Clinical trial results:
A Double-Blind, Randomized, Placebo-Controlled Study of the Efficacy, Safety/Tolerability, and Pharmacokinetic Profile of UCB0942 in Adults with Highly Drug-Resistant Focal Epilepsy

EudraCT number	2014-003330-12
Trial protocol	DE BE NL HU ES IT
Global end of trial date	18 July 2017

Result version number	v1 (current)
This version publication date	03 August 2018
First version publication date	03 August 2018

Sponsor protocol code	EP0069

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02495844
WHO universal trial number (UTN)	-

Notes:

Sponsor organisation name	UCB Biopharma SPRL
Sponsor organisation address	Allée de la Recherche 60, Brussels, Belgium, B-1070
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Notes:

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:

Analysis stage	Final
Date of interim/final analysis	31 July 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 July 2017
Was the trial ended prematurely?	No

Notes:

Main objective of the trial:

The primary objective was to evaluate the efficacy of UCB0942 administered concomitantly with each subject's current, stable antiepileptic drug (AED) regimen in subjects who had 4 or more focal seizures with or without secondary generalization per week and who failed to achieve seizure control with >= 4 AED regimens of adequate dose and duration.

Protection of trial subjects:

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

Background therapy:

Patients remained on their background antiepileptic medications during the entire study.

Evidence for comparator: -

Actual start date of recruitment	28 August 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Bulgaria: 5
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Spain: 22
Worldwide total number of subjects	55
EEA total number of subjects	55

Notes:

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)	55
From 65 to 84 years	0
85 years and over	0

Recruitment details:

Enrollment started in August 2015 and concluded in July 2017.

Screening details:

Participant Flow refers to the Randomized Set.

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

Are arms mutually exclusive?	Yes
	Placebo/UCB0942

Arm description:

After 2-week in the Inpatient Period, Placebo subjects received the experimental medicine (UCB0942).

Arm type	Placebo
Investigational medicinal product name	UCB0942
Investigational medicinal product code	UCB0942
Other name	Padsevonil
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Tablets in 2 strengths: 100 mg and 200 mg.
100 mg and 200 mg tablets have the same size and appearance.

	UCB0942/UCB0942

Arm description:

Subjects received UCB0942.

Arm type	Experimental
Investigational medicinal product name	UCB0942
Investigational medicinal product code	UCB0942
Other name	Padsevonil
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Tablets in 2 strengths: 100 mg and 200 mg.
100 mg and 200 mg tablets have the same size and appearance.

	Placebo/UCB0942	UCB0942/UCB0942
Started	27	28
Completed	26	24
Not completed	1	4
AE, non-fatal	-	1
Hepatitis Positivity	-	1
Lack of efficacy	1	2

Reporting group title	Placebo/UCB0942
Reporting group description:	
After 2-week in the Inpatient Period, Placebo subjects received the experimental medicine (UCB0942).	
Reporting group title	UCB0942/UCB0942
Reporting group description:	
Subjects received UCB0942.	

	Placebo/UCB0942	UCB0942/UCB0942	Total
Number of subjects	27	28	55
Age categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	27	28	55
>=65 years	0	0	0
Age continuous Units: years			
arithmetic mean	35.2	36.2	
standard deviation	± 8.7	± 11.4	-
Gender categorical Units: Subjects			
Male	13	13	26
Female	14	15	29
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	1	1
White	27	25	52
More than one race	0	2	2
Unknown or Not Reported	0	0	0
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	1	3	4
Not Hispanic or Latino	26	25	51
BMI (kg/m^2) Units: units on a scale			
arithmetic mean	25.66	27.20	
standard deviation	± 4.82	± 4.32	-

Reporting group title

	Statistical Analysis 1
Comparison groups	Placebo/UCB0942 (FAS) v UCB0942/UCB0942 (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0679
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	4.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	19.06

End point title	Median percent change in weekly focal seizure frequency during the 2-week Inpatient Period
End point description: A negative value in median percent change reflects a reduction from Baseline.	
End point type	Secondary
End point timeframe: During the 2-week Inpatient Period	

	Placebo/UCB0942 (FAS)	UCB0942/UCB0942 (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	26		
Units: percentage of change				
median (inter-quartile range (Q1-Q3))				
Median (Inter-Quartile Range)	-12.5 (-57.14 to 41.11)	-53.68 (-84.61 to -22.73)		

No statistical analyses for this end point

End point title	Median percent change in weekly focal seizure frequency during the Outpatient Maintenance Period
End point description: A negative value in median percent change reflects a reduction from Baseline.	
End point type	Secondary

End point timeframe:

During the Outpatient Maintenance Period (8 weeks)

	Placebo/UCB0942 (FAS)	UCB0942/UCB0942 (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	25		
Units: percentage of change				
median (inter-quartile range (Q1-Q3))				
Median (Inter-Quartile Range)	-57.94 (-76.23 to -29.09)	-26.32 (-77.38 to -3.07)		

No statistical analyses for this end point

End point title	Median percent change in weekly focal seizure frequency during the On-UCB0942 Overall Period

End point description:

A negative value in median percent change reflects a reduction from Baseline.

End point type	Secondary

End point timeframe:

During the On-UCB0942 Overall Period (approximately 11 weeks)

	Placebo/UCB0942 (FAS)	UCB0942/UCB0942 (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	27		
Units: percentage of change				
median (inter-quartile range (Q1-Q3))				
Median (Inter-Quartile Range)	-53.85 (-78.01 to -34.48)	-29.87 (-76.39 to -11.36)		

No statistical analyses for this end point

End point title	Seizure-free rate (all seizures) during the 2-week Inpatient Period

End point description:	
Seizure-free rate is reported as the percentage of seizure-free participants during the 2-week Inpatient Period.	
End point type	Secondary
End point timeframe:	
During the 2-week Inpatient Period	

	Placebo/UCB0942 (FAS)	UCB0942/UCB0942 (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	27		
Units: percentage of particpants				
number (not applicable)				
percentage of participants	3.7	7.4		

No statistical analyses for this end point

End point title	Seizure-free rate (all seizures) during the last 4 weeks of the Outpatient Maintenance Period
End point description:	
Seizure-free rate is reported as the percentage of seizure-free participants during the last 4 weeks of the Outpatient Maintenance Period.	
End point type	Secondary
End point timeframe:	
During the last 4 weeks of the Outpatient Maintenance Period	

	Placebo/UCB0942 (FAS)	UCB0942/UCB0942 (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	25		
Units: percentage of participants				
number (not applicable)				
percentage of participants	0	0		

No statistical analyses for this end point

End point title	Seizure-free rate (all seizures) during the On-UCB0942 Overall Period

End point description:

Seizure-free rate is reported as the percentage of seizure-free participants during the On-UCB0942 Overall Period.

End point type	Secondary

End point timeframe:

During the On-UCB0942 Overall Period (approximately 11 weeks)

	Placebo/UCB0942 (FAS)	UCB0942/UCB0942 (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	28		
Units: percentage of participants				
number (not applicable)				
percentage of participants	0	0		

No statistical analyses for this end point

End point title	75 % responder rate during the last 4 weeks of the Outpatient Maintenance Period

End point description:

The 75 % responder rate is defined as the percentage of subjects who achieve a 75 % or greater reduction in focal seizure frequency.

End point type	Secondary

End point timeframe:

During the last 4 weeks of the Outpatient Maintenance Period

	Placebo/UCB0942 (FAS)	UCB0942/UCB0942 (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: percentage of participants				
number (not applicable)				
75% responder rate	33.3	29.2		

No statistical analyses for this end point

End point title	75 % responder rate during the On-UCB0942 Overall Period
End point description:	
The 75 % responder rate is defined as the percentage of subjects who achieve a 75 % or greater reduction in focal seizure frequency.	
End point type	Secondary
End point timeframe:	
During the On-UCB0942 Overall Period (approximately 11 weeks)	

	Placebo/UCB0942 (FAS)	UCB0942/UCB0942 (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	27		
Units: percentage of participants				
number (not applicable)				
75% responder rate	25.9	25.9		

No statistical analyses for this end point

End point title	Percentage of seizure free days (all seizures) during the 2-week Inpatient Period
End point description:	
For the active group, the 2-week Inpatient Period refers to the last 2 weeks of the Inpatient Period, while for the Placebo group, it refers to the first 2 weeks of the Inpatient Period.	
End point type	Secondary
End point timeframe:	
During the 2-week Inpatient Period	

	Placebo/UCB0942 (FAS)	UCB0942/UCB0942 (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	27		
Units: percentage of days				
median (inter-quartile range (Q1-Q3))				
Median (Inter-Quartile Range)	21.43 (7.14 to 57.14)	57.14 (28.57 to 78.57)		

No statistical analyses for this end point

End point title	Percentage of seizure-free days (all seizures) during the Outpatient Maintenance Period

End point description:

End point type	Secondary

End point timeframe:

During the Outpatient Maintenance Period (8 weeks)

	Placebo/UCB0942 (FAS)	UCB0942/UCB0942 (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	26		
Units: percentage of days				
median (inter-quartile range (Q1-Q3))				
Median (Inter-Quartile Range)	51.79 (15.79 to 80.70)	51.35 (29.82 to 69.64)		

No statistical analyses for this end point

End point title	Number of patients reporting at least one Serious Adverse Event (SAE) during the course of the study

End point description:

Number of subjects experiencing at least one serious adverse event (reported by the subject and/or caregiver or observed by the Investigator or inpatient staff).

End point type	Secondary

End point timeframe:

All study duration (approximately 19 to 20 weeks)

	Placebo/UCB0942 (SS)	UCB0942/UCB0942 (SS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	28		
Units: Participants				
participants	0	2		

No statistical analyses for this end point

End point title	Number of subject withdrawals due to Adverse Events (AEs) during the course of the study

End point description:

Number of subjects who withdrew from the study due adverse event (reported by the subject and/or caregiver or observed by the Investigator or inpatient staff).

End point type	Secondary

End point timeframe:

All study duration (approximately 19 to 20 weeks)

	Placebo/UCB0942 (SS)	UCB0942/UCB0942 (SS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	28		
Units: Participants				
participants	0	1		

No statistical analyses for this end point

Timeframe for reporting adverse events:
Adverse Events were collected from Baseline until Safety Follow Up Visit (up to Week 28).
Adverse event reporting additional description:
Baseline Characteristics refer to the Safety Set consisting of all subjects in the Randomized Set who received at least 1 dose of Investigational Medicinal Product (IMP). 2 subjects reported multiple Serious Adverse Events (SAEs).

Assessment type	Non-systematic

Dictionary name	MedDRA
Dictionary version	19.1

Reporting group title	UCB0942/UCB0942
Reporting group description:	
Subjects received UCB0942.	
Reporting group title	Placebo/UCB0942
Reporting group description:	
After 2-week in the Inpatient Period, Placebo subjects received the experimental medicine (UCB0942).	

	UCB0942/UCB0942	Placebo/UCB0942	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 28 (7.14%)	0 / 27 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Judgement impaired			
subjects affected / exposed	1 / 28 (3.57%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	1 / 28 (3.57%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 28 (3.57%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Dysphoria			
subjects affected / exposed	1 / 28 (3.57%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

	UCB0942/UCB0942	Placebo/UCB0942	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 28 (96.43%)	26 / 27 (96.30%)	
Investigations			
Weight increased			
subjects affected / exposed	1 / 28 (3.57%)	3 / 27 (11.11%)	
occurrences (all)	1	3	
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 28 (7.14%)	1 / 27 (3.70%)	
occurrences (all)	3	1	
Nervous system disorders			
Somnolence			
subjects affected / exposed	17 / 28 (60.71%)	12 / 27 (44.44%)	
occurrences (all)	24	16	
Dizziness			
subjects affected / exposed	14 / 28 (50.00%)	12 / 27 (44.44%)	
occurrences (all)	19	51	
Headache			
subjects affected / exposed	10 / 28 (35.71%)	6 / 27 (22.22%)	
occurrences (all)	13	9	
Tremor			
subjects affected / exposed	2 / 28 (7.14%)	3 / 27 (11.11%)	
occurrences (all)	2	3	
Disturbance in attention			
subjects affected / exposed	3 / 28 (10.71%)	1 / 27 (3.70%)	
occurrences (all)	3	2	
Dysarthria			

subjects affected / exposed	3 / 28 (10.71%)	2 / 27 (7.41%)	
occurrences (all)	5	2	
Memory impairment			
subjects affected / exposed	3 / 28 (10.71%)	1 / 27 (3.70%)	
occurrences (all)	6	2	
Nystagmus			
subjects affected / exposed	1 / 28 (3.57%)	3 / 27 (11.11%)	
occurrences (all)	1	3	
Amnesia			
subjects affected / exposed	2 / 28 (7.14%)	1 / 27 (3.70%)	
occurrences (all)	2	1	
Paraesthesia			
subjects affected / exposed	2 / 28 (7.14%)	1 / 27 (3.70%)	
occurrences (all)	2	2	
Simple partial seizures			
subjects affected / exposed	2 / 28 (7.14%)	1 / 27 (3.70%)	
occurrences (all)	5	1	
Seizure			
subjects affected / exposed	3 / 28 (10.71%)	0 / 27 (0.00%)	
occurrences (all)	3	0	
Ataxia			
subjects affected / exposed	2 / 28 (7.14%)	0 / 27 (0.00%)	
occurrences (all)	3	0	
Restless legs syndrome			
subjects affected / exposed	2 / 28 (7.14%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 28 (14.29%)	9 / 27 (33.33%)	
occurrences (all)	23	14	
Gait disturbance			
subjects affected / exposed	3 / 28 (10.71%)	2 / 27 (7.41%)	
occurrences (all)	17	2	
Asthenia			

subjects affected / exposed	2 / 28 (7.14%)	2 / 27 (7.41%)	
occurrences (all)	2	2	
Pyrexia			
subjects affected / exposed	0 / 28 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Eye disorders			
Diplopia			
subjects affected / exposed	2 / 28 (7.14%)	1 / 27 (3.70%)	
occurrences (all)	2	1	
Vision blurred			
subjects affected / exposed	2 / 28 (7.14%)	1 / 27 (3.70%)	
occurrences (all)	5	1	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	3 / 28 (10.71%)	1 / 27 (3.70%)	
occurrences (all)	3	2	
Dry mouth			
subjects affected / exposed	2 / 28 (7.14%)	1 / 27 (3.70%)	
occurrences (all)	2	1	
Nausea			
subjects affected / exposed	2 / 28 (7.14%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
Abdominal pain upper			
subjects affected / exposed	0 / 28 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	4	
Diarrhoea			
subjects affected / exposed	0 / 28 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	3	
Dyspepsia			
subjects affected / exposed	0 / 28 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	4	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	3 / 28 (10.71%)	0 / 27 (0.00%)	
occurrences (all)	4	0	
Psychiatric disorders			

Irritability			
subjects affected / exposed	5 / 28 (17.86%)	4 / 27 (14.81%)	
occurrences (all)	5	5	
Insomnia			
subjects affected / exposed	4 / 28 (14.29%)	0 / 27 (0.00%)	
occurrences (all)	5	0	
Depressed mood			
subjects affected / exposed	2 / 28 (7.14%)	1 / 27 (3.70%)	
occurrences (all)	2	1	
Nervousness			
subjects affected / exposed	1 / 28 (3.57%)	2 / 27 (7.41%)	
occurrences (all)	1	3	
Disorientation			
subjects affected / exposed	2 / 28 (7.14%)	0 / 27 (0.00%)	
		0	

Decreased appetite			
subjects affected / exposed	2 / 28 (7.14%)	3 / 27 (11.11%)	
occurrences (all)	2	3	
Hyponatraemia			
subjects affected / exposed	2 / 28 (7.14%)	2 / 27 (7.41%)	
occurrences (all)	2	2	

Were there any global substantial amendments to the protocol? Yes

16 September 2015	Protocol Amendment 1 (dated 16-Sep-2015) was implemented after the date of first patient first visit (FPFV on 28-Aug-2015). Two subjects were randomized at the time of the amendment. The rationale for this amendment was to add an echocardiogram during dosing in response to a request from the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte). This echocardiogram was added at Day OP22. In addition, the following changes were made: - It was clarified that either urine or serum pregnancy tests could be used for all visits. - It was pointed out that the decision to continue in the OLE study (EP0073) occurred at Day OP43. - Clarification on the procedure for dose reduction in cases of poor tolerability of UCB0942 400 mg bid (ie, reduction to UCB0942 200 mg bid and in some cases to UCB0942 100 mg bid). - The withdrawal criteria for elevated transaminases were reworded as the previous description was not clear.
19 November 2015	Protocol Amendment 2 (dated 19-Nov-2015) was implemented after 22 subjects were randomized. The rationale for this amendment was to make the video monitoring language in the protocol more flexible so that sites/Investigators could perform this according to their usual practice. This new language also allowed video- electroencephalogram (EEG) monitoring as some sites did not perform video-only monitoring. A second change was the wording of the drug misuse exclusion criterion. As is customary in most UCB protocols, exclusion for drug misuse is only applicable if the Investigator deems that study participation is either a risk to the subject or that the drug misuse could confound the outcomes measured in the study. The wording of this exclusion criterion was changed to match that of other UCB studies.
13 May 2016	Protocol Amendment 3 (dated-13 May-2016) was implemented after 35 subjects were randomized. The rationale for this amendment was to add and describe an optional interim analysis for purposes of planning and designing of future studies. Other reasons for the amendment included the following: - To add an exploratory objective, variable and associated assessment (Diary Addendum). Note that this was already part of the study, but not clearly described in the protocol. - To clarify procedures for dosing when there was intolerance to IMP during the Inpatient Period. - To allow and specify flexibility in dosing during the Outpatient Maintenance Period. - To further specify which subjects required an echocardiogram at 6 months after the last dose of UCB0942. - To expand the range of body mass index (BMI) allowed for inclusion in the study. - To revise procedures for assessment of suicidality using the Columbia-Suicide Severity Rating Scale (C-SSRS) (specifically, the C-SSRS withdrawal criterion) in line with revision to UCB SOP, which became effective on 01-Apr-2016. - To update the protocol information pertaining to potential drug-induced liver injury (PDILI) (exclusion criteria, withdrawal criteria, adverse events (AEs) of special interest, and assessments) based on new standard language which was being applied across all protocols at UCB. Note that these additions do not reflect a change in the known safety of the compound.

10 October 2016	Protocol Amendment 4 (dated 10-Oct-2016) was implemented after all subjects were randomized. The rationale for this amendment was to describe a tiered approach to database lock and unblinding. Other changes included: - Correction of an inconsistency between the Summary section and the Study Design section pertaining to allowable dose changes - Clarification of the reporting period for AEs - Specification that the Baseline version of the Seizure Severity Questionnaire (SSQ) was to be used in all instances where it was administered - Correction of the number of questions in the SSQ from 11 to 10 - Correction of several cross references - Other minor administrative changes

Notes:

Were there any global interruptions to the trial? No

None reported