Clinical trial results:
An open-label adaptive study for the assessment of safety, tolerability, pharmacokinetics, and efficacy of multiple doses of radiprodil in subjects with drug-resistant infantile spasms

Summary

EudraCT number	2016-002107-26
Trial protocol	GB BE DE BG FR
Global end of trial date	02 October 2018

Results information

Result version number	v1 (current)
This version publication date	17 April 2019
First version publication date	17 April 2019

Trial information

Trial identification

Sponsor protocol code	EP0078

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02829827
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB Biopharma SPRL
Sponsor organisation address	Allée de la Recherche 60, Brussels, Belgium, 1070
Public contact	Clin Trial Reg & Results Disclosure, UCB BIOSCIENCES GmbH, clinicaltrials@ucb.com
Scientific contact	Clin Trial Reg & Results Disclosure, UCB BIOSCIENCES GmbH, clinicaltrials@ucb.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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 January 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 October 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Part A:
To
- Evaluate the safety and tolerability of radiprodil in subjects with drug-resistant infantile spasms
- Evaluate the pharmacokinetics of radiprodil in subjects with drug-resistant infantile spasms
- Evaluate the efficacy of radiprodil in abolishing clinical spasms in subjects with drug-resistant infantile spasms

Part B:
To
- Evaluate the efficacy of radiprodil in abolishing clinical spasms and achieving the resolution of hypsarrhythmia (or other disordered interictal electroencephalogram (EEG) patterns consistent with the diagnosis) in subjects with drug-resistant infantile spasms
- Evaluate the safety and tolerability of radiprodil in subjects with drug-resistant infantile spasms

Part C:
To
- Investigate the safety and tolerability of radiprodil over repeated treatment cycles
- Investigate the efficacy of radiprodil in infants who have responded to 2 treatment cycles in Part A but experienced a relapse within 3 days of treatment cessation

Protection of trial subjects:

During the conduct of the study all subjects were closely monitored.

Background therapy:

Background therapy as permitted in the protocol.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	04 December 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 3
Worldwide total number of subjects	3
EEA total number of subjects	3

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)	3
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study started to enroll patients in December 2017 and was terminated in October 2018.

Pre-assignment

Screening details:

The Participant Flow refers to the Safety Set (SS).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Radiprodil

Arm description:

Each subject entered an individualized dose titration schedule. The titration included 3 dose levels of radiprodil: low, medium, high, given bid for 3 days (Day 1L to Day 3L, Day 1M to Day 3M, Day 1H to Day 3H). Titration from L dose to M dose was decided by the investigator: if spasms continued with no safety/tolerability issues, the dose was increased to M, if spasms were absent for 24h, the L dose remained the Maintenance dose.
Dose titration from M to H and/or Maintenance of M dose was decided by the investigator, following the same procedure.
The Maintenance period occurred over a period of 14 Days (Day14Maint) if spasm continued on Day 3H and there were no safety/tolerability issues, or 28 days (Day28Maint) if spasms were absent for 24h. If spasms were still present at Day14Maint, radiprodil tapering took place: from L dose to L dose 1 per day for 3 days, from M dose to L dose, 3 days bid, from H dose to M dose, 3 days bid.

Arm type	Experimental
Investigational medicinal product name	Radiprodil
Investigational medicinal product code	UCB3491
Other name	
Pharmaceutical forms	Granules for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Subjects were administered 3 dose levels (low, medium, high) of radiprodil, given bid for 3 days, as follows: low dose from Day1L to Day 3L, with maintenance of low dose if spasms were absent 24h, or titration to middle dose, if spasms continued. Middle dose from Day1M to Day3M, with maintenance of middle dose if spasms were absent 24 hours, or titration to high dose if spasms continued. High dose from Day1H to day3H, with maintenance of high dose if spasms were absent 24h, for 28Days (28Maint), or tapering if spasms were still present over a period of 14 days (Day14Maint). Radiprodil tapering was done from low dose to low dose, once a day for 3 days; middle dose to low dose, 3 days bid and high dose to middle dose, 3 days bid.

