Clinical trial results:
An Open Label Study of the Safety and Efficacy of PRX 102 in Patients with Fabry Disease Currently Treated With REPLAGAL® (Agalsidase alfa)

Summary

EudraCT number	2016-001318-11
Trial protocol	GB ES CZ DE SI NL
Global end of trial date	17 December 2019

Results information

Result version number	v1 (current)
This version publication date	04 August 2021
First version publication date	04 August 2021

Trial information

Trial identification

Sponsor protocol code	PB-102-F30

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03018730
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Protalix.Ltd.
Sponsor organisation address	2 Snunit Street, Carmiel , Israel, 2161401
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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	04 November 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 December 2019
Global end of trial reached?	Yes
Global end of trial date	17 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and efficacy of PRX-102 (Pegunigalsidase alfa) in patients with Fabry disease treated with agalsidase alfa

Protection of trial subjects:

Premedication, if used for the agalsidase alfa infusions before enrolment, continued through the first infusion with pegunigalsidase alfa and then gradually tapered at the investigator's discretion during the first 2 months. The first infusions of PRX-102 will be administered under controlled conditions at the investigation site.
The patients received their infusions at a home care setup once the investigator and Sponsor Medical Director agreed that it is safe to do so.
Throughout the duration of the study, the Investigator closely monitor each subject for evidence of drug intolerance and for the development of clinical or laboratory evidence of adverse events.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 May 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety, Ethical reason
Long term follow-up duration	4 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Norway: 2
Country: Number of subjects enrolled	Slovenia: 1
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Czechia: 8
Worldwide total number of subjects	22
EEA total number of subjects	12

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)	0
Adults (18-64 years)	22
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients treated with agalsidase alfa for at least 2 years and on a stable dose (>80% labelled dose/kg) for at least 6 months. No more than 25% of treated patients will be female.

Pre-assignment

Screening details:

A total of 27 patients were screened and evaluated over 3 months while continuing on agalsidase alfa, of whom 22 patients (15 males and 7 females) were enrolled and treated with PRX-102, and 20 patients completed the study with 12 month of treatment.

Pre-assignment period milestones

Number of subjects started	22
Number of subjects completed	22

Period 1

Period 1 title	Overall trial (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 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 individual dose for each patient was prepared according to the patient's weight. pegunigalsidase alfa administrated at 1 mg/kg, intravenously over 3 hours, every 2 weeks. After the first 2 months of treatment with pegunigalsidase alfa, infusion time may be reduced gradually to 1.5 hours pending patient tolerability.

Number of subjects in period 1	pegunigalsidase alfa
Started	22
Completed	20
Not completed	2
Adverse event, non-fatal	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	22	22	
Age categorical Units: Subjects			
Adults (18-64 years)	22	22	
Age continuous Units: years			
arithmetic mean	44.0		
standard deviation	± 11.0	-	
Gender categorical Units: Subjects			
Female	7	7	
Male	15	15	
Presence of proteinuria (UPCR ≥0.5 g/g)			
Presence of proteinuria defined as subjects with urine protein to creatinine ratio ≥0.5 g/g			
Units: Subjects			
yes	4	4	
no	6	6	
Protein undetectable	12	12	
Treatment with ACEi or ARBs			
Treatment with Angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB)			
Units: Subjects			
yes	12	12	
no	10	10	
Baseline UPCR			
Urine Protein to Creatinine Ratio, assessed by spot urine test, based on 4 categories: Protein Undetectable (PU); Normal to mildly increased (UPCR <0.15 g/g); Moderately increased (UPCR ≥0.15 g/g and ≤0.5 g/g); Severely increased (UPCR >0.5 g/g).			
Units: Subjects			
No protein detectable	12	12	
Normal to mildly increased	3	3	
Moderately increased	3	3	
Severely increased	4	4	
Age started Fabry therapy			
Age at the start of Fabry therapy			
Units: years			
arithmetic mean	34.8		
standard deviation	± 11.9	-	
Residual enzyme activity in leukocytes (%)			
The residual Alpha-galactosidase-A enzymatic activity in leukocytes is a percentage of the normal laboratory mean			
Units: percentage			
arithmetic mean	12.2		

standard deviation	± 12.5	-	
Baseline eGFR (mL/min/1.73 m^2)			
An estimate of glomerular filtration rate (eGFR) is a mathematically derived value based on a patient's serum creatinine level, age, sex and race, which used to indicate the level of kidney function.			
Units: mL/min/1.73 m^2			
arithmetic mean	82.49		
standard deviation	± 23.38	-	
Baseline annualized eGFR slope (mL/min/1.73 m^2/year)			
Mean baseline annualized eGFR slope while on Replagal® (i.e., pre-switch to PRX-102 treatment)			
Units: mL/min/1.73 m^2/year			
arithmetic mean	-5.3		
standard deviation	± 6.3	-	
Baseline plasma Lyso-Gb3 (nmol/L)			
Baseline levels of Plasma Lyso-Gb3 (globotriaosylsphingosine)			
Units: nmol/L			
arithmetic mean	38.30		
standard deviation	± 41.22	-	

Subject analysis sets

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

Subject analysis set description:

The safety population consists of all subjects who received any dose of pegunigalsidase alfa (PRX-102) in the study.

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

Subject analysis set description:

The efficacy population (EP) consists of all subjects who have at least one visit with an efficacy evaluation after the first pegunigalsidase alfa (PRX-102) infusion.

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

Subject analysis set description:

Male subjects from Safety population.

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

Subject analysis set description:

Female subjects from Safety population.

Reporting group values	Safety population	Efficacy population	Male
Number of subjects	22	20	15
Age categorical Units: Subjects			
Adults (18-64 years)	22	20	15
Age continuous Units: years			
arithmetic mean	44.0	45.8	42.7
standard deviation	± 11.0	± 9.9	± 10.6
Gender categorical Units: Subjects			
Female	7	7	0
Male	15	13	15

Presence of proteinuria (UPCR ≥0.5 g/g)			
Presence of proteinuria defined as subjects with urine protein to creatinine ratio ≥0.5 g/g			
Units: Subjects			
yes	4	4	4
no	6	6	3
Protein undetectable	12	10	8
Treatment with ACEi or ARBs			
Treatment with Angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB)			
Units: Subjects			
yes	12	11	8
no	10	9	7
Baseline UPCR			
Urine Protein to Creatinine Ratio, assessed by spot urine test, based on 4 categories: Protein Undetectable (PU); Normal to mildly increased (UPCR <0.15 g/g); Moderately increased (UPCR ≥0.15 g/g and ≤0.5 g/g); Severely increased (UPCR >0.5 g/g).			
Units: Subjects			
No protein detectable	12	10	8
Normal to mildly increased	3	3	2
Moderately increased	3	3	1
Severely increased	4	4	4
Age started Fabry therapy			
Age at the start of Fabry therapy			
Units: years			
arithmetic mean	34.8	36.6	32.6
standard deviation	± 11.9	± 10.7	± 11.8
Residual enzyme activity in leukocytes (%)			
The residual Alpha-galactosidase-A enzymatic activity in leukocytes is a percentage of the normal laboratory mean			
Units: percentage			
arithmetic mean	12.2	13.1	4.8
standard deviation	± 12.5	± 12.7	± 2.5
Baseline eGFR (mL/min/1.73 m^2)			
An estimate of glomerular filtration rate (eGFR) is a mathematically derived value based on a patient's serum creatinine level, age, sex and race, which used to indicate the level of kidney function.			
Units: mL/min/1.73 m^2			
arithmetic mean	82.49	79.46	80.78
standard deviation	± 23.38	± 22.01	± 25.97
Baseline annualized eGFR slope (mL/min/1.73 m^2/year)			
Mean baseline annualized eGFR slope while on Replagal® (i.e., pre-switch to PRX-102 treatment)			
Units: mL/min/1.73 m^2/year			
arithmetic mean	-5.27	-5.90	-5.38
standard deviation	± 6.27	± 5.99	± 7.12
Baseline plasma Lyso-Gb3 (nmol/L)			
Baseline levels of Plasma Lyso-Gb3 (globotriaosylsphingosine)			
Units: nmol/L			
arithmetic mean	38.30	38.51	49.73
standard deviation	± 41.22	± 43.31	± 45.75

Reporting group values	Female		
Number of subjects	7		

Age categorical Units: Subjects			
Adults (18-64 years)	7		
Age continuous Units: years			
arithmetic mean	46.7		
standard deviation	± 12.3		
Gender categorical Units: Subjects			
Female	7		
Male	0		
Presence of proteinuria (UPCR ≥0.5 g/g)			
Presence of proteinuria defined as subjects with urine protein to creatinine ratio ≥0.5 g/g			
Units: Subjects			
yes	0		
no	3		
Protein undetectable	4		
Treatment with ACEi or ARBs			
Treatment with Angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB)			
Units: Subjects			
yes	4		
no	3		
Baseline UPCR			
Urine Protein to Creatinine Ratio, assessed by spot urine test, based on 4 categories: Protein Undetectable (PU); Normal to mildly increased (UPCR <0.15 g/g); Moderately increased (UPCR ≥0.15 g/g and ≤0.5 g/g); Severely increased (UPCR >0.5 g/g).			
Units: Subjects			
No protein detectable	4		
Normal to mildly increased	1		
Moderately increased	2		
Severely increased	0		
Age started Fabry therapy			
Age at the start of Fabry therapy			
Units: years			
arithmetic mean	39.4		
standard deviation	± 11.6		
Residual enzyme activity in leukocytes (%)			
The residual Alpha-galactosidase-A enzymatic activity in leukocytes is a percentage of the normal laboratory mean			
Units: percentage			
arithmetic mean	27.9		
standard deviation	± 10.2		
Baseline eGFR (mL/min/1.73 m^2)			
An estimate of glomerular filtration rate (eGFR) is a mathematically derived value based on a patient's serum creatinine level, age, sex and race, which used to indicate the level of kidney function.			
Units: mL/min/1.73 m^2			
arithmetic mean	86.14		
standard deviation	± 17.78		
Baseline annualized eGFR slope (mL/min/1.73 m^2/year)			
Mean baseline annualized eGFR slope while on Replagal® (i.e., pre-switch to PRX-102 treatment)			
Units: mL/min/1.73 m^2/year			

arithmetic mean	-5.03		
standard deviation	± 4.37		
Baseline plasma Lyso-Gb3 (nmol/L)			
Baseline levels of Plasma Lyso-Gb3 (globotriaosylsphingosine)			
Units: nmol/L			
arithmetic mean	13.81		
standard deviation	± 6.11		

End points

End points reporting groups

Reporting group title	pegunigalsidase alfa
Reporting group description: pegunigalsidase alfa 1mg/Kg every other week	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description: The safety population consists of all subjects who received any dose of pegunigalsidase alfa (PRX-102) in the study.	
Subject analysis set title	Efficacy population
Subject analysis set type	Per protocol
Subject analysis set description: The efficacy population (EP) consists of all subjects who have at least one visit with an efficacy evaluation after the first pegunigalsidase alfa (PRX-102) infusion.	
Subject analysis set title	Male
Subject analysis set type	Sub-group analysis
Subject analysis set description: Male subjects from Safety population.	
Subject analysis set title	Female
Subject analysis set type	Sub-group analysis
Subject analysis set description: Female subjects from Safety 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 possibly, probably, or definitely related to treatment	
End point type	Primary
End point timeframe: 12 months	

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	Safety population			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: subjects				
At least 1 TEAE	21			
At least 1 mild or moderate TEAE	19			
At least 1 severe TEAE	4			
At least 1 SAE	4			
At least 1 TEAE unrelated or unlikely related	19			
At least 1 TEAE related to study treatment	5			

At least 1 SAE related to study treatment	2			
At least 1 TEAE leading to discontinuation	2			
At least 1 TEAE leading to death	0			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Annualized Estimated Glomerular Filtration Rate Slope

End point title	Annualized Estimated Glomerular Filtration Rate Slope

End point description:

The annualized change in eGFR (slope) per patient was estimated using a linear regression, between the baseline annualized eGFR slope pre-switch to PRX-102 treatment (while on Replagal®) to the annualized eGFR slope post-switch to PRX-102 treatment, using all available eGFR values collected in the timeframe. eGFR was calculated based on the serum creatinine values according to the CKD-EPI formula.

End point type	Other pre-specified

End point timeframe:

12 months

End point values	Efficacy population	Male	Female	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	13	7	
Units: mL/min/1.73 m^2/year				
arithmetic mean (standard error)				
pre-switch	-5.90 (± 1.34)	-6.36 (± 1.89)	-5.03 (± 1.65)	
post-switch	-1.19 (± 1.77)	-1.73 (± 2.64)	-0.21 (± 1.47)	
Change in eGFR slope from pre- to post-switch	4.70 (± 2.26)	4.63 (± 3.48)	4.83 (± 1.09)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Estimated Glomerular Filtration Rate

End point title	Estimated Glomerular Filtration Rate

End point description:

eGFR was calculated based on the serum creatinine values according to the CKD-EPI formula. The absolute change in eGFR from baseline measurement at visit 1 to last measurement at Month 12 was summarized using descriptive statistics.

End point type	Other pre-specified

End point timeframe:

12 Month

End point values	Efficacy population	Male	Female	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	13	7	
Units: mL/min/1.73 m^2				
arithmetic mean (standard error)				
Baseline eGFR	79.46 (± 4.92)	75.87 (± 6.62)	86.14 (± 6.72)	
Month 12 eGFR	76.91 (± 5.22)	74.27 (± 7.15)	81.80 (± 7.09)	
Change in eGFR from baseline to Month 12	-2.56 (± 2.14)	-1.60 (± 2.76)	-4.34 (± 3.54)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Left Ventricular Mass Index

End point title	Left Ventricular Mass Index

End point description:

Left ventricular mass was determined based on cardiac MRI data and the LVMI was indexed to patient's body surface area (g/m^2). In male patients the normal range for LVMI was 57-91 g/m2, in female patients 47–77 g/m2.

End point type	Other pre-specified

End point timeframe:

12 Month

End point values	Efficacy population	Male	Female	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	13	7	
Units: g/m^2				
arithmetic mean (standard error)				
Baseline	86.9 (± 6.9)	97.6 (± 8.9)	66.9 (± 5.8)	
Visit 27 (Week 52)	89.4 (± 6.1)	98.3 (± 7.8)	74.1 (± 7.2)	
Change from Baseline	4.1 (± 2.8)	2.4 (± 3.4)	7.1 (± 5.0)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Quality of life by EQ VAS

End point title	Quality of life by EQ VAS

End point description:

The EQ VAS, of the EQ 5D 5L questionnaire, records the subject's self-rated health on a vertical, visual analogue scale where the endpoints are labelled 'Best imaginable health state' (score "100") and 'Worst imaginable health state' (score "0").

End point type	Other pre-specified

End point timeframe:

12 months

End point values	Efficacy population	Male	Female	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	13	7	
Units: score				
arithmetic mean (standard error)				
Baseline	71.8 (± 4.3)	66.8 (± 5.3)	81.1 (± 6.1)	
Month 12	76.9 (± 4.5)	71.5 (± 5.4)	86.7 (± 7.0)	
Change from Baseline	5.1 (± 3.3)	4.8 (± 4.9)	5.6 (± 3.0)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Plasma Lyso-Gb3

End point title	Plasma Lyso-Gb3

End point description:

Lyso-Gb3 is Fabry disease specific biomarker that can assess treatment outcome.

End point type	Other pre-specified

End point timeframe:

12 month

End point values	Efficacy population	Male	Female	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	13	7	
Units: nM				
arithmetic mean (standard error)				
Baseline	38.51 (± 9.68)	51.81 (± 13.60)	13.81 (± 2.31)	
Visit 27 (Week 52)	24.20 (± 5.10)	32.25 (± 6.89)	9.24 (± 1.08)	
Change from Baseline	-14.31 (± 5.13)	-19.55 (± 7.55)	-4.57 (± 1.42)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Urine Protein/Creatinine Ratio (UPCR)

End point title	Urine Protein/Creatinine Ratio (UPCR)

End point description:

Urine Protein to Creatinine Ratio (UPCR), assessed by spot urine test, at Visit 27 (Week 52).

End point type	Other pre-specified

End point timeframe:

12 month

End point values	Efficacy population	Male	Female	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	13	7	
Units: subjects				
Protein Undetectable	9	7	2	
Normal to Mildly increased	4	2	2	
Moderately increased	2	0	2	
Severely increased	5	4	1	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were collected from the beginning of the treatment throughout the 12 months of the study, including a follow-up at the end of the study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	All patients

Reporting group description:

Analysis of AEs was performed 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	4 / 22 (18.18%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Immune system disorders			
Type I hypersensitivity			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infectious mononucleosis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 22 (4.55%)		
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	21 / 22 (95.45%)		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Infusion related reaction			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	3		
Cardiac disorders			
Plapitations			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 22 (22.73%)		
occurrences (all)	5		
Dizziness			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	8		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Immune system disorders			
Type 1 hypersensitivity			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Gastrointestinal disorders			
Gastroesophageal reflux disease			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Toothache			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Oropharyngeal pain			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Rash pruritic			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Erythema			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Rash			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Back pain			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 22 (31.82%)		
occurrences (all)	9		
Lower respiratory tract infection			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		

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