Clinical trial results:
Long-term follow-up study to monitor the growth and development of pediatric patients previously treated with everolimus in study CRAD001M2301 (EXIST-LT)

Summary

EudraCT number	2013-003795-13
Trial protocol	BE PL
Global end of trial date	18 December 2023

Results information

Result version number	v2 (current)
This version publication date	17 November 2024
First version publication date	22 June 2024
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	CRAD001M2305

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02338609
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharmaceuticals
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 December 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 December 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the trial were:
- To assess percentage of participants who achieved Tanner Stage V at or before age of 16 (females) or 17 (males).
- To assess height and body mass index (BMI) standard deviation score by year since baseline.
- To assess mean endocrine laboratory values of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estrogen or testosterone by age.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 December 2014
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	Belgium: 1
Country: Number of subjects enrolled	United States: 11
Country: Number of subjects enrolled	Russian Federation: 3
Worldwide total number of subjects	15
EEA total number of subjects	1

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)	15

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

Subject disposition

Recruitment

Recruitment details:

Participants took part in 6 investigative sites in 3 countries.

Pre-assignment

Screening details:

All the pediatric patients enrolled into the current study had been treated with everolimus in the parent study CRAD001M2301.

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	Everolimus

Arm description:

Participants were treated with everolimus as part of CRAD001M2301. Continued treatment with everolimus is allowed but not required for participation in this study.

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

Dosage and administration details:

Participants were treated with everolimus as part of CRAD001M2301. Continued treatment with everolimus is allowed but not required for participation in this study.

Number of subjects in period 1	Everolimus
Started	15
Safety Analysis set	14
Completed	13
Not completed	2
Physician decision	1
Death	1

Baseline characteristics

Reporting groups	
Reporting group title	Everolimus
Reporting group description:	
Participants were treated with everolimus as part of CRAD001M2301. Continued treatment with everolimus is allowed but not required for participation in this study.	

Reporting group values	Everolimus	Total	
Number of subjects	15	15	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	15	15	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	6.390		
standard deviation	± 3.5647	-	
Sex: Female, Male Units: participants			
Female	8	8	
Male	7	7	
Race/Ethnicity, Customized Units: Subjects			
Black	1	1	
Caucasian	14	14	

End points

End points reporting groups

Reporting group title	Everolimus

Reporting group description:

Participants were treated with everolimus as part of CRAD001M2301. Continued treatment with everolimus is allowed but not required for participation in this study.

Primary: Number of participants who achieved Tanner Stage V at or before age 16 (females) or 17 (males)

End point title	Number of participants who achieved Tanner Stage V at or before age 16 (females) or 17 (males)[1]

End point description:

Tanner Staging, also known as Sexual Maturity Rating (SMR), is an objective classification system that providers use to document and track the development and sequence of secondary sex characteristics of children during puberty. Tanner Stage included two components for boys (testis and pubic hair) and two components for girls (breast development and pubic hair).
Tanner Stage V:
Males and females: Terminal hair that extends beyond the inguinal crease onto the thigh.
Female Breast Development Scale: Areolar mound recedes into single breast contour with areolar hyperpigmentation, papillae development, and nipple protrusion.
Male External Genitalia Scale: > 20 ml (or > 4.5 cm long)
The Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm.

End point type	Primary

End point timeframe:

Annually, up to 14 years from the first visit in parent study CRAD001M2301 (including up to 9 years of follow-up in study CRAD001M2305)

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: only analyzed descriptively.

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: participants				
Female(n=8)	4			
Male(n=7)	6			

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with notably low and notably high height and body mass index (BMI) standard deviation score (SDS)

End point title	Number of participants with notably low and notably high height and body mass index (BMI) standard deviation score (SDS)[2]

End point description:

Height and body weight (with minimal clothing, without shoes) were measured annually. The height standard deviation score (SDS) and BMI SDS were calculated based on height/BMI data collected during the study and published reference height/BMI information (De Onis M, et al. Development of a WHO growth reference for school-aged children and adolescents. Bull World Health Organ. 2007 Sep;85(9):660-7). The number of participants with height and BMI SDS values lower than the 5th percentile (notably low) or higher than the 95th percentile (notably high) are reported.
The baseline corresponds to the last available assessment on or before the start of everolimus in the parent study CRAD001M2301. The assessment is performed up to age of 12 years. The Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm.

End point type	Primary

End point timeframe:

Baseline, annually up to Year 10 of treatment since the start of everolimus in parent study CRAD001M2301 (including a median of 5 years of exposure to everolimus in study CRAD001M2305)

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: only analyzed descriptively.

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: participants				
Height SDS-notably low-Baseline (n=15)	2			
Height SDS-notably low- Year 1 (n=15)	1			
Height SDS-notably low- Year 2 (n=14)	2			
Height SDS-notably low- Year 3 (n=15)	2			
Height SDS-notably low- Year 4 (n=15)	2			
Height SDS-notably low- Year 5 (n=12)	2			
Height SDS-notably low- Year 6 (n=12)	1			
Height SDS-notably low- Year 7 (n=9)	1			
Height SDS-notably low- Year 8 (n=9)	0			
Height SDS-notably low- Year 9 (n=8)	0			
Height SDS-notably low- Year 10 (n=3)	0			
Height SDS-notably high-Baseline (n=15)	1			
Height SDS-notably high- Year 1 (n=15)	0			
Height SDS-notably high- Year 2 (n=14)	0			
Height SDS-notably high- Year 3 (n=15)	0			
Height SDS-notably high- Year 4 (n=15)	1			
Height SDS-notably high-Year 5 (n=12)	0			
Height SDS-notably high- Year 6 (n=12)	1			
Height SDS-notably high- Year 7 (n=9)	1			
Height SDS-notably high- Year 8 (n=9)	1			
Height SDS-notably high- Year 9 (n=8)	0			
Height SDS-notably high- Year 10 (n=3)	0			
BMI SDS-notably low-Baseline (n=15)	0			
BMI SDS-notably low- Year 1 (n=15)	0			
BMI SDS-notably low- Year 2 (n=14)	1			
BMI SDS-notably low- Year 3 (n=15)	0			
BMI SDS-notably low- Year 4 (n=15)	0			
BMI SDS-notably low- Year 5 (n=12)	1			
BMI SDS-notably low- Year 6 (n=12)	2			

BMI SDS-notably low- Year 7 (n=9)	0			
BMI SDS-notably low- Year 8 (n=9)	1			
BMI SDS-notably low- Year 9 (n=8)	2			
BMI SDS-notably low- Year 10 (n=3)	1			
BMI SDS-notably high-Baseline (n=15)	4			
BMI SDS-notably high- Year 1 (n=15)	1			
BMI SDS-notably high- Year 2 (n=14)	1			
BMI SDS-notably high- Year 3 (n=15)	0			
BMI SDS-notably high- Year 4 (n=15)	1			
BMI SDS-notably high- Year 5 (n=12)	1			
BMI SDS-notably high- Year 6 (n=12)	1			
BMI SDS-notably high- Year 7 (n=9)	2			
BMI SDS-notably high- Year 8 (n=9)	2			
BMI SDS-notably high- Year 9 (n=8)	1			
BMI SDS-notably high- Year 10 (n=3)	1			

Statistical analyses

No statistical analyses for this end point

Primary: Endocrine laboratory values LH and FSH in male participants

End point title	Endocrine laboratory values LH and FSH in male participants[3]

End point description:

Luteinizing hormone (LH) is a glycoprotein hormone that is co-secreted along with follicle-stimulating hormone by the gonadotrophin cells in the adenohypophysis (anterior pituitary). Untreated LH deficiency results in infertility, and if it occurs before puberty, the patient fails to develop puberty and secondary sexual characteristics. Follicle-stimulating hormone (FSH) is a hormone produced by the anterior pituitary in response to gonadotropin-releasing hormone (GnRH) from the hypothalamus. FSH plays a role in sexual development and reproduction in both males and females. The Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm.

End point type	Primary

End point timeframe:

Annually, starting at 10-year age until 16-year age (in both studies CRAD001M2301 and CRAD001M2305)

Notes:

[3] - 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: only analyzed descriptively.

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: IU/L				
arithmetic mean (standard deviation)				
10 years age-LH (n=4)	1.0 (± 1.47)			
10 years age-FSH (n=4)	1.5 (± 1.34)			
11 years age-LH (n=6)	1.0 (± 0.77)			
11 years age-FSH (n=6)	1.7 (± 1.11)			
12 years age-LH (n=7)	1.8 (± 1.22)			
12 years age-FSH (n=7)	2.1 (± 0.67)			

13 years age-LH (n=6)	2.4 (± 2.26)			
13 years age-FSH (n=6)	2.9 (± 1.81)			
14 years age-LH (n=6)	2.9 (± 2.18)			
14 years age-FSH (n=6)	4.6 (± 4.29)			
15 years age-LH (n=4)	2.5 (± 1.07)			
15 years age-FSH (n=4)	3.3 (± 0.61)			
16 years age-LH (n=3)	3.5 (± 0.32)			
16 years age-FSH (n=3)	6.0 (± 3.01)			

Statistical analyses

No statistical analyses for this end point

Primary: Endocrine laboratory values LH and FSH in female participants

End point title	Endocrine laboratory values LH and FSH in female

End point description:

Luteinizing hormone (LH) is a glycoprotein hormone that is co-secreted along with follicle-stimulating hormone by the gonadotrophin cells in the adenohypophysis (anterior pituitary). Untreated LH deficiency results in infertility, and if it occurs before puberty, the patient fails to develop puberty and secondary sexual characteristics. Follicle-stimulating hormone (FSH) is a hormone produced by the anterior pituitary in response to gonadotropin-releasing hormone (GnRH) from the hypothalamus. FSH plays a role in sexual development and reproduction in both males and females.The Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm.

End point type	Primary

End point timeframe:

Annually, starting at 10-year age until 16-year age (in both studies CRAD001M2301 and CRAD001M2305)

Notes:

[4] - 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: only analyzed descriptively.

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: IU/L				
arithmetic mean (standard deviation)				
10 years age-LH (n=2)	5.1 (± 3.89)			
10 years age-FSH (n=2)	3.4 (± 2.68)			
11 years age-LH (n=7)	3.2 (± 2.47)			
11 years age-FSH (n=7)	3.5 (± 1.61)			
12 years age-LH (n=7)	7.8 (± 6.73)			
12 years age-FSH (n=7)	5.6 (± 2.43)			
13 years age-LH (n=5)	4.4 (± 3.08)			
13 years age-FSH (n=5)	5.0 (± 0.80)			
14 years age-LH (n=6)	5.3 (± 6.97)			
14 years age-FSH (n=6)	2.6 (± 2.05)			
15 years age-LH (n=4)	7.5 (± 10.96)			
15 years age-FSH (n=4)	2.5 (± 2.28)			
16 years age-LH (n=4)	3.7 (± 2.69)			

16 years age-FSH (n=4)	2.8 (± 2.05)			

Statistical analyses

No statistical analyses for this end point

Primary: Endocrine laboratory values of testosterone in male participants

End point title	Endocrine laboratory values of testosterone in male participants[5]

End point description:

Testosterone is the primary male hormone responsible for regulating sex differentiation, producing male sex characteristics, spermatogenesis, and fertility. The Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm.

End point type	Primary

End point timeframe:

Annually, starting at 10-year age until 16-year age (in both studies CRAD001M2301 and CRAD001M2305)

Notes:

[5] - 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: only analyzed descriptively.

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: nmol/L				
arithmetic mean (standard deviation)				
10 years age (n=4)	0.7 (± 1.17)			
11 years age (n=6)	2.5 (± 4.60)			
12 years age (n=7)	3.8 (± 4.29)			
13 years age (n=6)	4.3 (± 4.04)			
14 years age (n=6)	7.2 (± 4.34)			
15 years age (n=4)	12.9 (± 6.28)			
16 years age (n=3)	15.5 (± 3.93)			

Statistical analyses

No statistical analyses for this end point

Primary: Endocrine laboratory values of estrogen in female participants

End point title	Endocrine laboratory values of estrogen in female

End point description:

Estrogen is a steroid hormone associated with the female reproductive organs and is responsible for developing female sexual characteristics. Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as ¨999¨. The Number of Subjects Analyzed differs as stated on the category column, in case of

difference from Number of subjects that started the Arm.

End point type	Primary

End point timeframe:

Annually, starting at 10-year age until 16-year age (in both studies CRAD001M2301 and CRAD001M2305)

Notes:

[6] - 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: only analyzed descriptively.

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: ng/L				
arithmetic mean (standard deviation)				
10 years age (n=1)	139.8 (± 999)			
11 years age (n=4)	80.5 (± 119.22)			
12 years age (n=3)	43.7 (± 41.26)			
13 years age (n=2)	50.0 (± 7.07)			
14 years age (n=2)	139.0 (± 141.42)			
15 years age (n=4)	47.7 (± 48.89)			
16 years age (n=4)	149.7 (± 128.21)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with treatment emergent adverse events (AEs) and serious adverse events (SAEs)

End point title	Number of participants with treatment emergent adverse events (AEs) and serious adverse events (SAEs)

End point description:

Number of participants with treatment emergent AEs (any AE regardless of seriousness), AEs led to study treatment discontinuation, SAEs and SAEs led to study treatment discontinuation.

End point type	Secondary

End point timeframe:

From enrollment in study CRAD001M2305 until end of study, up to approximately 9 years.

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: participants				
At least one AE	12			
At least one SAE	6			
AE leading to discontinuation	0			

SAE leading to discontinuation	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Participants age at Tanner Stage II, III, IV, V

End point title	Participants age at Tanner Stage II, III, IV, V

End point description:

Tanner Staging is a classification system that providers use to document and track the development of secondary sex characteristics during puberty.
Pubic Hair Scale
II-Downy hair
III-Scant terminal hair
IV-Terminal hair that fills the triangle overlying the pubic region
V-Terminal hair that extends beyond the inguinal crease onto the thigh
Female Breast Development Scale
II-Breast bud palpable under the areola-1stpubertal sign in females
III-Breast tissue palpable outside areola;no areolar development
IV-Areola elevated above the contour of the breast, forming a "double scoop" appearance
V-Areolar mound recedes into single breast contour with areolar hyperpigmentation, papillae development, and nipple protrusion
Male External Genitalia Scale
II-2.5 to3.3cm long,1st pubertal sign in males
III-3.4 to4.0cm long
IV-4.1 to4.5cm long
V-or>4.5cm long
The Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm.

End point type	Secondary

End point timeframe:

Up to approximately 14.4 years from the first dose of everolimus in parent study CRAD001M2301 (including up to 9 years of follow-up in study CRAD001M2305)

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	15[7]			
Units: years				
median (confidence interval 95%)				
Tanner stage II-pubic hair-male (n=6)	11.8 (10.2 to 999)			
Tanner stage II-genitalia (n=6)	11.9 (10.4 to 999)			
Tanner stage III-pubic hair-male (n=6)	13.3 (11.3 to 999)			
Tanner stage III-genitalia (n=6)	12.6 (11.3 to 14.2)			
Tanner stage IV-pubic hair-male (n=6)	14.2 (11.3 to 999)			
Tanner stage IV-genitalia (n=6)	14.2 (11.3 to 999)			

Tanner stage V-pubic hair-male (n=5)	16.4 (15.3 to 999)			
Tanner stage V-genitalia (n=6)	16.4 (12.7 to 999)			
Tanner stage II-pubic hair-female (n=8)	10.4 (7.3 to 11.8)			
Tanner stage II-Breast (n=7)	11.5 (9.9 to 11.8)			
Tanner stage III-pubic hair-female (n=8)	12.2 (10.4 to 12.8)			
Tanner stage III-Breast (n=7)	12.5 (10.4 to 14.6)			
Tanner stage IV-pubic hair-female (n=6)	13.4 (11.6 to 14.5)			
Tanner stage IV-Breast (n=7)	13.8 (12.7 to 14.6)			
Tanner stage V-pubic hair-female (n=4)	16.0 (13.8 to 999)			
Tanner stage V-Breast (n=2)	999 (13.8 to 999)			

Notes:

[7] - 999=Not estimable due to insufficient number of participants with events

Statistical analyses

No statistical analyses for this end point

Secondary: Participants age at menarche/thelarche (females) or adrenarche (males)

End point title	Participants age at menarche/thelarche (females) or adrenarche (males)

End point description:

Menarche is defined as the first menstrual period in a female.Menarche typically occurs between the ages of 10 and 16, with the average age of onset being 12.4 years. Thelarche is the beginning of adult breast development, marks the onset of puberty in the majority of women and occurs at a mean age of 10 years. Adrenarche refers to the time during puberty when the adrenal glands increase their production and secretion of adrenal androgens. Potential delayed puberty in girls is defined as failure to attain Tanner Stage II by age 13, or absence of menarche by age 15 or within 5 years of attainment of Tanner Stage II. Potential delayed puberty in boys is defined as failure to attain Tanner Stage II by age 14. Due to EudraCT system limitations, data fields in the table cannot contain letters. Therefore, not applicable values are indicated as ¨999¨. The Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm.

End point type	Secondary

End point timeframe:

Up to approximately 14.4 years from the first dose of everolimus in parent study CRAD001M2301 (including up to 9 years of follow-up in study CRAD001M2305)

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	14[8]			
Units: years				
median (confidence interval 95%)				
Menarche (n=7)	12.5 (11.0 to 13.6)			

Thelarche (n=5)	10.2 (9.1 to 999)			
Adrenarche (n=7)	11.0 (10.0 to 11.6)			

Notes:

[8] - 999=Not estimable due to insufficient number of participants with events

Statistical analyses

No statistical analyses for this end point

Secondary: TAND checklist - Number of Participants Achieved Basic Developmental Milestones and the Age at which Participants Achieved the Basic Developmental Milestones

End point title	TAND checklist - Number of Participants Achieved Basic Developmental Milestones and the Age at which Participants Achieved the Basic Developmental Milestones

End point description:

Tuberous Sclerosis Complex (TSC) is associated with a range of neuropsychiatric disorders which refers to as TAND (TSC–Associated–Neuropsychiatric–Disorders). A specific TAND Checklist has been developed to assess Behavioral, Psychiatric, Intellectual, Academic, Neuropsychological and Psychosocial areas. This outcome measure assesses the TAND checklist part about basic development skills. Baseline is defined as the first available assessment on or after the enrollment date of the CRAD001M2305 study. Overall consists of all responses including baseline.

End point type	Secondary

End point timeframe:

From enrollment in study CRAD001M2305 until end of study, up to approximately 9 years.

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	15[9]			
Units: age (months)				
arithmetic mean (standard error)				
First smile-BS	2.9 (± 1.85)			
First smile-OA	2.9 (± 1.85)			
Sat without support-BS	7.5 (± 3.68)			
Sat without support-OA	7.5 (± 3.68)			
Walked without holding on-BS	16.5 (± 8.23)			
Walked without holding on-OA	16.5 (± 8.23)			
First used words other than "mama" or "dada"-BS	29.5 (± 24.81)			
First used words other than "mama" or "dada"-OA	29.5 (± 24.81)			
First used two words/short phrases-BS	33.2 (± 16.66)			
First used two words/short phrases-OA	34.3 (± 19.77)			
Toilet trained during the day-BS	46.2 (± 31.22)			
Toilet trained during the day-OA	51.5 (± 35.89)			
Toilet trained at night-BS	52.5 (± 35.60)			
Toilet trained at night-OA	60.1 (± 43.23)			

Notes:

[9] - BS=baseline
OA=overall

Statistical analyses

No statistical analyses for this end point

Secondary: TAND checklist - Number of Participants with Behavioral Disorders

End point title	TAND checklist - Number of Participants with Behavioral Disorders

End point description:

Tuberous Sclerosis Complex (TSC) is associated with a range of neuropsychiatric disorders which refers to as TAND (TSC–Associated–Neuropsychiatric–Disorders). A specific TAND Checklist has been developed to assess Behavioral, Psychiatric, Intellectual, Academic, Neuropsychological and Psychosocial areas.
Behavioral level- This level refers to any observed behaviors that may cause concern to the individual. Behavioral presentations include anxiety, depressed mood, aggressive behaviors, temper tantrums, attention-related behaviors (such as difficulty concentrating, hyperactivity, impulsivity), social, and communication-related behaviors (such as speech and language delays, poor eye contact, difficulties in relationships with peers, repetitive behaviors), self-injurious behaviors, and eating or sleep difficulties. Baseline is defined as the first available assessment on or after the enrollment date of the CRAD001M2305 study. Overall consists of all responses including baseline.

End point type	Secondary

End point timeframe:

From enrollment in study CRAD001M2305 until end of study, up to approximately 9 years.

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	15[10]			
Units: participants				
Anxiety-BS	12			
Anxiety-OA	13			
Depressed mood-BS	6			
Depressed mood-OA	8			
Extreme shyness-BS	5			
Extreme shyness-OA	7			
Mood swings-BS	10			
Mood swings-OA	12			
Aggressive outbursts-BS	7			
Aggressive outbursts-OA	11			
Temper Tantrums-BS	9			
Temper Tantrums-OA	12			
Self-injury-hitting, biting, scratching self-BS	3			
Self-injury-hitting, biting, scratching self-OA	5			
Absent/delayed onset of language to communicate-BS	11			

Absent/delayed onset of language to communicate-OA	12			
Repeating words or phrases over and over again-BS	9			
Repeating words or phrases over and over again-OA	12			
Poor eye contact-BS	6			
Poor eye contact-OA	8			
Difficulty getting on with people similar age-BS	9			
Difficulty getting on with people similar age-OA	10			
Repetitive behaviours-BS	9			
Repetitive behaviours-OA	11			
Very rigid/inflexible-how to do things-BS	8			
Very rigid/inflexible-how to do things-OA	11			
Overactivity/hyperactivity-constantly on the go-BS	8			
Overactivity/hyperactivity-constantly on the go-OA	9			
Difficulty paying attention or concentrating-BS	13			
Difficulty paying attention or concentrating-OA	15			
Restlessness or fidgetiness-wriggling/squirming-BS	13			
Restlessness or fidgetiness-wriggling/squirming-OA	14			
Impulsivity - butting in, not waiting turn-BS	10			
Impulsivity - butting in, not waiting turn-OA	12			
Eat difficulties-too much/too little/unusual-BS	5			
Eat difficulties-too much/too little/unusual-OA	8			
Sleep difficulties-with falling asleep/waking-BS	6			
Sleep difficulties-with falling asleep/waking-OA	8			

Notes:

[10] - BS=baseline
OA=overall

Statistical analyses

No statistical analyses for this end point

Secondary: TAND checklist - Number of Participants with Psychiatric disorders

End point title	TAND checklist - Number of Participants with Psychiatric disorders

End point description:

Tuberous Sclerosis Complex (TSC) is associated with a range of neuropsychiatric disorders which refers to as TAND (TSC–Associated–Neuropsychiatric–Disorders). A specific TAND Checklist has been developed to assess Behavioral, Psychiatric, Intellectual, Academic, Neuropsychological and Psychosocial areas. For psychiatric disorders some behaviors of concern are examined and evaluated in the context of the individual's overall developmental level and in terms of their biological, psychological, and social profile. Baseline is defined as the first available assessment on or after the enrollment date of the CRAD001M2305 study. Overall consists of all responses including baseline.

End point type	Secondary

End point timeframe:

From enrollment in study CRAD001M2305 until end of study, up to approximately 9 years.

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	15[11]			
Units: participants				
Autism Spectrum Disorder(ASD)-autism/Asperger's-BS	4			
Autism Spectrum Disorder(ASD)-autism/Asperger's-OA	7			
Attention Deficit Hyperactivity Disorder (ADHD)-BS	5			
Attention Deficit Hyperactivity Disorder (ADHD)-OA	9			
Anxiety Disorder-panic/phobia/separation AD-BS	4			
Anxiety Disorder-panic/phobia/ separation AD-OA	7			
Depressive Disorder-BS	0			
Depressive Disorder-OA	0			
Obsessive Compulsive Disorder-BS	2			
Obsessive Compulsive Disorder-OA	2			
Psychotic Disorder, including schizophrenia-BS	0			
Psychotic Disorder, including schizophrenia-OA	0			

Notes:

[11] - BS=baseline
OA=overall
AD=Anxiety Disorder

Statistical analyses

No statistical analyses for this end point

Secondary: TAND checklist - Number of Participants with Scholastic issues

End point title	TAND checklist - Number of Participants with Scholastic issues

End point description:

Tuberous Sclerosis Complex (TSC) is associated with a range of neuropsychiatric disorders which refers to as TAND (TSC–Associated–Neuropsychiatric–Disorders). A specific TAND Checklist has been developed to assess Behavioral, Psychiatric, Intellectual, Academic, Neuropsychological and Psychosocial areas. At academic level, it is described the specific learning disorders associated with school performance, such as reading, writing, mathematics, and spelling. Baseline is defined as the first available assessment on or after the enrollment date of the CRAD001M2305 study. Overall consists of all responses including baseline.

End point type	Secondary

End point timeframe:

From enrollment in study CRAD001M2305 until end of study, up to approximately 9 years.

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: participants				
Reading-baseline	12			
Reading-overall	14			
Writing-baseline	12			
Writing-overall	14			
Spelling-baseline	12			
Spelling-overall	14			
Mathematics-baseline	12			
Mathematics-overall	14			

Statistical analyses

No statistical analyses for this end point

Secondary: TAND checklist - Number of Participants with Difficulty in Specific Brain Skills

End point title	TAND checklist - Number of Participants with Difficulty in Specific Brain Skills

End point description:

Tuberous Sclerosis Complex (TSC) is associated with a range of neuropsychiatric disorders which refers to as TAND (TSC–Associated–Neuropsychiatric–Disorders). A specific TAND Checklist has been developed to assess Behavioral, Psychiatric, Intellectual, Academic, Neuropsychological and Psychosocial areas. Neuropsychological evaluations are used to describe the strengths and weaknesses of brain referenced systems used for learning, thinking, and behavior regulation. Baseline is defined as the first available assessment on or after the enrollment date of the CRAD001M2305 study. Overall consists of all responses including baseline.

End point type	Secondary

End point timeframe:

From enrollment in study CRAD001M2305 until end of study, up to approximately 9 years.

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: participants				
Memory-baseline	7			
Memory-overall	12			
Attention-baseline	12			
Attention-overall	14			
Dual-tasking/ Multi-tasking-baseline	12			
Dual-tasking/ Multi-tasking-overall	14			
Visuo-spatial tasks-baseline	8			
Visuo-spatial tasks-overall	13			
Executive skills-baseline	10			
Executive skills-overall	15			
Getting disoriented-baseline	7			

Getting disoriented-overall	12			

Statistical analyses

No statistical analyses for this end point

Secondary: TAND checklist - Number of Participants with Psychological issues

End point title	TAND checklist - Number of Participants with Psychological issues

End point description:

Tuberous Sclerosis Complex (TSC) is associated with a range of neuropsychiatric disorders which refers to as TAND (TSC–Associated–Neuropsychiatric–Disorders). A specific TAND Checklist has been developed to assess Behavioral, Psychiatric, Intellectual, Academic, Neuropsychological and Psychosocial areas. At psychosocial level it is considered important determinants of quality of life, such as self-esteem, family functioning, parental stress, and relationship difficulties. All these are markers of resilience and burden of care, and all the psychosocial factors may be amenable to intervention and support. Baseline is defined as the first available assessment on or after the enrollment date of the CRAD001M2305 study. Overall consists of all responses including baseline.

End point type	Secondary

End point timeframe:

From enrollment in study CRAD001M2305 until end of study, up to approximately 9 years.

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	15[12]			
Units: participants				
Low self-esteem-baseline	2			
Low self-esteem-overall	6			
VHLS in families, for instance between siblings-BS	6			
VHLS in families, for instance between siblings-OA	8			
VHLS between parents leading to significant RD-BS	5			
VHLS between parents leading to significant RD-OA	7			

Notes:

[12] - BS=baseline
OA=overall
VHLS=very high level of stress
RD=relationship difficulties

Statistical analyses

No statistical analyses for this end point

Secondary: TAND checklist - Number of Participants with Varied Levels of Language skills

End point title	TAND checklist - Number of Participants with Varied Levels of

	Language skills

End point description:

Tuberous Sclerosis Complex (TSC) is associated with a range of neuropsychiatric disorders which refers to as TAND (TSC–Associated–Neuropsychiatric–Disorders). A specific TAND Checklist has been developed to assess Behavioral, Psychiatric, Intellectual, Academic, Neuropsychological and Psychosocial areas. Neuropsychological evaluations are used to describe the strengths and weaknesses of brain referenced systems used for learning, thinking, and behavior regulation. These include language skills (including non-verbal, simple language, fluence of language). All the responses are categorical in nature from the TAND Checklist. The frequency of (baseline and) worst-post baseline is summarized.

End point type	Secondary

End point timeframe:

From enrollment in study CRAD001M2305 until end of study, up to approximately 9 years.

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: participants				
Non-verbal	2			
Simple language	6			
Fluent	4			
Missing	3			

Statistical analyses

No statistical analyses for this end point

Secondary: TAND checklist - Number of Participants with Different Levels of Physical Dependency

End point title	TAND checklist - Number of Participants with Different Levels of Physical Dependency

End point description:

Tuberous Sclerosis Complex (TSC) is associated with a range of neuropsychiatric disorders which refers to as TAND (TSC–Associated–Neuropsychiatric–Disorders). A specific TAND Checklist has been developed to assess Behavioral, Psychiatric, Intellectual, Academic, Neuropsychological and Psychosocial areas. This outcome measure assesses the TAND checklist part about physical dependency. All the responses are categorical in nature from the TAND Checklist. The frequency of (baseline and) worst-post baseline is summarized.

End point type	Secondary

End point timeframe:

From enrollment in study CRAD001M2305 until end of study, up to approximately 9 years.

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: participants				
Dependent on others	4			
Some self-care skills	7			
Independent	1			
Missing	3			

Statistical analyses

No statistical analyses for this end point

Secondary: TAND checklist - Number of Participants with Different Levels of Mobility

End point title	TAND checklist - Number of Participants with Different Levels of Mobility

End point description:

Tuberous Sclerosis Complex (TSC) is associated with a range of neuropsychiatric disorders which refers to as TAND (TSC–Associated–Neuropsychiatric–Disorders). A specific TAND Checklist has been developed to assess Behavioral, Psychiatric, Intellectual, Academic, Neuropsychological and Psychosocial areas. This outcome measure assesses the TAND checklist part about mobility. All the responses are categorical in nature from the TAND Checklist. The frequency of (baseline and) worst-post baseline is summarized.

End point type	Secondary

End point timeframe:

From enrollment in study CRAD001M2305 until end of study, up to approximately 9 years.

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: participants				
Wheelchair	1			
Needs significant support	1			
Some difficulty	0			
Completely mobile	10			
Missing	3			

Statistical analyses

No statistical analyses for this end point

Secondary: TAND checklist - Number of Participants with Different Levels of Intelligence Quotient

End point title	TAND checklist - Number of Participants with Different Levels of Intelligence Quotient

End point description:

Tuberous Sclerosis Complex (TSC) is associated with a range of neuropsychiatric disorders which refers to as TAND (TSC–Associated–Neuropsychiatric–Disorders). A specific TAND Checklist has been developed to assess Behavioral, Psychiatric, Intellectual, Academic, Neuropsychological and Psychosocial areas. At intellectual level, it is described the intellectual developmental abilities of an individual in comparison with others of the same chronological age. All the responses are categorical in nature from the TAND Checklist. The frequency of (baseline and) worst-post baseline is summarized.

End point type	Secondary

End point timeframe:

From enrollment in study CRAD001M2305 until end of study, up to approximately 9 years.

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: participants				
Normal Intellectual Ability (IQ > 80)	2			
Borderline Intellectual Ability (IQ 70-80)	2			
Mild Intellectual Disability (IQ 50-69)	1			
Moderate Intellectual Disability (IQ 35-49)	5			
Severe Intellectual Disability (IQ 21-34)	0			
Profound Intellectual Disability (IQ <20)	1			
Missing	4			

Statistical analyses

No statistical analyses for this end point

Secondary: TAND checklist - Number of Participants with Different Levels of Intellectual Ability

End point title	TAND checklist - Number of Participants with Different Levels of Intellectual Ability

End point description:

Tuberous Sclerosis Complex (TSC) is associated with a range of neuropsychiatric disorders which refers to as TAND (TSC–Associated–Neuropsychiatric–Disorders). A specific TAND Checklist has been developed to assess Behavioral, Psychiatric, Intellectual, Academic, Neuropsychological and Psychosocial areas. At intellectual level, it is described the intellectual developmental abilities of an individual to identify their overall functional and adaptive behaviors in comparison with others of the same chronological age. This level is the combination of formal measures of intellectual ability (such as IQ-type tests) and evaluation of adaptive behaviors (such as self-care, daily living skills, communication, and social abilities in daily life). All the responses are categorical in nature from the TAND Checklist. The frequency of (baseline and) worst-post baseline is summarized.

End point type	Secondary

End point timeframe:

From enrollment in study CRAD001M2305 until end of study, up to approximately 9 years.

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: participants				
Normal Intellectual Ability	1			
Mild-Moderate Intellectual Disability	8			
Severe - Profound Intellectual Disability	3			
Missing	3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From enrollment in study CRAD001M2305 until end of study, up to approximately 9 years.	
Adverse event reporting additional description:	
Adverse events are assessed in the Safety Set. The Safety Set included all pediatric patients enrolled who had at least one-post baseline safety assessment.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups	
Reporting group title	CRAD001M2305
Reporting group description:	
CRAD001M2305	

Serious adverse events	CRAD001M2305		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 14 (42.86%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Astrocytoma, low grade			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Near drowning			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post procedural complication			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Status epilepticus				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	2 / 14 (14.29%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Pyrexia				
subjects affected / exposed	2 / 14 (14.29%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Drowning				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Pneumonia				
subjects affected / exposed	2 / 14 (14.29%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Arthritis infective				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal infection				
subjects affected / exposed	1 / 14 (7.14%)			
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	CRAD001M2305		
Total subjects affected by non-serious adverse events subjects affected / exposed	12 / 14 (85.71%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Astrocytoma, low grade subjects affected / exposed occurrences (all)	 1 / 14 (7.14%) 1		
General disorders and administration site conditions Gait disturbance subjects affected / exposed occurrences (all) Microsomia subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	 1 / 14 (7.14%) 1 1 / 14 (7.14%) 1 6 / 14 (42.86%) 11		
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	 3 / 14 (21.43%) 3		
Reproductive system and breast disorders Heavy menstrual bleeding subjects affected / exposed occurrences (all) Ovarian cyst subjects affected / exposed occurrences (all)	 1 / 14 (7.14%) 2 1 / 14 (7.14%) 1		
Respiratory, thoracic and mediastinal disorders			

Central sleep apnoea syndrome subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Cough subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 3		
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Rhinitis allergic subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Sleep apnoea syndrome subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Upper respiratory tract congestion subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Psychiatric disorders Aggression subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Anxiety subjects affected / exposed occurrences (all)	3 / 14 (21.43%) 4		
Attention deficit hyperactivity disorder subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2		
Euphoric mood subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Insomnia subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Investigations			

Cardiac murmur subjects affected / exposed occurrences (all) Cutibacterium test positive subjects affected / exposed occurrences (all) SARS-CoV-2 test negative subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1 1 / 14 (7.14%) 1 1 / 14 (7.14%) 1		
Injury, poisoning and procedural complications Clavicle fracture subjects affected / exposed occurrences (all) Contusion subjects affected / exposed occurrences (all) Limb injury subjects affected / exposed occurrences (all) Procedural pain subjects affected / exposed occurrences (all)	 1 / 14 (7.14%) 1 1 / 14 (7.14%) 1 1 / 14 (7.14%) 1 1 / 14 (7.14%) 1		
Cardiac disorders Bradycardia subjects affected / exposed occurrences (all) Right ventricular dilatation subjects affected / exposed occurrences (all)	 1 / 14 (7.14%) 1 1 / 14 (7.14%) 1		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Head discomfort subjects affected / exposed occurrences (all)	 1 / 14 (7.14%) 1 1 / 14 (7.14%) 1		

Headache subjects affected / exposed occurrences (all) Seizure subjects affected / exposed occurrences (all) Vasogenic cerebral oedema subjects affected / exposed occurrences (all)	 3 / 14 (21.43%) 3 4 / 14 (28.57%) 7 1 / 14 (7.14%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Hypofibrinogenaemia subjects affected / exposed occurrences (all) Iron deficiency anaemia subjects affected / exposed occurrences (all) Lymphadenopathy subjects affected / exposed occurrences (all)	 3 / 14 (21.43%) 3 1 / 14 (7.14%) 1 1 / 14 (7.14%) 1 1 / 14 (7.14%) 1		
Ear and labyrinth disorders Hypoacusis subjects affected / exposed occurrences (all)	 1 / 14 (7.14%) 1		
Eye disorders Periorbital swelling subjects affected / exposed occurrences (all)	 1 / 14 (7.14%) 1		
Gastrointestinal disorders Mouth ulceration subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all)	 2 / 14 (14.29%) 2 2 / 14 (14.29%) 3		

Constipation subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2		
Diarrhoea subjects affected / exposed occurrences (all)	3 / 14 (21.43%) 4		
Flatulence subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Gingival hypertrophy subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 2		
Nausea subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 2		
Oral pain subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Stomatitis subjects affected / exposed occurrences (all)	3 / 14 (21.43%) 3		
Vomiting subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 3		
Skin and subcutaneous tissue disorders Eczema subjects affected / exposed occurrences (all)	3 / 14 (21.43%) 3		
Acne subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Blister subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Musculoskeletal and connective tissue disorders			

Arthralgia subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1			
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1			
Neck pain subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1			
Pain in extremity subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1			
Tendonitis subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1			
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 2			
Cellulitis subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1			
Clostridium difficile infection subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1			
Conjunctivitis subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1			
Croup infectious subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1			
Ear infection subjects affected / exposed occurrences (all)	4 / 14 (28.57%) 5			
Fungal skin infection				

subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Infectious mononucleosis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	4 / 14 (28.57%)		
occurrences (all)	5		
Otitis media			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Pharyngitis streptococcal			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Pneumonia			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	5		
Sinusitis			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	6		
Upper respiratory tract infection			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Hyperlipidaemia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		

Vitamin D deficiency subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Abnormal weight gain subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 August 2014	This protocol was amended in order to address comments received from the reviewers at the Committee for Medicinal Products for Human Use (CHMP). In light of these comments from the Health Authority, the protocol was amended to clarify operational activities that were planned for each visit.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

It was anticipated that max. of 50 patients who have participated in Study M2301 would be eligible to enter Study M2305. However, only 15 patients were enrolled into this study, due to delays in study start-up at country level.

Notes: