Clinical trial results:
A Multi Center Extension Study of PRX-102 Administered by Intravenous Infusions Every 2 Weeks for up to 60 Months to Adult Fabry Patients

Summary

EudraCT number	2014-005544-18
Trial protocol	ES GB
Global end of trial date	26 August 2020

Results information

Result version number	v1 (current)
This version publication date	18 April 2022
First version publication date	18 April 2022

Trial information

Trial identification

Sponsor protocol code	PB-102-F03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01981720
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Protalix Ltd.
Sponsor organisation address	2 Snunit Street, Carmiel, Israel, 2161401
Public contact	Raul Chertkoff, Protalix Ltd., 972 4-902-8100, raul@protalix.com
Scientific contact	Sari Alon, Protalix Ltd., 972 4-902-8100, sari@protalix.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	09 November 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 August 2020
Global end of trial reached?	Yes
Global end of trial date	26 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the ongoing safety, tolerability and efficacy parameters of pegunigalsidase alfa (PRX-102) in adult Fabry patients who have successfully completed treatment with PRX-102 in studies PB-102-F01 and PB-102-F02.

Protection of trial subjects:

Throughout the study, infusion visits occurred EOW and at each infusion visit, vital signs were evaluated before starting the infusion, every 30 minutes during the first hour of infusion and then every 60 minutes up the end of the patient's clinical observation period. Also, the injection site was evaluated at each infusion visit. The patients received the treatment at a home care set-up once the Investigator and Sponsor Medical Director agreed that it is safe.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 January 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason
Long term follow-up duration	60 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 11
Country: Number of subjects enrolled	Paraguay: 1
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United Kingdom: 1
Worldwide total number of subjects	15
EEA total number of subjects	2

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)	1
Adults (18-64 years)	14
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Fabry patients who had completed 1 year of treatment with pegunigalsidase alfa (PRX-102) in studies PB-102-F01 and PB-102-F02 were continued to study PB-102-F03 for an additional 24-month treatment period, which was further amended to a 60-month treatment period.

Pre-assignment

Screening details:

A total of 15 adult patients (8 males and 7 females) who completed study PB-102-F02 were enrolled in this study and included in both the Safety and Efficacy populations.

Period 1

Period 1 title	Patients enrolled and treated in F03 (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Open Label

Arms

Arm title	pegunigalsidase alfa

Arm description:

pegunigalsidase alfa (PRX-102) 1mg/Kg every other week

Arm type	Experimental
Investigational medicinal product name	pegunigalsidase alfa
Investigational medicinal product code	
Other name	PRX-102
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

pegunigalsidase alfa (PRX-102) individual doses were prepared according to the each patient according to the patient's weight (measured every 6 months). PRX-102 was administered at the study dose of 1.0 mg/kg, as IV infusions, every other week (± 3 days). For patients who received 0.2 or 2.0 mg/kg in study PB-102-F02, the dose was gradually adjusted to 1.0 mg/kg during study PB-102-F03. Infusion time was reduced gradually up to 1.5 hours pending on patient tolerability.

Number of subjects in period 1	pegunigalsidase alfa
Started	15
Completed	10
Not completed	5
Consent withdrawn by subject	3
other reasons	1
Adverse event, non related, fatal	1

Baseline characteristics

Reporting groups	
Reporting group title	Patients enrolled and treated in F03

Reporting group description: -

Reporting group values	Patients enrolled and treated in F03	Total	
Number of subjects	15	15	
Age categorical Units: Subjects			
Adolescents (12-17 years)	1	1	
Adults (18-64 years)	14	14	
Age continuous Units: years			
arithmetic mean	33.4		
standard deviation	± 12.5	-	
Gender categorical Units: Subjects			
Female	7	7	
Male	8	8	

Subject analysis sets	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety population defined as all patients who received any dose (partial or complete) of study treatment as part of study PB-102-F03

Subject analysis set title	Efficacy population
Subject analysis set type	Per protocol

Subject analysis set description:

Efficacy population defined as all patients who received at least one complete dose of the study treatment as part of study PB-102-F03

Subject analysis set title	Male
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Male subjects from safety/ efficacy population

Subject analysis set title	Female
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Female subjects from Safety/ efficacy population.

Reporting group values	Safety population	Efficacy population	Male
Number of subjects	15	15	8
Age categorical Units: Subjects			
Adolescents (12-17 years)	1	1	1
Adults (18-64 years)	14	14	7

Age continuous Units: years			
arithmetic mean	33.4	33.4	29.8
standard deviation	± 12.5	± 12.5	± 9.9
Gender categorical Units: Subjects			
Female	7	7	0
Male	8	8	8

Reporting group values	Female		
Number of subjects	7		
Age categorical Units: Subjects			
Adolescents (12-17 years)	0		
Adults (18-64 years)	7		
Age continuous Units: years			
arithmetic mean	37.6		
standard deviation	± 14.5		
Gender categorical Units: Subjects			
Female	7		
Male	0		

End points

End points reporting groups

Reporting group title	pegunigalsidase alfa
Reporting group description: pegunigalsidase alfa (PRX-102) 1mg/Kg every other week	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description: Safety population defined as all patients who received any dose (partial or complete) of study treatment as part of study PB-102-F03	
Subject analysis set title	Efficacy population
Subject analysis set type	Per protocol
Subject analysis set description: Efficacy population defined as all patients who received at least one complete dose of the study treatment as part of study PB-102-F03	
Subject analysis set title	Male
Subject analysis set type	Sub-group analysis
Subject analysis set description: Male subjects from safety/ efficacy population	
Subject analysis set title	Female
Subject analysis set type	Sub-group analysis
Subject analysis set description: Female subjects from Safety/ efficacy population.	

Primary: Number of participants experiencing adverse events (AEs)

End point title	Number of participants experiencing adverse events (AEs)[1]
End point description: Results represent the number of treatment-emergent adverse events (TEAE) that were considered definitely, probably or possibly related to study treatment.	
End point type	Primary
End point timeframe: 60 month	

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 analysis was specified for this study, the data was summarized using descriptive statistics.

End point values	pegunigalsidase alfa	Safety population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	15	15		
Units: Subjects				
At least 1 TEAE	15	13		
At least 1 mild or moderate TEAE	15	13		
At least 1 severe TEAE	5	5		
At least 1 SAE	3	2		
At least 1 definitely, probably or possibly relate	9	4		
At least 1 TEAE leading to discontinuation	1	1		
At least 1 TEAE leading to death	1	1		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Plasma Lyso-Gb3 concentration

End point title	Plasma Lyso-Gb3 concentration

End point description:

Globotriaosylsphingosine (Lyso-Gb3) is Fabry disease specific biomarker.

End point type	Other pre-specified

End point timeframe:

60 Months

End point values	Efficacy population	Male	Female	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	15	8	7	
Units: ng/mL				
arithmetic mean (standard error)				
Baseline	70.8 (± 20.4)	124.4 (± 25.9)	9.6 (± 2.1)	
Month 60	6.4 (± 1.5)	9.2 (± 1.6)	2.1 (± 0.9)	
Change from Baseline to Month 60	-68.4 (± 25)	-111.0 (± 31)	-4.6 (± 0.9)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Estimated Glomerular Filtration Rate (eGFR)

End point title	Estimated Glomerular Filtration Rate (eGFR)

End point description:

eGFR was calculated based on the serum creatinine values according to the CKD-EPI equation. The absolute change in eGFR from baseline measurement at visit 1 to Month 60 was summarized using descriptive statistics.

End point type	Other pre-specified

End point timeframe:

Up to 60 months.

End point values	Efficacy population	Male	Female	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	15	8	7	
Units: ml/min/1.73 m^2				
arithmetic mean (standard error)				
Baseline	111.7 (± 5.5)	118.1 (± 7.7)	104.4 (± 7.5)	
Month 60	97.0 (± 6.4)	100.0 (± 8.3)	92.4 (± 11.4)	
Change from Baseline to Month 60	-10.9 (± 2.0)	-14.5 (± 1.7)	-5.6 (± 2.6)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The AD were collected during the overall treatment period: from baseline (Visit 1 in study PB-102-F01) up to the end of study PB-102-F03 (up to 72 months per protocol).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	All patients

Reporting group description:

Analysis of AEs was preformed on TEAEs, defined as any AE occurring after the start of the first infusion of study treatment.

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 15 (20.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 15 (6.67%)		
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	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 15 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anogenital warts			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Melanocytic naevus			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Fatigue			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Pyrexia			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Asthenia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Feeling hot			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Infusion site bruising			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Injection site pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Oedema			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Peripheral swelling			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Seasonal allergy			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Breast tenderness			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pruritus genital			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 15 (33.33%)		
occurrences (all)	6		
Nasal congestion			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Oropharyngeal pain			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Paranasal sinus hypersecretion			

subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Emphysema			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	4		
Pleuritic pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pulmonary embolism			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Respiratory tract congestion			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Sleep apnoea syndrome			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Sneezing			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Wheezing			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Insomnia			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	3		
Cardiac murmur			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Chest X-ray abnormal			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Electrocardiogram ST segment abnormal			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Electrocardiogram ST segment depression			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Nuclear magnetic resonance imaging abnormal			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Clavicle fracture			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Contusion			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		

Humerus fracture subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Post-traumatic pain subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Sunburn subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Vaccination complication subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Congenital, familial and genetic disorders Fabry's disease subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 2		
Cardiac disorders Left ventricular dysfunction subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Left ventricular hypertrophy subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Palpitations subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Sinus arrhythmia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Tachycardia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 3		
Tricuspid valve incompetence subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Ventricular hypertrophy			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	12		
Paraesthesia			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	6		
Dizziness			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Balance disorder			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Burning sensation			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Migraine			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Neuralgia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Visual field defect			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Vertigo			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Deafness bilateral			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Ear discomfort			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hypoacusis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	9		
Abdominal pain			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	9		
Diarrhoea			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	9		
Haemorrhoids			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Inguinal hernia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Tooth disorder			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Toothache			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Vomiting			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Urticaria			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Acne			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Dermatitis allergic			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Dermatitis contact			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hypohidrosis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Night sweats			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	4		
Back pain			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Pain in extremity			

subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	4		
Musculoskeletal pain			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Clubbing			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Groin pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Intervertebral disc protrusion			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Joint swelling			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Muscle spasms			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Musculoskeletal stiffness			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Osteoarthritis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Spondyloarthropathy			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 15 (33.33%)		
occurrences (all)	8		
Upper respiratory tract infection			
subjects affected / exposed	5 / 15 (33.33%)		
occurrences (all)	8		

Influenza				
subjects affected / exposed	3 / 15 (20.00%)			
occurrences (all)	4			
Gastroenteritis viral				
subjects affected / exposed	2 / 15 (13.33%)			
occurrences (all)	2			
Bronchitis				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Gastroenteritis				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	3			
Herpes virus infection				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Lower respiratory tract infection				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	3			
Onychomycosis				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Pharyngitis				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Pneumonia				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Respiratory tract infection				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	3			
Sinusitis				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Subcutaneous abscess				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			

Tooth infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Viral infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 January 2016	Study extension from 24 month to 60 month.

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.

Small sample size.

Notes: