Clinical trial results:
An Open-Label, Exploratory, Multicenter, Extension Study to Evaluate the Long-Term Safety, Tolerability, Pharmacokinetics and Efficacy of UCB5857 in Subjects with Activated Phosphoinositide 3 Kinase (PI3K) Delta Syndrome (APDS)

Summary

EudraCT number	2015-005541-30
Trial protocol	DE IT ES FR
Global end of trial date	13 December 2018

Results information

Result version number	v1 (current)
This version publication date	14 July 2019
First version publication date	14 July 2019

Trial information

Trial identification

Sponsor protocol code	APD003

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	UCB BioPharma SPRL
Sponsor organisation address	Allée de la Recherche 60, Brussels, Belgium, B-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	23 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 December 2018
Global end of trial reached?	Yes
Global end of trial date	13 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term safety and tolerability of UCB5857 in participants with activated PI3K delta syndrome (APDS).

Protection of trial subjects:

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

Background therapy:

Background therapy as permitted in the protocol.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	11 January 2017
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	France: 1
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Italy: 2
Worldwide total number of subjects	4
EEA total number of subjects	4

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)	3
Adults (18-64 years)	1
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study started to enroll participants in January 2017 and concluded in December 2018.

Pre-assignment

Screening details:

Participant Flow refers to the Safety Set (SS), which consisted of all participants in the Enrolled Set (ES) who received at least 1 dose of IMP in APD003.

Period 1

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

Arms

Arm title	UCB5857

Arm description:

Participants were administered the investigational medicinal product (IMP) once daily, in the morning, initially in the same dosage that was given last in the APD001 study. Dose adjustments could have occurred based on the opinion of the Investigator and confirmed by the recommendation of the Safety Monitoring Committee (SMC).

Arm type	Experimental
Investigational medicinal product name	Seletalisib
Investigational medicinal product code	UCB5857
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Capsules of UCB5857 5 mg, 15 mg or 30 mg, administered daily, by oral intake.

Number of subjects in period 1	UCB5857
Started	4
Completed	3
Not completed	1
Consent withdrawn by subject	1

Baseline characteristics

Reporting groups	
Reporting group title	UCB5857

Reporting group description:

Participants were administered the investigational medicinal product (IMP) once daily, in the morning, initially in the same dosage that was given last in the APD001 study. Dose adjustments could have occurred based on the opinion of the Investigator and confirmed by the recommendation of the Safety Monitoring Committee (SMC).

Reporting group values	UCB5857	Total	
Number of subjects	4	4	
Age categorical Units: Subjects			
<=18 years	3	3	
Between 18 and 65 years	1	1	
>=65 years	0	0	
Age continuous Units: years			
arithmetic mean	15.8		
standard deviation	± 5.7	-	
Gender categorical Units: Subjects			
Male	2	2	
Female	2	2	

Subject analysis sets	
Subject analysis set title	UCB5857 (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants were administered the IMP once daily, in the morning, initially in the same dosage that was given last in the APD001 study. Dose adjustments could have occurred based on the opinion of the Investigator and confirmed by the recommendation of the SMC, forming the Safety Set.

Reporting group values	UCB5857 (SS)		
Number of subjects	4		
Age categorical Units: Subjects			
<=18 years	3		
Between 18 and 65 years	1		
>=65 years	0		
Age continuous Units: years			
arithmetic mean	15.8		
standard deviation	± 5.7		
Gender categorical Units: Subjects			
Male	2		
Female	2		

End points

End points reporting groups

Reporting group title	UCB5857

Reporting group description:

Participants were administered the investigational medicinal product (IMP) once daily, in the morning, initially in the same dosage that was given last in the APD001 study. Dose adjustments could have occurred based on the opinion of the Investigator and confirmed by the recommendation of the Safety Monitoring Committee (SMC).

Subject analysis set title	UCB5857 (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants were administered the IMP once daily, in the morning, initially in the same dosage that was given last in the APD001 study. Dose adjustments could have occurred based on the opinion of the Investigator and confirmed by the recommendation of the SMC, forming the Safety Set.

Primary: The total number of participants experiencing at least one Treatment Emergent Adverse Event during the study

End point title	The total number of participants experiencing at least one Treatment Emergent Adverse Event during the study[1]

End point description:

Treatment-emergent Adverse Events (TEAEs) were defined as those events which started on or after the date of first dose of APD003 IMP, or events in which severity worsened on or after the date of first dose of APD003 study medication.

End point type	Primary

End point timeframe:

From Baseline, until the study end

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	UCB5857 (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: participants	4			

Statistical analyses

No statistical analyses for this end point

Primary: The total number of participants experiencing at least one Serious Adverse Event during the study

End point title	The total number of participants experiencing at least one Serious Adverse Event during the study[2]

End point description:

A Serious Adverse Event (SAE) must have met 1 or more of the following criteria:
•Death,
•Life threatening,
•Significant or persistent disability/incapacity,
•Congenital anomaly/birth defect (including that occurring in a fetus),
•Important medical event that, based upon appropriate medical judgment, may have jeopardized the

study participant and may have required medical or surgical intervention to prevent 1 of the other outcomes listed in the definition of serious,
•Initial inpatient hospitalization or prolongation of hospitalization.

End point type	Primary

End point timeframe:

From Baseline, until the study end

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	UCB5857 (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: participants	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentration of UCB5857

End point title	Plasma concentration of UCB5857

End point description:

Plasma concentrations of UCB5857 were measured using a validated high-performance liquid chromatography method with tandem mass spectrometry.

Note 1: Due to technical reasons, BLQ (below limit of quantification) could not be entered in the system, thus a placeholder value “999” was used instead.

End point type	Secondary

End point timeframe:

From Baseline, until the Final Treatment Period Visit

End point values	UCB5857 (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: ng/mL				
number (not applicable)				
Subject 1 - Day 1	999			
Subject 1 - Week 12	364			
Subject 1 - Week 24	352			
Subject 1 - Final Treatment Period Visit	318			
Subject 2 - Day 1	6.43			
Subject 2 - Week 12	245			
Subject 2 - Week 24	533			
Subject 2 - Week 36	403			
Subject 2 - Week 48	231			
Subject 2 - Week 60	360			

Subject 2 - Week 72	306			
Subject 2 - Week 84	391			
Subject 2 - Final Treatment Period Visit	282			
Subject 3 - Day 1	999			
Subject 3 - Week 12	610			
Subject 3 - Week 24	485			
Subject 3 - Week 36	298			
Subject 3 - Week 48	434			
Subject 3 - Week 60	503			
Subject 3 - Week 72	756			
Subject 3 - Week 84	307			
Subject 3 - Final Treatment Period Visit	587			
Subject 4 - Day 1	1.26			
Subject 4 - Week 12	1480			
Subject 4 - Week 24	1230			
Subject 4 - Week 36	1210			
Subject 4 - Week 48	999			
Subject 4 - Week 60	504			
Subject 4 - Week 72	449			
Subject 4 - Week 84	541			
Subject 4 - Final Treatment Period Visit	677			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From Baseline, until the study end	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1
Reporting groups	
Reporting group title	UCB5857 (SS)
Reporting group description:	
Participants were administered the IMP once daily, in the morning, initially in the same dosage that was given last in the APD001 study. Dose adjustments could have occurred based on the opinion of the Investigator and confirmed by the recommendation of the SMC, forming the Safety Set.	

Serious adverse events	UCB5857 (SS)		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 4 (25.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Gastrointestinal disorders			
Stomatitis			
subjects affected / exposed	1 / 4 (25.00%)		
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	UCB5857 (SS)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Vascular disorders			
Haematoma			

subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	5		
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Asthenia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Influenza like illness			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Vessel puncture site haematoma			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Tonsillar hypertrophy			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	3		
Catarrh			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Dysphonia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Snoring			

subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	 1 / 4 (25.00%) 1		
Investigations C-reactive protein increased subjects affected / exposed occurrences (all) Haemoglobin decreased subjects affected / exposed occurrences (all) Weight decreased subjects affected / exposed occurrences (all)	 1 / 4 (25.00%) 1 1 / 4 (25.00%) 1 1 / 4 (25.00%) 1		
Injury, poisoning and procedural complications Ligament sprain subjects affected / exposed occurrences (all)	 1 / 4 (25.00%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Aphonia subjects affected / exposed occurrences (all)	 2 / 4 (50.00%) 8 1 / 4 (25.00%) 1		
Blood and lymphatic system disorders Lymphadenopathy subjects affected / exposed occurrences (all)	 1 / 4 (25.00%) 1		
Ear and labyrinth disorders Deafness subjects affected / exposed occurrences (all) Ear pain	 1 / 4 (25.00%) 2 		

subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Otorrhoea			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Eye disorders			
Lacrimation increased			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Aphthous ulcer			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	8		
Vomiting			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	3		
Coating in mouth			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Eczema			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Night sweats			

subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	2		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 4 (75.00%)		
occurrences (all)	8		
Sinusitis			
subjects affected / exposed	3 / 4 (75.00%)		
occurrences (all)	7		
Rhinitis			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	3		
Conjunctivitis			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Otitis media acute			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Ear infection			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Upper respiratory tract infection			

subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 February 2016	Global Protocol Amendment 1, dated 24 Feb 2016, provided the following key changes: •Prohibited the co-administration of known P-glycoprotein (PGP) inhibitors with UCB5857. Since UCB5857 was likely (although not yet confirmed) to be a substrate of PGP, the possibility existed that UCB5857 might be susceptible to pharmacokinetic (PK) interactions as victim drug when coadministered with a PGP inhibitor. •The local Protocol Amendment 0.1, for Germany only, was included. The local amendment restricted the maximum number of years in the study to 5 years per study participant, since insurance coverage in Germany was limited to 5 years per participant or 8 years for the duration of the complete APD003 study.
22 September 2016	Global Protocol Amendment 2, an urgent safety measure amendment dated 22 Sep 2016, provided the following key changes: •Included updated and new potential drug-induced liver injury (PDILI) exclusion criteria, withdrawal criteria, and guidance for the management of such cases. Cases of elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) had been observed in 3 participants receiving UCB5857 in ongoing studies (2 participants in SS0004 and 1 participant in APD001). All available blinded clinical data for these cases were medically assessed and, in addition, all available data from other participants in the ongoing studies were reviewed to identify any other potential cases of interest but no other clinically relevant elevations in aminotransferases or other hepatobiliary laboratory values were noted. UCB considered that from the currently available information, there was a possible causal association of UCB5857 with increased aminotransferases. Consequently, additional risk minimization and pharmacovigilance measures were implemented in the protocol in order to safeguard participants against any possible liver injury caused by UCB5857. •Provided further guidance on suspected transmission of an infectious agent via a medicinal product in alignment with UCB's updated procedures.
05 April 2017	Global Protocol Amendment 3, a substantial amendment dated 05 Apr 2017, provided the following key changes: •Modified the restriction regarding P-glycoprotein (PGP) inhibitors and removed the table of PGP inhibitors from the protocol based on newly available nonclinical data. •Added procedures for assessment and management of tuberculosis (TB) in order to comply with the UCB policy applied to all UCB-sponsored studies (excluding noninterventional studies) that include participants with immunological diseases, who are at increased risk of TB infection either associated with the investigational drug, underlying disease, concomitant treatments, or other medical or sociological factors. •Aligned local versions of the protocol into a single global version. •Added guidance on adverse events of interest (AEOI), management of AEOIs, and immediate reporting of Adverse Events (AEs).

22 January 2018	Global Protocol Amendment 4, a substantial amendment dated 22 Jan 2018, provided the following key changes: •Changed the duration for safety follow up. UCB5857 has a relative short half-life of 18 hours and therefore 30 days was considered long enough to ascertain any potential late safety events and the 90-day follow-up call was removed from the schedule of assessments. •Adjusted the frequency of an imaging technique scan (high-resolution computer tomography [HRCT] only) for the assessment of global lung disease and hepatosplenomegaly, due to the high level of exposure to radiation. Based on the date of the amendment, 4 participants were enrolled at the time of the amendment. This protocol amendment was not submitted in France because at the time of submission, the single participant enrolled in APD001 in France was withdrawn.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported