units: Units on a scale				
arithmetic mean (standard deviation)	0.814 (± 0.2936)	0.821 (± 0.2839)		

Statistical analyses

Statistical analysis title	Placebo vs. Concerta
Comparison groups	Placebo v Concerta
Number of subjects included in analysis	131
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.9729
Method	Mixed models analysis
Parameter estimate	LS Mean DIfference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0.09

Secondary: Hour 8.75 Packet Activity - Complete Sentences Using Words Provided

End point title	Hour 8.75 Packet Activity - Complete Sentences Using Words Provided

End point description:

Packet Activities: Assessment of ability to organize, listen to instructions, initiate task, complete task, and distractibility, by completing a word search, reading a short story for comprehension on a multiple choice test, reading a longer story for comprehension on a true/false test, decoding a mystery sentence, and completing various vocabulary assessments (word choice, homophones; base/root words, alphabetic order) (range: 0, 1 represents correct responses divided by the number of possible responses).

End point type	Secondary

End point timeframe:

Hour 8.75 of the Lab School Day During the Double-Blind Assessment Period

End point values	Placebo	Concerta		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	67		
Units: Units on a scale				
arithmetic mean (standard deviation)	0.73 (± 0.3101)	0.781 (± 0.2926)		

Statistical analyses

Statistical analysis title	Placebo vs. Concerta
Comparison groups	Placebo v Concerta
Number of subjects included in analysis	131
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.3486
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.04

Secondary: Hour 8.75 Packet Activity - Word Search

End point title	Hour 8.75 Packet Activity - Word Search

End point description:

Packet Activities: Assessment of ability to organize, listen to instructions, initiate task, complete task, and distractibility, by completing a word search, reading a short story for comprehension on a multiple choice test, reading a longer story for comprehension on a true/false test, decoding a mystery sentence, and completing various vocabulary assessments (word choice, homophones; base/root words, alphabetic order) (range: 0, 1 represents correct responses divided by the number of possible responses).

End point type	Secondary

End point timeframe:

Hour 8.75 of the Lab School Day During the Double-Blind Assessment Period

End point values	Placebo	Concerta		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	67		
Units: Units on a scale				
arithmetic mean (standard deviation)	0.955 (± 0.1272)	0.984 (± 0.0862)		

Statistical analyses

Statistical analysis title	Placebo vs. Concerta
Comparison groups	Placebo v Concerta
Number of subjects included in analysis	131
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.1466
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.01

Secondary: Hour 8.75 Packet Activity - Decode the Mystery Sentence

End point title	Hour 8.75 Packet Activity - Decode the Mystery Sentence

End point description:

Packet Activities: Assessment of ability to organize, listen to instructions, initiate task, complete task, and distractibility, by completing a word search, reading a short story for comprehension on a multiple choice test, reading a longer story for comprehension on a true/false test, decoding a mystery sentence, and completing various vocabulary assessments (word choice, homophones; base/root words, alphabetic order) (range: 0, 1 represents correct responses divided by the number of possible responses).

End point type	Secondary

End point timeframe:

Hour 8.75 of the Lab School Day During the Double-Blind Assessment Period

End point values	Placebo	Concerta		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	67		
Units: Units on a scale				
arithmetic mean (standard deviation)	0.989 (± 0.0278)	0.955 (± 0.1661)		

Statistical analyses

Statistical analysis title	Placebo vs. Concerta
Comparison groups	Placebo v Concerta
Number of subjects included in analysis	131
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.1368
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.08

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The sponsor collects adverse events for 14 weeks starting with the signing of the informed consent (up to 4 weeks prior to treatment) continuing until the final visit at early discontinuation or study completion (up to 10 weeks after start of treatment).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups

Reporting group title	CONCERTA

Reporting group description:

Concerta was received during the lab school day

Reporting group title	CONCERTA/PLACEBO

Reporting group description:

Children randomized to receive Concerta at lab school day 1 and Placebo at lab school day 2

Reporting group title	PLACEBO/CONCERTA

Reporting group description:

Children randomized to receive Placebo at lab school day 1 and Concerta lab school day 2

Serious adverse events	CONCERTA	CONCERTA/PLACEBO	PLACEBO/CONCERTA
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 21 (0.00%)	0 / 34 (0.00%)	0 / 34 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	CONCERTA	CONCERTA/PLACEBO	PLACEBO/CONCERTA
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 21 (0.00%)	32 / 34 (94.12%)	31 / 34 (91.18%)
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 21 (0.00%)	3 / 34 (8.82%)	2 / 34 (5.88%)
occurrences (all)	0	3	2
Irritability			

subjects affected / exposed	0 / 21 (0.00%)	5 / 34 (14.71%)	3 / 34 (8.82%)
occurrences (all)	0	5	4
Pain			
subjects affected / exposed	0 / 21 (0.00%)	1 / 34 (2.94%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 34 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Thirst			
subjects affected / exposed	0 / 21 (0.00%)	1 / 34 (2.94%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 21 (0.00%)	0 / 34 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 21 (0.00%)	2 / 34 (5.88%)	1 / 34 (2.94%)
occurrences (all)	0	3	1
Epistaxis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 34 (2.94%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Dyspnoea			
subjects affected / exposed	0 / 21 (0.00%)	0 / 34 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Nasal Congestion			
subjects affected / exposed	0 / 21 (0.00%)	4 / 34 (11.76%)	3 / 34 (8.82%)
occurrences (all)	0	5	3
Oropharyngeal Pain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 34 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	0 / 21 (0.00%)	1 / 34 (2.94%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			

Abnormal Behaviour			
subjects affected / exposed	0 / 21 (0.00%)	2 / 34 (5.88%)	1 / 34 (2.94%)
occurrences (all)	0	2	1
Aggression			
subjects affected / exposed	0 / 21 (0.00%)	1 / 34 (2.94%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Affect Lability			
subjects affected / exposed	0 / 21 (0.00%)	5 / 34 (14.71%)	6 / 34 (17.65%)
occurrences (all)	0	5	6
Anxiety			
subjects affected / exposed	0 / 21 (0.00%)	0 / 34 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Emotional Disorder			
subjects affected / exposed	0 / 21 (0.00%)	2 / 34 (5.88%)	0 / 34 (0.00%)
occurrences (all)	0	4	0
Impulsive Behaviour			
subjects affected / exposed	0 / 21 (0.00%)	1 / 34 (2.94%)	0 / 34 (0.00%)
occurrences (all)	0	3	0
Initial Insomnia			
subjects affected / exposed	0 / 21 (0.00%)	11 / 34 (32.35%)	9 / 34 (26.47%)
occurrences (all)	0	12	9
Insomnia			
subjects affected / exposed	0 / 21 (0.00%)	3 / 34 (8.82%)	0 / 34 (0.00%)
occurrences (all)	0	4	0
Mood Swings			
subjects affected / exposed	0 / 21 (0.00%)	0 / 34 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	3
Onychophagia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 34 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Social Avoidant Behaviour			
subjects affected / exposed	0 / 21 (0.00%)	1 / 34 (2.94%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Tic			
subjects affected / exposed	0 / 21 (0.00%)	1 / 34 (2.94%)	0 / 34 (0.00%)
occurrences (all)	0	1	0

Investigations			
Blood Pressure Increased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 34 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Heart Rate Increased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 34 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	2
Weight Decreased			
subjects affected / exposed	0 / 21 (0.00%)	4 / 34 (11.76%)	3 / 34 (8.82%)
occurrences (all)	0	4	3
Injury, poisoning and procedural complications			
Excoriation			
subjects affected / exposed	0 / 21 (0.00%)	3 / 34 (8.82%)	1 / 34 (2.94%)
occurrences (all)	0	3	1
Facial Bones Fracture			
subjects affected / exposed	0 / 21 (0.00%)	0 / 34 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Fracture			
subjects affected / exposed	0 / 21 (0.00%)	1 / 34 (2.94%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Joint Sprain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 34 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	2
Limb Injury			
subjects affected / exposed	0 / 21 (0.00%)	1 / 34 (2.94%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Muscle Strain			
subjects affected / exposed	0 / 21 (0.00%)	1 / 34 (2.94%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Skin Laceration			
subjects affected / exposed	0 / 21 (0.00%)	1 / 34 (2.94%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 21 (0.00%)	0 / 34 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1

Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 21 (0.00%)	2 / 34 (5.88%)	0 / 34 (0.00%)
occurrences (all)	0	2	0
Dizziness Postural			
subjects affected / exposed	0 / 21 (0.00%)	1 / 34 (2.94%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	0 / 21 (0.00%)	12 / 34 (35.29%)	14 / 34 (41.18%)
occurrences (all)	0	16	26
Lethargy			
subjects affected / exposed	0 / 21 (0.00%)	0 / 34 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Psychomotor Hyperactivity			
subjects affected / exposed	0 / 21 (0.00%)	2 / 34 (5.88%)	0 / 34 (0.00%)
occurrences (all)	0	4	0
Ear and labyrinth disorders			
Ear Pain			
subjects affected / exposed	0 / 21 (0.00%)	1 / 34 (2.94%)	2 / 34 (5.88%)
occurrences (all)	0	1	2
Eye disorders			
Conjunctivitis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 34 (2.94%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	0 / 21 (0.00%)	13 / 34 (38.24%)	9 / 34 (26.47%)
occurrences (all)	0	15	11
Diarrhoea			
subjects affected / exposed	0 / 21 (0.00%)	3 / 34 (8.82%)	3 / 34 (8.82%)
occurrences (all)	0	4	4
Constipation			
subjects affected / exposed	0 / 21 (0.00%)	1 / 34 (2.94%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Gastritis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 34 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1

Dry Mouth			
subjects affected / exposed	0 / 21 (0.00%)	0 / 34 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	2
Nausea			
subjects affected / exposed	0 / 21 (0.00%)	3 / 34 (8.82%)	1 / 34 (2.94%)
occurrences (all)	0	5	1
Toothache			
subjects affected / exposed	0 / 21 (0.00%)	1 / 34 (2.94%)	3 / 34 (8.82%)
occurrences (all)	0	1	3
Vomiting			
subjects affected / exposed	0 / 21 (0.00%)	4 / 34 (11.76%)	2 / 34 (5.88%)
occurrences (all)	0	6	3
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 21 (0.00%)	1 / 34 (2.94%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 21 (0.00%)	1 / 34 (2.94%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 34 (2.94%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Back Pain			
subjects affected / exposed	0 / 21 (0.00%)	1 / 34 (2.94%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Muscle Spasms			
subjects affected / exposed	0 / 21 (0.00%)	0 / 34 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 34 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Neck Pain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 34 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1

Pain in Extremity			
subjects affected / exposed	0 / 21 (0.00%)	1 / 34 (2.94%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 34 (2.94%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 34 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	0 / 21 (0.00%)	2 / 34 (5.88%)	0 / 34 (0.00%)
occurrences (all)	0	2	0
Gastroenteritis Viral			
subjects affected / exposed	0 / 21 (0.00%)	0 / 34 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Pharyngitis			
subjects affected / exposed	0 / 21 (0.00%)	2 / 34 (5.88%)	6 / 34 (17.65%)
occurrences (all)	0	2	6
Pharyngitis Streptococcal			
subjects affected / exposed	0 / 21 (0.00%)	0 / 34 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Pneumonia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 34 (2.94%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 21 (0.00%)	5 / 34 (14.71%)	6 / 34 (17.65%)
occurrences (all)	0	5	6
Viral Infection			
subjects affected / exposed	0 / 21 (0.00%)	0 / 34 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Viral Pharyngitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 34 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			

Anorexia			
subjects affected / exposed	0 / 21 (0.00%)	4 / 34 (11.76%)	4 / 34 (11.76%)
occurrences (all)	0	4	6
Decreased Appetite			
subjects affected / exposed	0 / 21 (0.00%)	8 / 34 (23.53%)	7 / 34 (20.59%)
occurrences (all)	0	8	7

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