Number of subjects in period 1	Radiprodil
Started	3
Completed	0
Not completed	3
Sponsor study termination	3

Baseline characteristics

Reporting groups

Reporting group title	Radiprodil

Reporting group description:

Each subject entered an individualized dose titration schedule. The titration included 3 dose levels of radiprodil: low, medium, high, given bid for 3 days (Day 1L to Day 3L, Day 1M to Day 3M, Day 1H to Day 3H). Titration from L dose to M dose was decided by the investigator: if spasms continued with no safety/tolerability issues, the dose was increased to M, if spasms were absent for 24h, the L dose remained the Maintenance dose.
Dose titration from M to H and/or Maintenance of M dose was decided by the investigator, following the same procedure.
The Maintenance period occurred over a period of 14 Days (Day14Maint) if spasm continued on Day 3H and there were no safety/tolerability issues, or 28 days (Day28Maint) if spasms were absent for 24h. If spasms were still present at Day14Maint, radiprodil tapering took place: from L dose to L dose 1 per day for 3 days, from M dose to L dose, 3 days bid, from H dose to M dose, 3 days bid.

Reporting group values	Radiprodil	Total	
Number of subjects	3	3	
Age categorical Units: Subjects			
<=18 years	3	3	
Between 18 and 65 years	0	0	
>=65 years	0	0	
Age continuous			
Note: Due to low number of subjects (n=3) the Mean and SD could not be calculated, thus 999 is a placeholder value.			
Units: months			
arithmetic mean	999		
standard deviation	± 999	-	
Gender categorical Units: Subjects			
Male	2	2	
Female	1	1	

Subject analysis sets

Subject analysis set title	Radiprodil (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

Each subject entered an individualized dose titration schedule. The titration included 3 dose levels of radiprodil: low, medium, high, given bid for 3 days (Day 1L to Day 3L, Day 1M to Day 3M, Day 1H to Day 3H). Titration from L dose to M dose was decided by the investigator: if spasms continued with no safety/tolerability issues, the dose was increased to M, if spasms were absent for 24h, the L dose remained the Maintenance dose.
Dose titration from M to H and/or Maintenance of M dose was decided by the investigator, following the same procedure.
The Maintenance period occurred over a period of 14 Days (Day14Maint) if spasm continued on Day 3H and there were no safety/tolerability issues, or 28 days (Day28Maint) if spasms were absent for 24h. If spasms were still present at Day14Maint, radiprodil tapering took place: from L dose to L dose 1 per day for 3 days, from M dose to L dose, 3 days bid, from H dose to M dose, 3 days bid forming the Safety Set (SS).

Reporting group values	Radiprodil (SS)		
Number of subjects	3		
Age categorical Units: Subjects			
<=18 years	3		
Between 18 and 65 years	0		
>=65 years	0		
Age continuous			
Note: Due to low number of subjects (n=3) the Mean and SD could not be calculated, thus 999 is a placeholder value.			
Units: months			
arithmetic mean	999		
standard deviation	± 999		
Gender categorical Units: Subjects			
Male	2		
Female	1		

End points

End points reporting groups

Reporting group title	Radiprodil

Reporting group description:

Each subject entered an individualized dose titration schedule. The titration included 3 dose levels of radiprodil: low, medium, high, given bid for 3 days (Day 1L to Day 3L, Day 1M to Day 3M, Day 1H to Day 3H). Titration from L dose to M dose was decided by the investigator: if spasms continued with no safety/tolerability issues, the dose was increased to M, if spasms were absent for 24h, the L dose remained the Maintenance dose.
Dose titration from M to H and/or Maintenance of M dose was decided by the investigator, following the same procedure.
The Maintenance period occurred over a period of 14 Days (Day14Maint) if spasm continued on Day 3H and there were no safety/tolerability issues, or 28 days (Day28Maint) if spasms were absent for 24h. If spasms were still present at Day14Maint, radiprodil tapering took place: from L dose to L dose 1 per day for 3 days, from M dose to L dose, 3 days bid, from H dose to M dose, 3 days bid.

Subject analysis set title	Radiprodil (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

Each subject entered an individualized dose titration schedule. The titration included 3 dose levels of radiprodil: low, medium, high, given bid for 3 days (Day 1L to Day 3L, Day 1M to Day 3M, Day 1H to Day 3H). Titration from L dose to M dose was decided by the investigator: if spasms continued with no safety/tolerability issues, the dose was increased to M, if spasms were absent for 24h, the L dose remained the Maintenance dose.
Dose titration from M to H and/or Maintenance of M dose was decided by the investigator, following the same procedure.
The Maintenance period occurred over a period of 14 Days (Day14Maint) if spasm continued on Day 3H and there were no safety/tolerability issues, or 28 days (Day28Maint) if spasms were absent for 24h. If spasms were still present at Day14Maint, radiprodil tapering took place: from L dose to L dose 1 per day for 3 days, from M dose to L dose, 3 days bid, from H dose to M dose, 3 days bid forming the Safety Set (SS).

Primary: Percentage of subjects with clinical response on Day 14 of treatment with the maintenance dose of radiprodil

End point title	Percentage of subjects with clinical response on Day 14 of treatment with the maintenance dose of radiprodil[1]

End point description:

Clinical response was defined as no spasms on Day 14 of treatment with the maintenance dose of radiprodil. This is the primary efficacy variable for Part A.

End point type	Primary

End point timeframe:

Day 14, counting from the first day of radiprodil at maintenance dose

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized as descriptive statistics only.

End point values	Radiprodil (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	3			
Units: percentage of subjects				
number (not applicable)	33.33			

Statistical analyses

No statistical analyses for this end point

Primary: Plasma concentration of radiprodil at Day 1

End point title	Plasma concentration of radiprodil at Day 1[2]

End point description:

This is a primary variable for Part A.
Radiprodil plasma concentration was expressed in nanograms per millilitre (ng/mL).
Concentrations that were Below the lower Limit of Quantification (BLQ) (1ng/mL) were imputed with half of the Lower Limit of Quatification (LLOQ) for the purpose of calculating descriptive statistics.

Note: 9999 is a placeholder value as the radiprodil plasma concentration was not analysed for one subject at Day 1.

End point type	Primary

End point timeframe:

PK samples were collected at baseline, any time from Day -14/Day -1 prior dosing and 3h, 4h, 5h, 12h post 1st dose on Day 1 of radiprodil low dose.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized as descriptive statistics only.

End point values	Radiprodil (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	3			
Units: ng/mL				
number (not applicable)				
Subject 1 - Day 1 - 3h	9999			
Subject 1 - Day 1 - 4h	9999			
Subject 1 - Day 1 - 5h	9999			
Subject 1 - Day 1 - 12h	9999			
Subject 2 - Day 1 - 3h	12.3			
Subject 2 - Day 1 - 4h	10.7			
Subject 2 - Day 1 - 5h	9.18			
Subject 2 - Day 1 - 12h	3.58			
Subject 3 - Day 1 - 3h	13.4			
Subject 3 - Day 1 - 4h	10.3			
Subject 3 - Day 1 - 5h	11.7			
Subject 3 - Day 1 - 12h	4.17			

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the concentration time-Curve (AUC) generated from a population - Pharmacokinetic model

End point title	Area Under the concentration time-Curve (AUC) generated from a population - Pharmacokinetic model[3]

End point description:

This is a primary variable for Part A.
Sampling for pharmacokinetic (PK) analyses was done using the Mitra microsampling technique.

Note: AUC results are from Day 2 low dose, since not all subjects had usable data from Day 1

End point type	Primary

End point timeframe:

PK samples were collected at baseline, any time from Day -14/Day -1 prior dosing and 3h, 4h, 5h, 12h post 1st dose on Day 1 of radiprodil low dose, mid dose and high dose. Samples were taken at same timepoints after 1st radiprodil low dose on Day 2.

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized as descriptive statistics only.

End point values	Radiprodil (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	3			
Units: ng/ml*h				
number (not applicable)				
Subject 1 - Day 2	214			
Subject 2 - Day 2	185			
Subject 3 - Day 2	198			

Statistical analyses

No statistical analyses for this end point

Primary: Maximum plasma concentration (Cmax) generated from a population - Pharmacokinetic model

End point title	Maximum plasma concentration (Cmax) generated from a population - Pharmacokinetic model[4]

End point description:

This is a primary variable for Part A.
Sampling for pharmacokinetic (PK) analyses was done using the Mitra microsampling technique.

Note: Cmax results are from Day 2 low dose, since not all subjects had usable data from Day 1.

End point type	Primary

End point timeframe:

PK samples were collected at baseline, any time from Day -14/Day -1 prior dosing and 3h, 4h, 5h, 12h post 1st dose on Day 1 of radiprodil low dose, mid dose and high dose. Samples were taken at same timepoints after 1st radiprodil low dose on Day 2.

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized as descriptive statistics only.

End point values	Radiprodil (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	3			
Units: ng/ml				
number (not applicable)				
Subject 1	47.1			
Subject 2	44.3			

Subject 3	45.8			

Statistical analyses

No statistical analyses for this end point

Primary: Apparent terminal half-life (t 1/2) generated from a population - Pharmacokinetic model

End point title	Apparent terminal half-life (t 1/2) generated from a population - Pharmacokinetic model[5]

End point description:

This is a primary variable for Part A.
Sampling for pharmacokinetic (PK) analyses was done using the Mitra microsampling technique.

Note: t 1/2 results are from Day 2 low dose, since not all subjects had usable data from Day 1.

End point type	Primary

End point timeframe:

PK samples were collected at baseline, any time from Day -14/Day -1 prior dosing and 3h, 4h, 5h, 12h post 1st dose on Day 1 of radiprodil low dose, mid dose and high dose. Samples were taken at same timepoints after 1st radiprodil low dose on Day 2.

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized as descriptive statistics only.

End point values	Radiprodil (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	3			
Units: Hours				
number (not applicable)				
Subject 1	6.7			
Subject 2	5.3			
Subject 3	5.9			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of subjects with electro-clinical response on Day 14 of treatment with the maintenance dose of radiprodil

End point title	Percentage of subjects with electro-clinical response on Day 14 of treatment with the maintenance dose of radiprodil[6]

End point description:

Electro-clinical response was defined as no spasms and resolution of hypsarrhythmia on Day 14 of treatment with the maintenance dose of radiprodil. This is the primary efficacy variable for Part B.

Note: Due to insufficient enrollment (n=3), the study was terminated during Part A by the Sponsor.

End point type	Primary

End point timeframe:

Day 14, counting from the first day of radiprodil at maintenance dose

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized as descriptive statistics only.

End point values	Radiprodil (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	0[7]			
Units: percentage of subjects				
number (not applicable)				

Notes:

[7] - Due to insufficient enrollment (n=3), the study was terminated during Part A by the Sponsor.

Statistical analyses

No statistical analyses for this end point

Primary: Incidence of Adverse Events (AEs) during the study

End point title	Incidence of Adverse Events (AEs) during the study[8]

End point description:

An AE is any untoward medical occurrence in a subject or trial subject that is administered a drug or biologic (medicinal product) or that is using a medical device. The event does not necessarily have a causal relationship with that treatment or usage. This is a primary variable for all parts.

End point type	Primary

End point timeframe:

From Baseline (Day -1) to the end of the Post-treatment Period (28 days post last dosing)

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized as descriptive statistics only.

End point values	Radiprodil (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	3			
Units: participants	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with electro-clinical response on Day 14 of treatment with the maintenance dose of radiprodil Part A

End point title	Percentage of subjects with electro-clinical response on Day 14 of treatment with the maintenance dose of radiprodil Part A

End point description:

Electro-clinical response was defined as no spasms and resolution of hypsarrhythmia on Day 14 of

treatment with the maintenance dose of radiprodil. This is the secondary efficacy variable for Part A.

End point type	Secondary

End point timeframe:

Day 14, counting from the first day of radiprodil at maintenance dose

End point values	Radiprodil (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	3			
Units: percentage of subjects				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with clinical response on Day 14 of treatment with the maintenance dose of radiprodil Part B

End point title	Percentage of subjects with clinical response on Day 14 of treatment with the maintenance dose of radiprodil Part B

End point description:

Clinical response was defined as no spasms on Day 14 of treatment with the maintenance dose of radiprodil. This is the secondary efficacy variable for Part B.

Note: Due to insufficient enrollment (n=3), the study was terminated during Part A by the Sponsor.

End point type	Secondary

End point timeframe:

Day 14, counting from Day 14 of treatment with the maintenance dose of radiprodil

End point values	Radiprodil (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	0[9]			
Units: percentage of subjects				
number (not applicable)				

Notes:

[9] - Due to insufficient enrollment (n=3), the study was terminated during Part A by the Sponsor.

Statistical analyses

No statistical analyses for this end point

Secondary: Estimates of exposure generated from a population-Pharmacokinetic model

End point title	Estimates of exposure generated from a population-Pharmacokinetic model

End point description:

This is a secondary variable for Part B.

Note: Due to insufficient enrollment (n=3), the study was terminated during Part A by the Sponsor.

End point type	Secondary

End point timeframe:

Pharmacokinetic samples were collected on Day 1 of radiprodil low dose, mid dose and high dose. Additionally, blood samples were taken after 1st dose on Day 2 of radiprodil low dose.

End point values	Radiprodil (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	0[10]			
Units: ng/ml*h				
number (not applicable)				

Notes:

[10] - Due to insufficient enrollment (n=3), the study was terminated during Part A by the Sponsor.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to cessation of spasms

End point title	Time to cessation of spasms

End point description:

Time to cessation of spasms for clinical responders on Day 14 of treatment with the maintenance dose of radiprodol. This is a secondary efficacy variable for parts A and B.

Note 1: Due to insufficient enrollment (n=3), the study was terminated during Part A by the Sponsor.
Note 2: If spasms have not stopped by Day 14 Maint, then the time to cessation of spasms was considered to be right-censored at Day 14 Maint.

End point type	Secondary

End point timeframe:

During the first 14 days of treatment with radiprodil

End point values	Radiprodil (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	3			
Units: days				
number (not applicable)				
Subject 1	3			
Subject 2	0			
Subject 3	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of responders with clinical relapse

End point title	Percentage of responders with clinical relapse

End point description:

The percentage of clinical responders on Day 14 of treatment with the maintenance dose of radiprodil with clinical relapse within 12 months. This is a secondary efficacy variable for parts A and B.

Note: Due to insufficient enrollment (n=3), the study was terminated during Part A by the Sponsor.

End point type	Secondary

End point timeframe:

12 months, counting from Day 14 of treatment with the maintenance dose of radiprodil

End point values	Radiprodil (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	3			
Units: percentage of subjects				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to clinical relapse from the day of spasm cessation

End point title	Time to clinical relapse from the day of spasm cessation

End point description:

This is a secondary efficacy variable for parts A and B.

Note: Due to insufficient enrollment (n=3), the study was terminated during Part A by the Sponsor.

End point type	Secondary

End point timeframe:

From day of spasms cessation up to 42 months of age

End point values	Radiprodil (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	3[11]			
Units: days				
number (not applicable)	0			

Notes:

[11] - No subjects presented clinical relapse.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of electro-clinical responders with electro-clinical relapse

End point title	Percentage of electro-clinical responders with electro-clinical relapse

End point description:

The percentage of electro-clinical responders on Day 14 of treatment with the maintenance dose of radiprodil with electro-clinical relapse within 12 months. This is a secondary efficacy variable for parts A and B.

Note: Due to insufficient enrollment (n=3), the study was terminated during Part A by the Sponsor.

End point type	Secondary

End point timeframe:

12 months, counting from Day 14 of treatment with the maintenance dose of radiprodil

End point values	Radiprodil (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	3			
Units: percentage of subjects				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to electro-clinical relapse from the day of spasm cessation

End point title	Time to electro-clinical relapse from the day of spasm cessation

End point description:

This is a secondary efficacy variable for parts A and B.

Note: Due to insufficient enrollment (n=3), the study was terminated during Part A by the Sponsor.

End point type	Secondary

End point timeframe:

From day of spasms cessation up to 42 months of age

End point values	Radiprodil (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	3			
Units: days				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with extended electro-clinical response

End point title	Percentage of subjects with extended electro-clinical response

End point description:

Extended electro-clinical response is defined as no spasms and resolution of hypsarrhythmia for 28 consecutive days from Day 14 of treatment with the maintenance dose of radiprodil. This is a secondary efficacy variable for parts A and B.

Note: Due to insufficient enrollment (n=3), the study was terminated during Part A by the Sponsor.

End point type	Secondary

End point timeframe:

28 days, counting from Day 14 (inclusive) of treatment with the maintenance dose of radiprodil

End point values	Radiprodil (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	3			
Units: percentage of subjects				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with extended clinical response to each additional treatment cycle on Day 14 of treatment with the maintenance dose of radiprodil

End point title	Percentage of subjects with extended clinical response to each additional treatment cycle on Day 14 of treatment with the maintenance dose of radiprodil

End point description:

Extended clinical response was defined as no spasms for 28 consecutive days from Day 14 of treatment with the maintenance dose of radiprodil. This is a secondary efficacy variable for part C.

Note: Due to insufficient enrollment (n=3), the study was terminated during Part A by the Sponsor.

End point type	Secondary

End point timeframe:

28 days, counting from Day 14 (inclusive) of maintenance dose

End point values	Radiprodil (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	0[12]			
Units: percentage of subjects				
number (not applicable)				

Notes:

[12] - Due to insufficient enrollment (n=3), the study was terminated during Part A by the Sponsor.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment cycles per subject

End point title	Number of treatment cycles per subject

End point description:

This is a secondary variable for Part C.

Note: Due to insufficient enrollment (n=3), the study was terminated during Part A by the Sponsor.

End point type	Secondary

End point timeframe:

During Part C (Day -1 to Day 28 of the Maintenance Period)

End point values	Radiprodil (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	0[13]			
Units: treatment cycles				
number (not applicable)				

Notes:

[13] - Due to insufficient enrollment (n=3), the study was terminated during Part A by the Sponsor.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with electro-clinical response to each additional treatment cycle on Day 14 of treatment with the maintenance dose of radiprodil

End point title	Percentage of subjects with electro-clinical response to each additional treatment cycle on Day 14 of treatment with the maintenance dose of radiprodil

End point description:

Electro-clinical response was defined as no spasms and resolution of hypsarrhythmia on Day 14 of treatment with the maintenance dose of radiprodil. This is a secondary efficacy variable for Part C.

Note: Due to insufficient enrollment (n=3), the study was terminated during Part A by the Sponsor.

End point type	Secondary

End point timeframe:

Day 14, counting from the first day of maintenance dose

End point values	Radiprodil (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	0[14]			
Units: percentage of subjects				
number (not applicable)				

Notes:

[14] - Due to insufficient enrollment (n=3), the study was terminated during Part A by the Sponsor.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to clinical relapse from the first day of no witnessed spasms for each treatment cycle

End point title	Time to clinical relapse from the first day of no witnessed spasms for each treatment cycle

End point description:

This is a secondary efficacy variable for part C.

Note: Due to insufficient enrollment (n=3), the study was terminated during Part A by the Sponsor.

End point type	Secondary

End point timeframe:

From the first day of no witnessed spasms up to 42 months of age

End point values	Radiprodil (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	0[15]			
Units: days				
number (not applicable)				

Notes:

[15] - Due to insufficient enrollment (n=3), the study was terminated during Part A by the Sponsor.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline (Day -1) to the end of the Post-treatment Period (28 days post last dosing).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Radiprodil (SS)

Reporting group description:

Each subject entered an individualized dose titration schedule. The titration included 3 dose levels of radiprodil: low, medium, high, given bid for 3 days (Day 1L to Day 3L, Day 1M to Day 3M, Day 1H to Day 3H). Titration from L dose to M dose was decided by the investigator: if spasms continued with no safety/tolerability issues, the dose was increased to M, if spasms were absent for 24h, the L dose remained the Maintenance dose.
Dose titration from M to H and/or Maintenance of M dose was decided by the investigator, following the same procedure.
The Maintenance period occurred over a period of 14 Days (Day14Maint) if spasm continued on Day 3H and there were no safety/tolerability issues, or 28 days (Day28Maint) if spasms were absent for 24h. If spasms were still present at Day14Maint, radiprodil tapering took place: from L dose to L dose 1 per day for 3 days, from M dose to L dose, 3 days bid, from H dose to M dose, 3 days bid forming the Safety Set (SS).

Serious adverse events	Radiprodil (SS)		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 3 (66.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung disorder			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Radiprodil (SS)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)		
Congenital, familial and genetic disorders			
Cortical dysplasia			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	4		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Lower respiratory tract congestion			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Infections and infestations			
Ear infection			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	3		
Conjunctivitis			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	2		
Influenza			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Rhinitis			

subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 September 2016	Protocol Amendment 1 (16 Sept 2016) was a substantial amendment and included the addition of language to clarify when substantial protocol amendments would be made. In addition, additional dose escalation criteria were added.
24 February 2017	Protocol Amendment 3 (24 Feb 2017) was a substantial amendment and included clarification of the interpretation of the 4-hour video electroencephalogram (EEG) assessment in Part A and Part B of the study. The protocol was amended to make the independent review of the EEGs in Part A optional, and to clarify the requirement for the primary investigator's interpretation. Additionally, perampanel was listed as a specific prohibited medication for this study.
05 January 2018	Protocol Amendment 5 (05 Jan 2018) was a substantial amendment and included amending the inclusion/exclusion criteria so infants could have been enrolled within 6 months of diagnosis in order to increase the ability to recruit with no detrimental effect on the study quality or safety; and removing prior use of non-standard of care (StoC) infantile spasms (IS) treatments as an exclusion criterion but including non-StoC IS treatments as prohibited concomitant medications. The subject referral timeframe for the failure of StoC was modified to allow flexibility, as the previous limit of a maximum of 28 days was considered too restrictive. Additional countries were added for Part A of the study to support recruitment, and additional information was added to clarify a group of subjects in relation to dose titration stopping criteria.
16 March 2018	Protocol Amendment 6 (16 Mar 2018) was a substantial amendment and allowed individual subjects who had shown a benefit from radiprodil treatment in Part A of the study access to additional treatment cycles by adding study Part C. Access to additional treatment cycles was limited to only those subjects who showed evidence of a direct pharmacological relationship with spasm control in Part A; ie, showed a response, followed by a relapse within 5 half-lives (3 days), and then again a response to a second cycle. Additionally, the subjects must have shown good acute tolerability and safety to both treatment cycles in Part A.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

After reviewing the feasibility and projected completion date of the study, UCB has made the decision to stop the study.

Notes: