Clinical trial results:
The efficacy, safety and tolerability of Sativex as an adjunctive treatment to existing anti-spasticity medications in children aged 8 to 18 years with spasticity due to cerebral palsy or traumatic central nervous system injury who have not responded adequately to their existing anti-spasticity medications: a parallel group randomised, double-blind, placebo-controlled study followed by a 24-week open label extension phase.

Summary

EudraCT number	2012-003771-18
Trial protocol	GB CZ
Global end of trial date	23 March 2017

Results information

Result version number	v1 (current)
This version publication date	04 October 2018
First version publication date	04 October 2018

Trial information

Trial identification

Sponsor protocol code	GWSP08258

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01898520
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GW Research Ltd
Sponsor organisation address	Sovereign House, Vision Park, Chivers Way, Histon, Cambridge, United Kingdom, CB24 9BZ
Public contact	GW Research Ltd, Alternate contact: medinfo@greenwichbiosciences.com, medinfo@gwpharm.com
Scientific contact	GW Research Ltd, Alternate contact: medinfo@greenwichbiosciences.com, medinfo@gwpharm.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000181-PIP01-08
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	23 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 March 2017
Global end of trial reached?	Yes
Global end of trial date	23 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of Sativex on spasticity in a population of children and adolescents aged from 8 to 18 years with cerebral palsy (CP) or traumatic central nervous system (CNS) injury.

Protection of trial subjects:

This trial was conducted in compliance with International Conference on Harmonisation Good Clinical Practice guidelines for conducting, recording, and reporting trials, as well as for archiving essential documents. Consistent with ethical principles for the protection of human research participants, no study procedures were performed on study participants until written consent had been obtained from them. The informed consent form, protocol, and amendments for this trial were submitted to and approved by the Institutional Review Board or Ethics Committee at each participating trial site.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 December 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	United Kingdom: 61
Country: Number of subjects enrolled	Czech Republic: 4
Worldwide total number of subjects	72
EEA total number of subjects	65

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)	35
Adolescents (12-17 years)	37
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In order to be eligible for the trial, participants had to be to be suffering from spasticity due to CP or traumatic CNS injury.

Pre-assignment

Screening details:

Participants were 8 to 18 years old with CP or traumatic CNS injury, were under treatment for spasticity for ≥1 year and had reached a stage of non-progressive spasticity, had Gross Motor Function Classification Scale Level III - V, and had a Modified Ashworth Scale (MAS) score of ≥2 in at least one muscle group.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Sativex (Randomised Phase)

Arm description:

Sativex was presented as an oromucosal spray. Sativex was administered by participants or caregivers to the sub-lingual or oral mucosa up to a maximum of 12 sprays per day, for 12 weeks. Each actuation delivered 100 µL (2.7 milligrams [mg] delta-9-tetrahydrocannabinol [THC] and 2.5 mg cannabidiol [CBD]). Sativex was administered as per the following titration schedule (subject to tolerability): Week 1: 1 spray every evening; Week 2: 1 spray twice daily (morning and evening); Weeks 3-4: 1 spray 3 times a day (morning, noon, and evening); Weeks 5 -6: 2 sprays 3 times a day; Weeks 7-8: 3 sprays 3 times a day; Weeks 9-12: 4 sprays 3 times a day. The maximum number of sprays at each stage of titration did not have to be reached. Participants were permitted to stop titrating at any well tolerated dose of 1–12 sprays per day.

Arm type	Experimental
Investigational medicinal product name	Sativex
Investigational medicinal product code	
Other name	Nabiximols, THC:CBD spray, GW-1000-02
Pharmaceutical forms	Oromucosal spray
Routes of administration	Oromucosal use

Dosage and administration details:

Sativex was presented as an oromucosal spray in an amber plastic coated glass vial. Sativex contained THC (27 mg/mL) and CBD (25 mg/mL) in ethanol:propylene glycol (50:50) with peppermint oil (0.05%) as flavouring. Each actuation delivered 100 µL (2.7 mg THC and 2.5 mg CBD) and was administered sublingually or to oral mucosa. In those participants whose disabilities made this difficult, a caregiver administered the medication. If participants complained of oral discomfort, they were advised to apply the spray to varying sites in the mouth and were not to continue spraying onto sore or inflamed mucous membranes. If lesions were observed or persistent soreness was reported, the dosing of Sativex was to be stopped until complete resolution occurred.

Arm title	Placebo (Randomised Phase)

Arm description:

Placebo was presented as an oromucosal spray. Placebo was administered by participants or caregivers to the sub-lingual or oral mucosa up to a maximum of 12 sprays per day, for 12 weeks. Placebo contained ethanol: propylene glycol (50:50) excipients. Each actuation delivered 100 µL. Placebo was administered as per the following titration schedule (subject to tolerability): Week 1: 1 spray every evening; Week 2: 1 spray twice daily (morning and evening); Weeks 3-4: 1 spray 3 times a day (morning, noon, and evening); Weeks 5 -6: 2 sprays 3 times a day; Weeks 7-8: 3 sprays 3 times a day; Weeks 9-12: 4 sprays 3 times a day. The maximum number of sprays at each stage of titration did not have to be reached. Participants were permitted to stop titrating at any well tolerated dose of 1–12

sprays per day.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	GW-4000-01
Pharmaceutical forms	Oromucosal spray
Routes of administration	Oromucosal use

Dosage and administration details:

Placebo was presented as an oromucosal spray in an amber plastic coated glass vial. Placebo contained ethanol:propylene glycol (50:50) with peppermint oil (0.05%) as flavouring, and FD&C Yellow No.5 (E102 tartrazine) (0.0260%), FD&C Yellow No.6 (E110 sunset yellow) (0.0038%), FD&C Red No. 40 (E129 Allura red AC) (0.00330%) and FD&C Blue No.1 (E133 Brilliant blue FCF) (0.00058%) as colourant. Each actuation delivered 100 µL of placebo and was administered sublingually or to oral mucosa. In those participants whose disabilities made this difficult, a caregiver administered the medication. If participants complained of oral discomfort, they were advised to apply the spray to varying sites in the mouth and were not to continue spraying onto sore or inflamed mucous membranes. If lesions were observed or persistent soreness was reported, the dosing of placebo was to be stopped until complete resolution occurred.

Number of subjects in period 1	Sativex (Randomised Phase)	Placebo (Randomised Phase)
Started	47	25
Received at least 1 dose of study drug	47	25
Completed	44	24
Not completed	3	1
Withdrawn by investigator	1	-
Consent withdrawn by subject	-	1
Adverse event	2	-

Period 2

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

Arms

Arm title	Sativex (OLE Phase)

Arm description:

Following the final assessment of the randomised phase of the trial on Day 84, all participants were invited to participate in the OLE phase. All participants who chose to continue were re-titrated with Sativex using the same titration schedule in the randomization phase. Sativex was presented as an oromucosal spray and was administered by participants or caregivers to the sub-lingual or oral mucosa up to a maximum of 12 sprays per day, for up to 24 weeks. Each actuation delivered 100 µL (2.7 mg THC and 2.5 mg CBD).

Arm type	Experimental

Investigational medicinal product name	Sativex
Investigational medicinal product code	
Other name	Nabiximols, THC:CBD spray, GW-1000-02
Pharmaceutical forms	Oromucosal spray
Routes of administration	Oromucosal use

Dosage and administration details:

Sativex was presented as an oromucosal spray. Sativex contained THC (27 mg/mL) and CBD (25 mg/mL) in ethanol:propylene glycol (50:50) with peppermint oil (0.05%) as flavouring. Each actuation delivered 100 µL (2.7 mg THC and 2.5 mg CBD) and was administered sublingually or to oral mucosa. In those participants whose disabilities made this difficult, a caregiver administered the medication. If participants complained of oral discomfort, they were advised to apply the spray to varying sites in the mouth and were not to continue spraying onto sore or inflamed mucous membranes. If lesions were observed or persistent soreness was reported, the dosing of Sativex was to be stopped until complete resolution occurred.

Number of subjects in period 2[1]	Sativex (OLE Phase)
Started	67
Received at least 1 dose of study drug	67
Safety Population	67
Completed	54
Not completed	13
Withdrawn by investigator	1
Consent withdrawn by subject	3
Adverse event	9

Notes:

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

Justification: Participation in the OLE phase was optional. One participant who received Sativex in the randomised phase did not continue to the optional OLE phase.

Baseline characteristics

Reporting groups

Reporting group title	Sativex (Randomised Phase)

Reporting group description:

Sativex was presented as an oromucosal spray. Sativex was administered by participants or caregivers to the sub-lingual or oral mucosa up to a maximum of 12 sprays per day, for 12 weeks. Each actuation delivered 100 µL (2.7 milligrams [mg] delta-9-tetrahydrocannabinol [THC] and 2.5 mg cannabidiol [CBD]). Sativex was administered as per the following titration schedule (subject to tolerability): Week 1: 1 spray every evening; Week 2: 1 spray twice daily (morning and evening); Weeks 3-4: 1 spray 3 times a day (morning, noon, and evening); Weeks 5 -6: 2 sprays 3 times a day; Weeks 7-8: 3 sprays 3 times a day; Weeks 9-12: 4 sprays 3 times a day. The maximum number of sprays at each stage of titration did not have to be reached. Participants were permitted to stop titrating at any well tolerated dose of 1–12 sprays per day.

Reporting group title	Placebo (Randomised Phase)

Reporting group description:

Placebo was presented as an oromucosal spray. Placebo was administered by participants or caregivers to the sub-lingual or oral mucosa up to a maximum of 12 sprays per day, for 12 weeks. Placebo contained ethanol: propylene glycol (50:50) excipients. Each actuation delivered 100 µL. Placebo was administered as per the following titration schedule (subject to tolerability): Week 1: 1 spray every evening; Week 2: 1 spray twice daily (morning and evening); Weeks 3-4: 1 spray 3 times a day (morning, noon, and evening); Weeks 5 -6: 2 sprays 3 times a day; Weeks 7-8: 3 sprays 3 times a day; Weeks 9-12: 4 sprays 3 times a day. The maximum number of sprays at each stage of titration did not have to be reached. Participants were permitted to stop titrating at any well tolerated dose of 1–12 sprays per day.

Reporting group values	Sativex (Randomised Phase)	Placebo (Randomised Phase)	Total
Number of subjects	47	25	72
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	22	13	35
Adolescents (12-17 years)	25	12	37
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	12.58	11.90	
standard deviation	± 3.340	± 2.390	-
Gender categorical			
Units: Subjects			
Female	18	10	28
Male	29	15	44

End points

End points reporting groups

Reporting group title	Sativex (Randomised Phase)

Reporting group description:

Sativex was presented as an oromucosal spray. Sativex was administered by participants or caregivers to the sub-lingual or oral mucosa up to a maximum of 12 sprays per day, for 12 weeks. Each actuation delivered 100 µL (2.7 milligrams [mg] delta-9-tetrahydrocannabinol [THC] and 2.5 mg cannabidiol [CBD]). Sativex was administered as per the following titration schedule (subject to tolerability): Week 1: 1 spray every evening; Week 2: 1 spray twice daily (morning and evening); Weeks 3-4: 1 spray 3 times a day (morning, noon, and evening); Weeks 5 -6: 2 sprays 3 times a day; Weeks 7-8: 3 sprays 3 times a day; Weeks 9-12: 4 sprays 3 times a day. The maximum number of sprays at each stage of titration did not have to be reached. Participants were permitted to stop titrating at any well tolerated dose of 1–12 sprays per day.

Reporting group title	Placebo (Randomised Phase)

Reporting group description:

Placebo was presented as an oromucosal spray. Placebo was administered by participants or caregivers to the sub-lingual or oral mucosa up to a maximum of 12 sprays per day, for 12 weeks. Placebo contained ethanol: propylene glycol (50:50) excipients. Each actuation delivered 100 µL. Placebo was administered as per the following titration schedule (subject to tolerability): Week 1: 1 spray every evening; Week 2: 1 spray twice daily (morning and evening); Weeks 3-4: 1 spray 3 times a day (morning, noon, and evening); Weeks 5 -6: 2 sprays 3 times a day; Weeks 7-8: 3 sprays 3 times a day; Weeks 9-12: 4 sprays 3 times a day. The maximum number of sprays at each stage of titration did not have to be reached. Participants were permitted to stop titrating at any well tolerated dose of 1–12 sprays per day.

Reporting group title	Sativex (OLE Phase)

Reporting group description:

Following the final assessment of the randomised phase of the trial on Day 84, all participants were invited to participate in the OLE phase. All participants who chose to continue were re-titrated with Sativex using the same titration schedule in the randomization phase. Sativex was presented as an oromucosal spray and was administered by participants or caregivers to the sub-lingual or oral mucosa up to a maximum of 12 sprays per day, for up to 24 weeks. Each actuation delivered 100 µL (2.7 mg THC and 2.5 mg CBD).

Primary: Change From Baseline In Spasticity Severity 0-10 Numerical Rating Scale (NRS) Score To End Of Treatment (EOT) (12-Week Randomised Phase)

End point title	Change From Baseline In Spasticity Severity 0-10 Numerical Rating Scale (NRS) Score To End Of Treatment (EOT) (12-Week Randomised Phase)

End point description:

The spasticity 0-10 NRS was completed daily at bedtime using a study diary. The primary caregiver was asked the following question: "This question is about your child's muscles and how soft or tight/hard they have felt today. Think carefully about how your child's muscles have felt today and circle a number from 0 to 10 that best describes this, where: 0 = 'my child's muscles have felt totally relaxed' and 10 = 'my child's muscles have felt the tightest/hardest they have ever felt'". Baseline was defined as the average of the assessments recorded on Day −7 to Day −1, inclusive. EOT was the average of the last 7 days of diary data up to the earliest of Day 84, the last dose of IMP and the last day with relevant efficacy data. Least Squares Means (LS Means) were calculated using an analysis of covariance (ANCOVA) with baseline score as a covariate and treatment as fixed effect.
A reduction in score indicates an improvement in condition

End point type	Primary

End point timeframe:

Baseline, EOT (12-Week Randomised Phase)

End point values	Sativex (Randomised Phase)	Placebo (Randomised Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	25		
Units: units on a scale				
least squares mean (standard error)	-1.812 (± 0.2807)	-1.645 (± 0.3854)		

Statistical analyses

Statistical analysis title	Change in Spasticity Severity NRS Score

Statistical analysis description:

Change from baseline was compared between groups using ANCOVA with baseline score as a covariate and treatment as a fixed effect. A 2-sided significance test was used in all comparisons at the 5% level of significance. All participants who were treated and received IMP were included and analysed according to their randomised treatment.

Comparison groups	Sativex (Randomised Phase) v Placebo (Randomised Phase)
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7291
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	-0.166
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.119
upper limit	0.787
Variability estimate	Standard error of the mean
Dispersion value	0.4777

Secondary: Change From Baseline In Modified Tardieu Scale (MTS) Score Of The Worst Affected Limb To EOT (12-Week Randomised Phase)

End point title	Change From Baseline In Modified Tardieu Scale (MTS) Score Of The Worst Affected Limb To EOT (12-Week Randomised Phase)

End point description:

The MTS of the worst affected limb (identified for each participant at Baseline) was assessed. Individuals were positioned in sitting position to test upper extremities and supine position to test lower extremities. MTS was based on the following criteria:

- 3 speed definitions of limb movement: V1 (as slow as possible), V2 (falling under gravity), V3 (as fast as possible)
- MTS describes R1 and R2: R1 is the angle of muscle reaction; R2 is the full passive range of movement.
- R2 was measured at V1 and R1 at V3. R2-R1 = dynamic tone component of the muscle. The relationship between R1 and R2 estimates the relative contributions of spasticity compared to contracture.

EOT was defined Day 84. LS Means were calculated using ANCOVA with baseline score as a covariate and treatment as fixed effect; using Last observation carried forward (LOCF) if observations were missing at EOT. A reduction in score indicates an improvement in condition.

End point type	Secondary

End point timeframe:

Baseline, EOT (12-Week Randomised Phase)

End point values	Sativex (Randomised Phase)	Placebo (Randomised Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	25		
Units: units on a scale				
least squares mean (standard error)	-6.603 (± 3.4070)	-1.925 (± 4.7281)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In MAS Score Of The Main Muscle Groups Of The Upper And Lower Limbs To EOT (12-Week Randomised Phase)

End point title	Change From Baseline In MAS Score Of The Main Muscle Groups Of The Upper And Lower Limbs To EOT (12-Week Randomised Phase)

End point description:

This trial assessed the MAS of the main muscle groups of the upper and lower limb using the MAS Examination and Scoring System. The MAS was performed by the same examiner at each clinic visit (where possible), with the participant in the supine position and the participant was requested to relax. If a muscle that primarily flexed a joint was tested, the joint was placed in a maximally flexed position and moved to a position of maximal extension in 1 second (counted 'one thousand one'). If a muscle that primarily extended a joint was tested, the joint was placed in a maximally extended position and moved to a position of maximal flexion in 1 second (counted 'one thousand one').
EOT was defined as Day 84. LS Means were calculated using ANCOVA with baseline score as a covariate and treatment as fixed effect; using LOCF if observations were missing at EOT. A reduction in score indicates an improvement in condition.

End point type	Secondary

End point timeframe:

Baseline, EOT (12-Week Randomised Phase)

End point values	Sativex (Randomised Phase)	Placebo (Randomised Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	25		
Units: units on a scale				
least squares mean (standard error)	-10.92 (± 1.715)	-10.26 (± 2.303)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Sleep Quality 0-10 NRS Score To EOT (12-Week Randomised Phase)

End point title	Change From Baseline In Sleep Quality 0-10 NRS Score To EOT (12-Week Randomised Phase)

End point description:

Sleep quality was assessed using a 0-10 NRS questionnaire completed at the same time each day, ideally when waking in the morning. This questionnaire was designed to record the level of sleep disturbance. The primary caregiver was asked the following question: "This question is about how badly your child slept last night. Please mark a number from 0 to 10 that indicates how bad your child's sleep was, where a score of 0 indicated "My child had a night of non-stop sleep" and a score 10 indicated "My child was unable to sleep at all." EOT is the average of the last 7 days of diary data up to the earliest of Day 84, the last dose of IMP and the last day with relevant efficacy data. LS Means were calculated using ANCOVA with baseline score as a covariate and treatment as fixed effect. A reduction in score indicates an improvement in condition.

End point type	Secondary

End point timeframe:

Baseline, EOT (12-Week Randomised Phase)

End point values	Sativex (Randomised Phase)	Placebo (Randomised Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	25		
Units: units on a scale				
least squares mean (standard error)	-1.308 (± 0.2078)	-0.984 (± 0.2855)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Paediatric Pain Profile (PPP) Score To EOT (12-Week Randomised Phase)

End point title	Change From Baseline In Paediatric Pain Profile (PPP) Score To EOT (12-Week Randomised Phase)

End point description:

The PPP is a 20-item behaviour rating scale designed to assess pain in children with severe neurological disability. Each item was scored on a 4-point scale of 0 to 3 as occurring 'not at all' (zero) to 'a great deal' (three) in the given time period. Therefore, the total score ranged from 0 to 60. The questionnaire was designed to be completed by the child's primary caregiver and was completed at each assessment visit during the trial.
EOT was defined as Day 84. LS Means were calculated using ANCOVA with baseline score as a covariate and treatment as fixed effect; using Last observation carried forward (LOCF) if observations were missing at EOT. A reduction in score indicates an improvement in condition.

End point type	Secondary

End point timeframe:

Baseline, EOT (12-Week Randomised Phase)

End point values	Sativex (Randomised Phase)	Placebo (Randomised Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	25		
Units: units on a scale				
least squares mean (standard error)				
On a Good Day	-1.6 (± 1.47)	-6.0 (± 2.02)		
Most Troublesome Pain	-16.9 (± 1.59)	-21.8 (± 2.21)		
Second Most Troublesome Pain	-9.0 (± 2.07)	-17.4 (± 2.76)		
Third Most Troublesome Pain	-11.2 (± 5.27)	-24.0 (± 6.15)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Cerebral Palsy Quality Of Life (CP QOL) Score To EOT (12-Week Randomised Phase)

End point title	Change From Baseline In Cerebral Palsy Quality Of Life (CP QOL) Score To EOT (12-Week Randomised Phase)

End point description:

CP QOL-child (4-12 years old) questionnaire assessed the following domains of life: social wellbeing and acceptance, feelings about functioning, participation and physical health, emotional wellbeing and self-esteem, access to services, pain and impact on disability, family health. CP QOL-teen (13-18 years old) questionnaire completed by the participant (if possible) assessed the following domains of life: feelings about functioning, access to services, general wellbeing and participation, communication and physical health, school wellbeing, social wellbeing. Scores from both questionnaires were transformed to a 0–100 scale. Domain scores were calculated by taking the average of the converted question response scores for the questions included in that domain.
EOT was Day 84. LS Means were calculated using ANCOVA with baseline score as a covariate and treatment as fixed effect; using LOCF if observations were missing at EOT. Increase in score indicates improvement in condition.

End point type	Secondary

End point timeframe:

Baseline, EOT (12-Week Randomised Phase)

End point values	Sativex (Randomised Phase)	Placebo (Randomised Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	25		
Units: units on a scale				
least squares mean (standard error)				
CP QOL-Child: Social Wellbeing and Acceptance	1.155 (± 2.8603)	2.424 (± 3.3030)		
CP QOL-Child: Feelings about Functioning	3.273 (± 1.9984)	5.316 (± 2.4972)		

CP QOL-Child: Participation and Physical Health	4.749 (± 2.5455)	9.101 (± 3.0558)		
CP QOL-Child: Emotional Wellbeing and Self-esteem	-1.088 (± 3.5408)	2.118 (± 4.1104)		
CP QOL-Child: Access to Services	1.760 (± 2.4464)	-1.645 (± 3.0746)		
CP QOL-Child: Pain and Impact of Disability	-3.104 (± 2.9696)	-5.691 (± 3.5527)		
CP QOL-Child: Family Health	-3.243 (± 3.8529)	8.427 (± 4.6147)		
CP QOL-Child: Total Score	0.116 (± 1.7158)	2.198 (± 2.0669)		
CP QOL-Teen: Feelings about Functioning	2.513 (± 2.8097)	1.751 (± 4.6322)		
CP QOL-Teen: Access to Services	5.693 (± 2.2325)	-2.011 (± 3.6795)		
CP QOL-Teen: General Wellbeing and Participation	1.684 (± 2.5737)	3.733 (± 4.2435)		
CP QOL-Teen: Communication and Physical Health	0.817 (± 2.6631)	5.282 (± 4.3968)		
CP QOL-Teen: School Wellbeing	-2.839 (± 3.3714)	7.930 (± 5.5701)		
CP QOL-Teen: Social Wellbeing	-4.560 (± 2.9490)	-1.440 (± 4.8597)		
CP QOL-Teen: Total Score	0.548 (± 1.9262)	2.549 (± 3.1742)		
CP QOL: Overall Total Score	0.649 (± 1.2865)	1.717 (± 1.7568)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Comfort Questionnaire Outcome To EOT (12-Week Randomised Phase)

End point title	Change From Baseline In Comfort Questionnaire Outcome To EOT (12-Week Randomised Phase)

End point description:

The comfort questionnaire was completed at the same time each day, that is, bedtime in the evening. The caregiver was asked to reflect on the whole day and record the longest number of minutes at any 1 time during which their child was able to sit in comfort for, without moving position.
Baseline was defined as the average of Day −7 to Day −1. EOT was the average of the last 7 days of diary data up to the earliest of Day 84, the last dose of IMP and the last day with relevant efficacy data.
LS Means were calculated using ANCOVA with baseline score as a covariate and treatment as fixed effect.
An increase in time indicates an improvement in condition.

End point type	Secondary

End point timeframe:

Baseline, EOT (12-Week Randomised Phase)

End point values	Sativex (Randomised Phase)	Placebo (Randomised Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	25		
Units: minutes				
least squares mean (standard error)	0.611 (± 0.6905)	0.232 (± 0.9271)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Children's Depression Inventory (CDI) 2 Score To EOT (12-Week Randomised Phase)

End point title	Change From Baseline In Children's Depression Inventory (CDI) 2 Score To EOT (12-Week Randomised Phase)

End point description:

The CDI 2 contains 12 items, each of which consists of 3 statements (each scored 0-2 [0=best outcome, 2=worst outcome]). For each item, the participant was asked to select the statement that best describes his or her feelings. The assessment addressed a variety of situations, including schools, child guidance clinics, paediatric practices, and child psychiatric settings. If the participant was unable to complete the questionnaire, the questionnaire was left blank. All CDI 2 forms were administered and scored using the Multi-health System Inc. QuikScore™ format. Each QuikScore form included conversion tables, which were used to convert raw scores to T-scores. EOT was defined as Day 84.
LS Means were calculated using ANCOVA with baseline score as a covariate and treatment as fixed effect; using LOCF if observations were missing at EOT. A reduction in T-score indicates an improvement in condition.

End point type	Secondary

End point timeframe:

Baseline, EOT (12-Week Randomised Phase)

End point values	Sativex (Randomised Phase)	Placebo (Randomised Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	25		
Units: T-score				
least squares mean (standard error)	-6.4 (± 4.723)	-1.2 (± 4.723)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Caregiver QOL (SF-36-II) Score To EOT (12-Week Randomised Phase)

End point title	Change From Baseline In Caregiver QOL (SF-36-II) Score To EOT (12-Week Randomised Phase)

End point description:

The SF-36-II is a 36 item questionnaire that measures 8 multi-item dimensions of health: physical functioning (10 items) social functioning (2 items) role limitations due to physical problems (4 items), role limitations due to emotional problems (3 items), mental health (5 items), energy/vitality (4 items), pain (2 items), and general health perception (5 items). There is a further unscaled single item asking respondents about health change over the past year. For each dimension item scores were coded, summed, and transformed on to a scale from 0 (worst possible health state measured by the questionnaire) to 100 (best possible health state).
EOT was defined as Day 84. LS Means were calculated using ANCOVA with baseline score as a covariate and treatment as fixed effect; using LOCF if observations were missing at EOT. An increase in score indicates an improvement in condition.

End point type	Secondary

End point timeframe:

Baseline, EOT (12-Week Randomised Phase)

End point values	Sativex (Randomised Phase)	Placebo (Randomised Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	25		
Units: units on a scale				
least squares mean (standard error)				
Bodily Pain	1.8 (± 3.14)	-3.7 (± 4.22)		
General Health Perception	-2.5 (± 1.16)	0.6 (± 1.55)		
General Mental Health	2.6 (± 1.95)	2.5 (± 2.62)		
Physical Functioning	-1.2 (± 3.06)	6.5 (± 4.11)		
Role Limitations due to Emotional Problems	2.7 (± 3.08)	12.1 (± 4.13)		
Role Limitations due to Physical Health Problems	0.5 (± 3.78)	11.1 (± 5.07)		
Social Functioning	-0.4 (± 1.72)	-1.8 (± 2.30)		
Vitality, Energy or Fatigue	4.0 (± 1.92)	2.6 (± 2.58)		

Statistical analyses

No statistical analyses for this end point

Secondary: Caregiver Global Impression Of Change (CGIC) Response On Participants General Functional Capabilities At Last Visit (12-Week Randomised Phase)

End point title	Caregiver Global Impression Of Change (CGIC) Response On Participants General Functional Capabilities At Last Visit (12-Week Randomised Phase)

End point description:

The main caregiver was asked to assess the change in the participant's condition. At Visit 2 (Baseline) carers were asked to write a brief description of the participant's general functional abilities. This acted as a memory aid that the carer could refer to when answering the CGIC question at later time points in the trial. The caregiver was asked, "How have the participant's general functional abilities changed since Visit 2?" (Baseline). The question was rated on a 7-point scale: Very much worse, Much worse, Minimally worse, No change, Minimally better, Much better, Very much better.
The number of participants for each marker is presented.

End point type	Secondary

End point timeframe:

Last Visit (12-Week Randomised Phase)

End point values	Sativex (Randomised Phase)	Placebo (Randomised Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	25		
Units: participants				
number (not applicable)				
Very Much Better	2	1		
Much Better	12	8		
Minimally Better	9	8		
No Change	17	7		
Minimally Worse	4	1		
Much Worse	2	0		
Very Much Worse	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: CGIC Response On Participants Ease Of Transfer At EOT (12-Week Randomised Phase)

End point title	CGIC Response On Participants Ease Of Transfer At EOT (12-Week Randomised Phase)

End point description:

The main caregiver was asked to assess the change in the participant's condition. At Visit 2 (Baseline) carers were asked to write a brief description of the participant's ease of transfer. This acted as a memory aid that the carer could refer to when answering the CGIC question at later time points in the trial. The caregiver was asked, "How has the participant's ease of transfer changed since Visit 2?" (Baseline). The question was rated on a 7-point scale: Very much worse, Much worse, Minimally worse, No change, Minimally better, Much better, Very much better. The number of participants for each marker is presented.
EOT was defined as Day 84.

End point type	Secondary

End point timeframe:

EOT (12-Week Randomised Phase)

End point values	Sativex (Randomised Phase)	Placebo (Randomised Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	25		
Units: participants				
number (not applicable)				
Very Much Better	2	1		

Much Better	10	6		
Minimally Better	10	8		
No Change	19	8		
Minimally Worse	3	1		
Much Worse	1	0		
Very Much Worse	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After first dose of IMP through Day 266

Adverse event reporting additional description:

Any adverse changes in the participant's medical condition, following completion of the consent form, were recorded on the case report form (CRF) as adverse events (AEs). All AEs that occurred during the trial, whether or not attributed to the IMP, observed by the investigator or reported by the participant were recorded in the CRF.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Sativex (Randomised Phase)

Reporting group description:

Safety Analysis Set: All participants who received at least 1 dose of Sativex during the 12-week Randomised Phase.

Reporting group title	Placebo (Randomised Phase)

Reporting group description:

Safety Analysis Set: All participants who received at least 1 dose of placebo during the 12-week Randomised Phase.

Reporting group title	Sativex (OLE Phase)

Reporting group description:

Safety Analysis Set: All participants who received at least 1 dose of Sativex during the 24-week OLE Phase.

Serious adverse events	Sativex (Randomised Phase)	Placebo (Randomised Phase)	Sativex (OLE Phase)
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 47 (8.51%)	3 / 25 (12.00%)	19 / 67 (28.36%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Body temperature fluctuation			
subjects affected / exposed	0 / 47 (0.00%)	0 / 25 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Shunt malfunction			
subjects affected / exposed	0 / 47 (0.00%)	1 / 25 (4.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 47 (2.13%)	0 / 25 (0.00%)	5 / 67 (7.46%)
occurrences causally related to treatment / all	0 / 1	0 / 0	2 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dystonia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 25 (0.00%)	2 / 67 (2.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Grand mal convulsion			
subjects affected / exposed	1 / 47 (2.13%)	0 / 25 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lethargy			
subjects affected / exposed	0 / 47 (0.00%)	0 / 25 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures			
subjects affected / exposed	0 / 47 (0.00%)	1 / 25 (4.00%)	0 / 67 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 47 (0.00%)	0 / 25 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Speech disorder			
subjects affected / exposed	0 / 47 (0.00%)	0 / 25 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Unresponsive to stimuli			
subjects affected / exposed	0 / 47 (0.00%)	0 / 25 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration			

site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 47 (0.00%)	0 / 25 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site erythema			
subjects affected / exposed	0 / 47 (0.00%)	0 / 25 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site swelling			
subjects affected / exposed	0 / 47 (0.00%)	0 / 25 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device occlusion			
subjects affected / exposed	0 / 47 (0.00%)	0 / 25 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug interaction			
subjects affected / exposed	0 / 47 (0.00%)	0 / 25 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug withdrawal syndrome			
subjects affected / exposed	0 / 47 (0.00%)	0 / 25 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 47 (0.00%)	0 / 25 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal hypomotility			
subjects affected / exposed	0 / 47 (0.00%)	0 / 25 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ileus			
subjects affected / exposed	0 / 47 (0.00%)	0 / 25 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus paralytic			
subjects affected / exposed	0 / 47 (0.00%)	0 / 25 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retching			
subjects affected / exposed	1 / 47 (2.13%)	0 / 25 (0.00%)	0 / 67 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 47 (0.00%)	0 / 25 (0.00%)	4 / 67 (5.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 47 (0.00%)	0 / 25 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anger			
subjects affected / exposed	0 / 47 (0.00%)	0 / 25 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Food aversion			
subjects affected / exposed	1 / 47 (2.13%)	0 / 25 (0.00%)	0 / 67 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 47 (0.00%)	0 / 25 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Thinking abnormal			
subjects affected / exposed	0 / 47 (0.00%)	0 / 25 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 25 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 25 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 47 (0.00%)	0 / 25 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 47 (0.00%)	1 / 25 (4.00%)	3 / 67 (4.48%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 47 (0.00%)	0 / 25 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 47 (2.13%)	0 / 25 (0.00%)	0 / 67 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 47 (0.00%)	0 / 25 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Sativex (Randomised Phase)	Placebo (Randomised Phase)	Sativex (OLE Phase)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 47 (59.57%)	17 / 25 (68.00%)	37 / 67 (55.22%)
Nervous system disorders			
Convulsion			
subjects affected / exposed	2 / 47 (4.26%)	2 / 25 (8.00%)	5 / 67 (7.46%)
occurrences (all)	6	3	9
Poor quality sleep			
subjects affected / exposed	3 / 47 (6.38%)	1 / 25 (4.00%)	1 / 67 (1.49%)
occurrences (all)	4	1	1
Somnolence			
subjects affected / exposed	6 / 47 (12.77%)	2 / 25 (8.00%)	4 / 67 (5.97%)
occurrences (all)	6	4	5
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 47 (6.38%)	2 / 25 (8.00%)	2 / 67 (2.99%)
occurrences (all)	3	3	2
Fatigue			
subjects affected / exposed	1 / 47 (2.13%)	2 / 25 (8.00%)	2 / 67 (2.99%)
occurrences (all)	3	2	3
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 47 (2.13%)	3 / 25 (12.00%)	5 / 67 (7.46%)
occurrences (all)	1	7	5
Diarrhoea			
subjects affected / exposed	1 / 47 (2.13%)	2 / 25 (8.00%)	5 / 67 (7.46%)
occurrences (all)	3	3	6
Oral pain			
subjects affected / exposed	1 / 47 (2.13%)	2 / 25 (8.00%)	1 / 67 (1.49%)
occurrences (all)	1	2	1

Retching			
subjects affected / exposed	5 / 47 (10.64%)	0 / 25 (0.00%)	3 / 67 (4.48%)
occurrences (all)	6	0	4
Vomiting			
subjects affected / exposed	6 / 47 (12.77%)	4 / 25 (16.00%)	6 / 67 (8.96%)
occurrences (all)	7	5	8
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 47 (0.00%)	2 / 25 (8.00%)	1 / 67 (1.49%)
occurrences (all)	0	2	1
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	4 / 47 (8.51%)	3 / 25 (12.00%)	2 / 67 (2.99%)
occurrences (all)	5	3	3
Lower respiratory tract infection			
subjects affected / exposed	4 / 47 (8.51%)	2 / 25 (8.00%)	6 / 67 (8.96%)
occurrences (all)	5	3	7
Nasopharyngitis			
subjects affected / exposed	4 / 47 (8.51%)	1 / 25 (4.00%)	3 / 67 (4.48%)
occurrences (all)	4	3	3
Upper respiratory tract infection			
subjects affected / exposed	4 / 47 (8.51%)	3 / 25 (12.00%)	11 / 67 (16.42%)
occurrences (all)	6	3	13
Viral infection			
subjects affected / exposed	2 / 47 (4.26%)	2 / 25 (8.00%)	1 / 67 (1.49%)
occurrences (all)	2	2	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 47 (0.00%)	1 / 25 (4.00%)	4 / 67 (5.97%)
occurrences (all)	0	1	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 March 2015	- A change in an inclusion no longer requires participants to currently be on spasticity therapy as paediatric participants are less likely than adults to continue on medications that are not sufficiently alleviating their symptoms or if side effects occur. The protocol amendment now required participants to have received inadequate efficacy and/or experienced unacceptable side effects from previous or current treatment with at least one of the following medications for spasticity: Baclofen, diazepam (or another benzodiazepine), dantrolene, tizanidine, gabapentin and trihexyphenidyl. - A parental/legal representative can withdraw participant assent/consent. -Before any open-label procedures are performed, the Investigator must reiterate the known adverse reactions to Sativex and ensure participants and parents/legal guardians are fully informed of the trial requirements. The signed informed consent/assent forms can be referred to for this. Participants who decline will receive a follow up telephone call 14 days after the end of treatment to check for AEs and concomitant medication changes. - If a participant does not possess adequate understanding, assent will be taken along with parental/legal representative consent. The investigator should also give consideration to a child's wishes not to participate, or wishes to withdraw at any time during the trial regardless of their level of understanding and regardless of parental/legal representative consent.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported