Clinical trial results:
A Non-Randomised, Open Label, Pilot Trial of Sirolimus Therapy for Segmental Overgrowth Due to PIK3CA Related Overgrowth

Summary

EudraCT number	2014-000484-41
Trial protocol	GB
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	18 November 2017
First version publication date	18 November 2017

Trial information

Trial identification

Sponsor protocol code	PROMISE

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Cambridge University Hospital
Sponsor organisation address	Hills Road, Cambridge, United Kingdom,
Public contact	Carrie Bayliss, CCTU, 0044 01223348158, cctu@addenbrookes.nhs.uk
Scientific contact	Carrie Bayliss, CCTU, 0044 01223348158, cctu@addenbrookes.nhs.uk

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	Interim
Date of interim/final analysis	10 October 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 May 2017
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate if sirolimus is effective at reducing overgrowth in PIK3CA-related overgrowth, and to quantify its efficacy.

To measure the effect size of sirolimus therapy in reducing pathological overgrowth in PIK3CA related overgrowth to enable statistical power calculations for a future randomised controlled trial (RCT)

Protection of trial subjects:

Prior to commencement and during the trial all subjects underwent safety assessments to ensure protection from harm. Subjects were assessed 6 months prior to the start of the trial at baseline and throughout the trial at every subject trial visit. Physician review and physical examination were performed along with safety blood tests, vitals taken and AE review, DXA scan, urine analysis as well as pregnancy test. Initial safety questionnaires were also undertaken prior to MRIs scans to exclude the presence of a pacemaker, defibrillator, aneurysm clips, orbital metal or recent surgical insertion of metal in the prior 6 weeks. Lose dosing of Sirolimus and levels monitored throughout the trial and dose adjustment were made where necessary along with monitoring any adverse effects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2015
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	United Kingdom: 11
Worldwide total number of subjects	11
EEA total number of subjects	11

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)	2
Adolescents (12-17 years)	4

Adults (18-64 years)	5
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

11 subjects were recruited from within the UK, with the first subject recruited February 16th 2016 and the last subject recruited October 21st 2016.

Pre-assignment

Screening details:

Subjects were identified with the inclusion criteria of having a confirmed PIK3CA mutation with measurable progressive growth between the ages of 3-65yrs and exclusion criteria of pregnancy and breastfeeding. All subjects who were enrolled in the trial had dxa scans and bloods

Period 1

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

Arms

Arm title	Sirolimus

Arm description:

Subjects who administered sirolimus drug.

Arm type	Experimental
Investigational medicinal product name	Sirolimus
Investigational medicinal product code	
Other name	Rapamune
Pharmaceutical forms	Coated tablet, Concentrate for oral solution
Routes of administration	Oral use

Dosage and administration details:

Sirolimus was administered in tablet form for adults - 1mg daily

Sirolimus solution was administered by children (17 years old and under) - 0.5 mg bd twice daily

For participants aged 17 years old and under, the upper dosing limit was 1.5 mg total daily dose, and tablet therapy was administered where possible.

Participants were advised to take sirolimus in the morning each day before breakfast and for children on twice daily dosing, again before the evening meal each day.

Number of subjects in period 1	Sirolimus
Started	11
Trial Initiation	11
Completed	11

Baseline characteristics

Reporting groups

Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	11	11	
Age categorical			
Subjects enrolled were between 3 years old and 65 years old			
Units: Subjects			
Children (2-11 years)	2	2	
Adolescents (12-17 years)	4	4	
Adults (18-64 years)	5	5	
Gender categorical Units: Subjects			
Female	4	4	
Male	7	7	

Subject analysis sets

Subject analysis set title	UK subjects analysis
Subject analysis set type	Full analysis

Subject analysis set description:

Results from 11 subjects from the UK trial on Sirolimus were analysed.

Reporting group values	UK subjects analysis		
Number of subjects	11		
Age categorical			
Subjects enrolled were between 3 years old and 65 years old			
Units: Subjects			
Children (2-11 years)	2		
Adolescents (12-17 years)	4		
Adults (18-64 years)	5		
Gender categorical Units: Subjects			
Female	4		
Male	7		

End points

End points reporting groups

Reporting group title	Sirolimus
Reporting group description:	
Subjects who administered sirolimus drug.	
Subject analysis set title	UK subjects analysis
Subject analysis set type	Full analysis
Subject analysis set description:	
Results from 11 subjects from the UK trial on Sirolimus were analysed.	

Primary: Primary endpoint - relative percentage tissue change

End point title	Primary endpoint - relative percentage tissue change
End point description:	
Of the 11 enrolled, 8 subjects were evaluable for the primary end point as 1 subject was withdrawn and 2 subjects had diffuse disease making it not possible to calculate the primary endpoint of relative % tissue change.	
End point type	Primary
End point timeframe:	
Baseline assessment (run-in) 6 months prior to treatment phase and post 6 months treatment phase.	

End point values	Sirolimus	UK subjects analysis		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	8[1]	8[2]		
Units: change in relative % growth				
arithmetic mean (standard deviation)	-3 (± 5.82)	-3 (± 5.82)		

Notes:

[1] - Of the 11 enrolled, 8 subjects were evaluable for the primary end point as 1 subject was withdrawn a

[2] - Of the 11 enrolled, 8 subjects were evaluable for the primary end point as 1 subject was withdrawn a

Statistical analyses

Statistical analysis title	Paired Student's t test - Relative % tissue change
Statistical analysis description:	
In subjects with established serial growth data, a measure of relative percent excess tissue volume at the affected site was taken at baseline (run-in 6 months prior) and following treatment phase of sirolimus to enable calculation of effect size. Paired student's t test was used to evaluate the relative % change in tissue growth during the run-in period and treatment phase.	
Comparison groups	Sirolimus v UK subjects analysis
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.21 [4]
Method	t-test, 2-sided
Parameter estimate	Percentage change from baseline
Point estimate	-3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.2
upper limit	2.2
Variability estimate	Standard error of the mean
Dispersion value	2.2

Notes:

[3] - Of the 11 enrolled, 8 subjects were evaluable for the primary end point as 1 subject was withdrawn and 2 subjects had diffuse disease making it not possible to calculate the primary endpoint of relative % tissue change.

The number of 16 patients reported, is just an artifact of Eudract not allowing a one-sample hypothesis test, and is double-counting each patient.
[4] - Change in relative % growth between run-in and treatment phase (n=8) = -3.0% (95% CI -8.2, 2.2). The null hypothesis is a mean value of 0.

Secondary: Secondary endpoints - Exploratory

End point title	Secondary endpoints - Exploratory

End point description:

Mean plasma sirolimus level = 3.1 ng/ml (95% CI 2.6, 3.1); Median plasma sirolimus level = 2.85 ng/ml; Correlation between mean sirolimus plasma level and tissue % change R=0.54, p=0.15; Mean daily sirolimus dose = 1.08 mg (95% CI 0.68, 1.48); Median daily sirolimus dose = 1mg
QoL - No significant difference in scores from baseline to end of treatment phase.
Adults WHO-QoL-Bref across all domains mean difference in physical health score = 6.5 (95% CI 1.7, 11.3) p=0.02, mean difference in psychological health score 1.3 (95% CI -10.2, 12.8), p=0.21 mean environmental score = 21 (95% CI =77.7, 35.2), p=0.07
PedsQL Parental report physical health mean difference 129.2 (95% CI=8.08, 266),p0.06, psychosocial health mean difference 129.2 (95% CI=-.77.7,35.2),p0.07
Hospitalisations - Run in phase = 2, treatment phase = 4, no significant difference, p=0.64 (odds ratio 0.39, 95% CI (0.06, 2.5)
Surgical Interventions - Run-in = 2, treatment phase = 0, p=0.48 (1/[Odds ratio]=0, 95% CI (0,2.1

End point type	Secondary

End point timeframe:

Sirolimus - treatment phase 6 months
QoL - start of treatment phase and post treatment phase
Hospitalisations - Run-in and treatment phase
Surgical Interventions - Run-in and treatment phase

End point values	UK subjects analysis			
Subject group type	Subject analysis set			
Number of subjects analysed	11			
Units: siroliums levels/doses and other				
number (not applicable)	11			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs during treatment phase:
5/11 (45%) of subjects had at least 1 AE (any grade)
3/11 (27% subjects had a grade 3 AE

Adverse event reporting additional description:

Adverse event information collected during trial visits or when subject contacted study steam.
Assessment by clinical examinations, monitoring and blood tests where needed.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Overall Adverse Events

Reporting group description:

11 subjects enrolled, 4 SAEs, 1 subject withdrawal (2 x SAEs)
Overall:
- 5/11 (45%) subjects had at least 1 AE (any grade)
- 3/11 (27%) subjects had a grade 3 AE
- No grade 4/5 AEs
- 4 grade 3 AEs
- 5 grade 2 AEs
- 12 grade 1 AE

Serious adverse events	Overall Adverse Events		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 8 (37.50%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Skin and subcutaneous tissue disorders			
Epstein-Barr virus	Additional description: EBV infection		
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis syndrome			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis	Additional description: Cellulitis of the foot (where overgrowth is)		

subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Overall Adverse Events		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 8 (62.50%)		
Skin and subcutaneous tissue disorders			
Diarrhoea	Additional description: Diarrhoaea and vomiting		
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Temperature intolerance	Additional description: Fever experienced		
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		

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