Clinical trial results:
A PLACEBO-CONTROLLED RANDOMIZED WITHDRAWAL EVALUATION OF THE EFFICACY AND SAFETY OF BACLOFEN ER CAPSULES (GRS) IN SUBJECTS WITH SPASTICITY DUE TO MULTIPLE SCLEROSIS

Summary

EudraCT number	2016-001356-22
Trial protocol	HU
Global end of trial date	25 August 2017

Results information

Result version number	v1 (current)
This version publication date	25 May 2019
First version publication date	25 May 2019

Trial information

Trial identification

Sponsor protocol code	CLR_09_21

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01457352
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sun Pharma Advanced Research Company Limited
Sponsor organisation address	17 B Mahal Industrial Estate, Near Paperbox, off Mahakali Caves, Road, Andheri (East), India, Mumbai, India, 400 093
Public contact	Head- Clinical development, Sun Pharma Advanced Research Company, Ltd., +91 2266455645, clinical.trials@sparcmail.com
Scientific contact	Head- Clinical development, Sun Pharma Advanced Research Company, Ltd., +91 91266455645, clinical.trials@sparcmail.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	25 August 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 August 2017
Global end of trial reached?	Yes
Global end of trial date	25 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives are to compare the continued treatment with Baclofen ER Capsules (GRS) versus down-titration to placebo in subjects stabilized on Baclofen ER Capsules (GRS) with respect to:
-Demonstrating efficacy of Baclofen ER Capsules (GRS) in the treatment of spasticity
-Indirectly demonstrating long-term efficacy over >12 weeks
-Determining the safety profile when administered over >12 weeks

Protection of trial subjects:

Concomitant rehabilitation therapy and/or exercises ongoing at enrolment were maintained at the same level during the study period.

Background therapy:

To the extent possible, changes to the usage of proton pump inhibitors and H2-antagonists was minimized during the course of the study.

Evidence for comparator:

Following conversion to an appropriate dose of Baclofen ER Capsules (GRS), subjects were treated for at least 12 weeks on a fixed dose after which they were randomly assigned to continue on the same dose or placebo.

A 12-week treatment duration is sufficient to provide evidence of long-term benefit in the context of a controlled clinical trial as well as to provide safety information.

Rebound spasticity occurs rapidly when the study drug is stopped abruptly, within 48 hours after stopping drug but not following gradual discontinuation. As the study drug could not be immediately discontinued due to the possibility of hallucinations and seizures upon abrupt withdrawal, subjects were down-titrated in certain increments.

Actual start date of recruitment	01 October 2012
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	Russian Federation: 41
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Hungary: 16
Country: Number of subjects enrolled	United States: 214
Country: Number of subjects enrolled	Ukraine: 19
Worldwide total number of subjects	296
EEA total number of subjects	22

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	272
From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 500 subjects were screened of which, 392 subjects were enrolled in the study.

Pre-assignment

Screening details:

A total of 500 subjects were screened, of which 392 subjects were enrolled in the study.

Pre-assignment period milestones

Number of subjects started	392[1]
Intermediate milestone: Number of subjects	Part 2 of the study: 376
Number of subjects completed	296

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Physician decision: 3
Reason: Number of subjects	Protocol deviation: 8
Reason: Number of subjects	Adverse event, non-fatal: 24
Reason: Number of subjects	Consent withdrawn by subject: 25
Reason: Number of subjects	worsening of condition/Other: 36

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The study was conducted in part 1, 2, and 3:

Part 1: 392 subjects
Part 2: 376 subjects (SPARC0921) (One death occurred in Part 2 of the study. It was not related to treatment)
Part 3: 296 subjects (SPARC0921 or Placebo0921)

Efficacy and safety results are presented for Part 3 of the study per the objectives of the study.

Period 1

Period 1 title	Baseline period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	SPARC0921

Arm description: -

Arm type	Experimental
Investigational medicinal product name	SPARC0921
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

once a day

Arm title	Placebo0921
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo0921
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
once a day

Number of subjects in period 1	SPARC0921	Placebo0921
Started	147	149
Completed	147	146
Not completed	0	3
Consent withdrawn by subject	-	1
incorrect treatment	-	1
Adverse event, non-fatal	-	1

Baseline characteristics

Reporting groups	
Reporting group title	SPARC0921
Reporting group description: -	
Reporting group title	Placebo0921
Reporting group description: -	

Reporting group values	SPARC0921	Placebo0921	Total
Number of subjects	147	149	296
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)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	136	136	272
From 65-84 years	11	13	24
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	48.8	51.0	
standard deviation	± 10.39	± 9.39	-
Gender categorical Units: Subjects			
Female	105	100	205
Male	42	49	91

End points

End points reporting groups	
Reporting group title	SPARC0921
Reporting group description: -	
Reporting group title	Placebo0921
Reporting group description: -	

Primary: Treatment failure rate

End point title	Treatment failure rate
End point description:	
End point type	Primary
End point timeframe: 22 weeks	

End point values	SPARC0921	Placebo0921		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	146		
Units: percentage of subjects				
number (not applicable)	36.1	43.2		

Statistical analyses

Statistical analysis title	Superiority
Comparison groups	Placebo0921 v SPARC0921
Number of subjects included in analysis	293
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2062
Method	Cochran-Mantel-Haenszel

Secondary: Severity of spasticity assessed by Subject global impression of severity scale

End point title	Severity of spasticity assessed by Subject global impression of severity scale
End point description:	
End point type	Secondary
End point timeframe: Week 22	

End point values	SPARC0921	Placebo0921		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	146		
Units: percentage of subjects				
number (not applicable)				
Normal, no spasticity	19.7	10.3		
Borderline spasticity	6.8	13		
Mild spasticity	26.5	20.5		
Moderate spasticity	27.9	33.6		
Marked spasticity	15.0	14.4		
Severe spasticity	4.1	6.2		
Worst spasticity ianigable	0	2.1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Week 22

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Placebo0921
Reporting group description: -	
Reporting group title	SPARC0921

Reporting group description: -

Serious adverse events	Placebo0921	SPARC0921	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 149 (0.00%)	3 / 147 (2.04%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	0 / 149 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 149 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 149 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo0921	SPARC0921	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 149 (31.54%)	52 / 147 (35.37%)	
Investigations			
Blood pressure increased			
subjects affected / exposed	25 / 149 (16.78%)	23 / 147 (15.65%)	
occurrences (all)	7	3	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 149 (2.68%)	6 / 147 (4.08%)	
occurrences (all)	13	20	
Muscle spasticity			
subjects affected / exposed	15 / 149 (10.07%)	14 / 147 (9.52%)	
occurrences (all)	34	30	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 149 (0.00%)	4 / 147 (2.72%)	
occurrences (all)	0	13	
Musculoskeletal and connective tissue disorders			
Muscle spasm			
subjects affected / exposed	4 / 149 (2.68%)	2 / 147 (1.36%)	
occurrences (all)	11	7	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 149 (0.00%)	4 / 147 (2.72%)	
occurrences (all)	7	14	
Urinary tract infection			
subjects affected / exposed	6 / 149 (4.03%)	3 / 147 (2.04%)	
occurrences (all)	13	9	

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