Clinical trial results:
An Open-Label Exploratory Study of UCB5857 in Subjects with Activated Phosphoinositide 3 Kinase (PI3K) Delta Syndrome (APDS)

Summary

EudraCT number	2015-002900-10
Trial protocol	IT DE ES FR
Global end of trial date	23 January 2018

Results information

Result version number	v1 (current)
This version publication date	05 August 2018
First version publication date	05 August 2018

Trial information

Trial identification

Sponsor protocol code	APD001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	UCB Celltech, UK Registered Branch of UCB Pharma SA
Sponsor organisation address	208 Bath Road, Slough, United Kingdom, SL1 3WE
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	20 February 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of UCB5857 in subjects with Activated PI3K delta syndrome (APDS).

Protection of trial subjects:

During the conduct of the study all subjects were closely monitored, including a Safety Monitoring Committee review of ongoing safety and efficacy data.

Background therapy:

Background therapy as permitted in the protocol.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	23 May 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Spain: 2
Worldwide total number of subjects	7
EEA total number of subjects	7

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)	6
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 subjects in May 2016 and concluded in Jan 2018.

Pre-assignment

Screening details:

The study included 8 subjects in the Enrollment Set. 1 subject represented a screen failure due to being underweight, leaving 7 subjects that formed the Safety Set (SS) and the Pharmacokinetic Set (PKS).

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	UCB5857

Arm description:

UCB5857 capsules were supplied at doses of 5 mg, 15 mg, and 30 mg, depending on body weight, to allow a flexible dosing regimen by combining the capsule strengths. The study investigational medicinal product (IMP) was administered orally, once per day, in the morning, during a 12-week Treatment Period.

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 for 12 weeks.

Number of subjects in period 1	UCB5857
Started	7
Completed	5
Not completed	2
Adverse event, non-fatal	2

Baseline characteristics

Reporting groups	
Reporting group title	UCB5857
Reporting group description:	
UCB5857 capsules were supplied at doses of 5 mg, 15 mg, and 30 mg, depending on body weight, to allow a flexible dosing regimen by combining the capsule strengths. The study investigational medicinal product (IMP) was administered orally, once per day, in the morning, during a 12-week Treatment Period.	

Reporting group values	UCB5857	Total	
Number of subjects	7	7	
Age categorical Units: Subjects			
<=18 years	6	6	
Between 18 and 65 years	1	1	
>=65 years	0	0	
Age continuous Units: years			
arithmetic mean	15.7		
standard deviation	± 4.1	-	
Gender categorical Units: Subjects			
Male	5	5	
Female	2	2	

End points

End points reporting groups

Reporting group title	UCB5857

Reporting group description:

UCB5857 capsules were supplied at doses of 5 mg, 15 mg, and 30 mg, depending on body weight, to allow a flexible dosing regimen by combining the capsule strengths. The study investigational medicinal product (IMP) was administered orally, once per day, in the morning, during a 12-week Treatment Period.

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

Subject analysis set description:

At least one dose of UCB5857 capsules was administered orally to all subjects forming the Safety Set (SS), once per day during a 12-week Treatment Period, supplied at doses of 5 mg, 15 mg, and 30 mg, depending on body weight, to allow a flexible dosing regimen by combining the capsule strengths.

Subject analysis set title	UCB5857 (PKS)
Subject analysis set type	Full analysis

Subject analysis set description:

At least one dose of UCB5857 capsules was administered orally to all subjects forming the Pharmacokinetic Set (PKS), once per day during a 12-week Treatment Period, supplied at doses of 5 mg, 15 mg, and 30 mg, depending on body weight, to allow a flexible dosing regimen by combining the capsule strengths. Subjects had at least 1 measurable plasma concentration available of the UCB5857 investigational medicinal product.

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

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

End point description:

Treatment-Emergent Adverse Events (TEAEs) are any untoward medical incidence in a subject during administered study treatment, whether or not these events are related to study treatment.

End point type	Primary

End point timeframe:

Baseline to week 16

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	7			
Units: Subjects				
Subjects	7			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

A Serious Adverse Event (SAE) is any untoward medical incidence that occurs at any dose.

End point type	Primary

End point timeframe:

Baseline to week 16

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	7			
Units: Subjects				
Subjects	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of UCB5857 at Baseline Visit, 15-30 minutes post-dose

End point title	Plasma Concentration of UCB5857 at Baseline Visit, 15-30 minutes post-dose

End point description:

UCB5857 concentration in plasma was expressed in nanograms per milliliter (ng/mL) as measured by a validated high-performance liquid chromatography method with tandem mass spectrometry (HPLC-MS). Summary statistics (except for n, Min, and Max) were only performed if at least 2/3 of the concentrations were quantified at the respective time-point.

*Note: -9999 is a placeholder value that replaced missing or bellow limit of quantification values

End point type	Secondary

End point timeframe:

Baseline Visit, 15-30 minutes post-dose

End point values	UCB5857 (PKS)			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: ng/mL				
median (full range (min-max))				
15-30 minutes	-9999 (-9999 to 127)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of UCB5857 at Baseline Visit, 2-4 hours post-dose

End point title	Plasma Concentration of UCB5857 at Baseline Visit, 2-4 hours post-dose

End point description:

UCB5857 concentration in plasma was expressed in nanograms per milliliter (ng/mL) as measured by a validated high-performance liquid chromatography method with tandem mass spectrometry (HPLC-MS). Summary statistics (except for n, Min, and Max) were only performed if at least 2/3 of the concentrations were quantified at the respective time-point.

End point type	Secondary

End point timeframe:

Baseline Visit, 2-4 hours post-dose

End point values	UCB5857 (PKS)			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: ng/mL				
median (full range (min-max))				
2-4 hours	988 (256 to 1650)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of UCB5857 at Baseline Visit, 24 hours post-dose

End point title	Plasma Concentration of UCB5857 at Baseline Visit, 24 hours post-dose

End point description:

UCB5857 concentration in plasma was expressed in nanograms per milliliter (ng/mL) as measured by a validated high-performance liquid chromatography method with tandem mass spectrometry (HPLC-MS). Summary statistics (except for n, Min, and Max) were only performed if at least 2/3 of the concentrations were quantified at the respective time-point.

End point type	Secondary

End point timeframe:

Baseline Visit, 24 hours post-dose

End point values	UCB5857 (PKS)			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: ng/mL				
median (full range (min-max))				
24 hours	271 (75.7 to 735)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of UCB5857 at Week 2, pre-dose

End point title	Plasma Concentration of UCB5857 at Week 2, pre-dose

End point description:

UCB5857 concentration in plasma was expressed in nanograms per milliliter (ng/mL) as measured by a validated high-performance liquid chromatography method with tandem mass spectrometry (HPLC-MS). Summary statistics (except for n, Min, and Max) were only performed if at least 2/3 of the concentrations were quantified at the respective time-point.

End point type	Secondary

End point timeframe:

Week 2, pre-dose

End point values	UCB5857 (PKS)			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: ng/mL				
median (full range (min-max))				
pre-dose	435 (128 to 814)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of UCB5857 at Week 2, 2-4 hours post-dose

End point title	Plasma Concentration of UCB5857 at Week 2, 2-4 hours post-dose

End point description:

UCB5857 concentration in plasma was expressed in nanograms per milliliter (ng/mL) as measured by a validated high-performance liquid chromatography method with tandem mass spectrometry (HPLC-MS). Summary statistics (except for n, Min, and Max) were only performed if at least 2/3 of the concentrations were quantified at the respective time-point.

End point type	Secondary

End point timeframe:

Week 2, 2-4 hours post-dose

End point values	UCB5857 (PKS)			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: ng/mL				
median (full range (min-max))				
2-4 hours	1170 (781 to 1500)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of UCB5857 at Week 6, pre-dose

End point title	Plasma Concentration of UCB5857 at Week 6, pre-dose

End point description:

UCB5857 concentration in plasma was expressed in nanograms per milliliter (ng/mL) as measured by a validated high-performance liquid chromatography method with tandem mass spectrometry (HPLC-MS). Summary statistics (except for n, Min, and Max) were only performed if at least 2/3 of the concentrations were quantified at the respective time-point.

End point type	Secondary

End point timeframe:

Week 6, pre-dose

End point values	UCB5857 (PKS)			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: ng/mL				
median (full range (min-max))				
pre-dose	532 (307 to 1140)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of UCB5857 at Week 6, 2-4 hours post-dose

End point title	Plasma Concentration of UCB5857 at Week 6, 2-4 hours post-dose

End point description:

UCB5857 concentration in plasma was expressed in nanograms per milliliter (ng/mL) as measured by a validated high-performance liquid chromatography method with tandem mass spectrometry (HPLC-MS). Summary statistics (except for n, Min, and Max) were only performed if at least 2/3 of the concentrations were quantified at the respective time-point.

End point type	Secondary

End point timeframe:

Week 6, 2-4 hours post-dose

End point values	UCB5857 (PKS)			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: ng/mL				
median (full range (min-max))				
2-4 hours	1111 (640 to 1910)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of UCB5857 at Week 12, pre-dose

End point title	Plasma Concentration of UCB5857 at Week 12, pre-dose

End point description:

UCB5857 concentration in plasma was expressed in nanograms per milliliter (ng/mL) as measured by a validated high-performance liquid chromatography method with tandem mass spectrometry (HPLC-MS). Summary statistics (except for n, Min, and Max) were only performed if at least 2/3 of the concentrations were quantified at the respective time-point.

End point type	Secondary

End point timeframe:

Week 12, pre-dose

End point values	UCB5857 (PKS)			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: ng/mL				
median (full range (min-max))				
pre-dose	345 (309 to 1240)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of UCB5857 at Week 12, 15-30 minutes post-dose

End point title	Plasma Concentration of UCB5857 at Week 12, 15-30 minutes post-dose

End point description:

UCB5857 concentration in plasma was expressed in nanograms per milliliter (ng/mL) as measured by a validated high-performance liquid chromatography method with tandem mass spectrometry (HPLC-MS). Summary statistics (except for n, Min, and Max) were only performed if at least 2/3 of the concentrations were quantified at the respective time-point.

End point type	Secondary

End point timeframe:

Week 12, 15-30 minutes post-dose

End point values	UCB5857 (PKS)			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: ng/mL				
median (full range (min-max))				
15-30 minutes	460 (339 to 1200)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of UCB5857 at Week 12, 2-4 hours post-dose

End point title	Plasma Concentration of UCB5857 at Week 12, 2-4 hours post-dose

End point description:

UCB5857 concentration in plasma was expressed in nanograms per milliliter (ng/mL) as measured by a validated high-performance liquid chromatography method with tandem mass spectrometry (HPLC-MS). Summary statistics (except for n, Min, and Max) were only performed if at least 2/3 of the concentrations were quantified at the respective time-point.

End point type	Secondary

End point timeframe:

Week 12, 2-4 hours post-dose

End point values	UCB5857 (PKS)			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: ng/mL				
median (full range (min-max))				
2-4 hours	892 (683 to 1740)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of UCB5857 at Week 12, 24 hours post-dose

End point title	Plasma Concentration of UCB5857 at Week 12, 24 hours post-dose

End point description:

UCB5857 concentration in plasma was expressed in nanograms per milliliter (ng/mL) as measured by a validated high-performance liquid chromatography method with tandem mass spectrometry (HPLC-MS). Summary statistics (except for n, Min, and Max) were only performed if at least 2/3 of the concentrations were quantified at the respective time-point.

*Note: 999 is a placeholder value, as mean concentration was not calculated.

End point type	Secondary

End point timeframe:

Week 12, 24 hours post-dose

End point values	UCB5857 (PKS)			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: ng/mL				
median (full range (min-max))				
24 hours	999 (671 to 2090)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline to week 24	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	UCB5857 (SS)

Reporting group description:

At least one dose of UCB5857 capsules was administered orally to all subjects forming the Safety Set (SS), once per day during a 12-week Treatment Period, supplied at doses of 5 mg, 15 mg, and 30 mg, depending on body weight, to allow a flexible dosing regimen by combining the capsule strengths.

Serious adverse events	UCB5857 (SS)		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 7 (42.86%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Surgical and medical procedures			
Hospitalisation			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	1 / 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	7 / 7 (100.00%)		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	7		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Vessel puncture site haematoma			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Catarrh			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	2		
Dyspnoea			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Tonsillar hypertrophy			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Psychiatric disorders			
Restlessness			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Investigations			

Hepatic enzyme increased subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 2		
Weight increased subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Injury, poisoning and procedural complications Foot fracture subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 3		
Aphonia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Dizziness subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 2		
Splenomegaly subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Ear and labyrinth disorders Deafness subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Ear discomfort subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Gastrointestinal disorders			

Aphthous ulcer subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Stomatitis subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 3 1 / 7 (14.29%) 2 1 / 7 (14.29%) 1 1 / 7 (14.29%) 1		
Hepatobiliary disorders Hypertransaminasaemia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Arthritis subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) Tendon disorder subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1 1 / 7 (14.29%) 1 1 / 7 (14.29%) 1 1 / 7 (14.29%) 1		
Infections and infestations Nasopharyngitis			

subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	3		
Rhinitis			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Sinusitis			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Abscess			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Conjunctivitis			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	2		
Ear infection			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Epstein-Barr virus infection			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Gastroenteritis viral			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Respiratory tract infection			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Tonsillitis			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		

Increased appetite subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 March 2016	Protocol Amendment 2 was implemented to prohibit the co-administration of known P-glycoprotein (PGP) inhibitors with UCB5857. Since UCB5857 is likely (although not yet confirmed) to be a substrate of PGP, the possibility exists that UCB5857 might be susceptible to Pharmacokinetic (PK) interactions as a victim drug when co administered with a PGP inhibitor. In addition, subjects were required to remain at the site for 24 hours after their first dose of Investigational Medicinal Product (IMP) at Baseline (Visit 2). Subjects were observed as a safety precaution, and had vital signs and electrocardiogram (ECG) recordings taken, in addition to obtaining 24 hour blood samples for PK and phospho-S6 ribosomal protein (p-S6) measurements.
05 April 2017	Protocol Amendment 4, provided the following key changes: •Modified the restriction regarding 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 subjects with immunological diseases, who are at increased risk of TB infection either associated with the IMP, 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 AEOI, and immediate reporting of Adverse Events (AEs)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported