Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Intranasal Midazolam (USL261) in the Outpatient Treatment of Subjects with Seizure Clusters
ARTEMIS-1: Acute Rescue Therapy in Epilepsy with Midazolam Intranasal Spray-1

Summary

EudraCT number	2011-001318-32
Trial protocol	ES DE IT HU PL
Global end of trial date	20 March 2017

Results information

Result version number	v1
This version publication date	21 September 2019
First version publication date	21 September 2019

Trial information

Trial identification

Sponsor protocol code	P261-401

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01390220
WHO universal trial number (UTN)	-
Other trial identifiers	US IND number: 77,421

Notes:

Sponsors

Sponsor organisation name	Proximagen, LLC
Sponsor organisation address	505 North Highway 169, Plymouth, MN, United States, 55441
Public contact	David Sequeira, Proximagen, LLC, +1 952-658-7438, dsequeira@proximagen.com
Scientific contact	David Sequeira, Proximagen, LLC, +1 952-658-7438, dsequeira@proximagen.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	17 April 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 March 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary efficacy objective of this study was to evaluate the efficacy of USL261 compared with that of intranasal (IN) placebo for the outpatient treatment of seizure clusters based on Treatment Success, which was defined as achieving both of the following:
• Termination of seizure(s) within 10 minutes after study drug administration, and
• No recurrence of seizure(s) beginning 10 minutes after study drug administration to 6 hours after study drug administration

Protection of trial subjects:

Before the initiation of the clinical trial, the protocol, consent form, and advertisements for the recruitment of participants were reviewed and approved by the institutional review board (IRB) of the participating study center, in accordance with current Good Clinical Practices (GCP) and all applicable regulatory requirements. All protocol amendments and changes to the informed consent form (ICF) occurring during the study were also approved by the IRB. This clinical trial was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki, 1964, and with adherence to the principles of GCP, outlined by the International Council for Harmonisation's (ICH's) GCP Guidelines, effective 1997. If new safety information resulted in significant changes to the risk/benefit assessment, the consent form was to be reviewed and updated if necessary. All participants (including those already being treated) were to be informed, given a copy of the revised form, and asked to give their consent to continue in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 June 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 14
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Hungary: 18
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	New Zealand: 1
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	United States: 118
Country: Number of subjects enrolled	Ukraine: 70
Country: Number of subjects enrolled	Israel: 18
Country: Number of subjects enrolled	Australia: 19

Worldwide total number of subjects	292
EEA total number of subjects	62

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)	18
Adults (18-64 years)	272
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This multicenter trial was conducted at 105 trial sites in the following 11 countries: United States of America (USA), Canada, Australia, Germany, Hungary, Israel, Italy, New Zealand, Poland, Spain, Ukraine.

Pre-assignment

Screening details:

Participants underwent in-clinic administration of open-label USL261 5 mg followed by USL261 5 mg 10 minutes in absence of a seizure (Test Dose Phase [TDP]). Participants were then randomized to double-blind USL261 5 mg or Placebo to be administered by caregiver to treat a seizure cluster in Comparative Phase (CP) in the outpatient setting.

Period 1

Period 1 title	TDP
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

USL261 was not blinded for the Test Dose Phase

Arms

Arm title	USL261 TDP

Arm description:

Participants received at least 1 open-label USL261 5 mg dose in TDP.

Arm type	Experimental
Investigational medicinal product name	USL261
Investigational medicinal product code	USL261
Other name	
Pharmaceutical forms	Nasal spray, solution
Routes of administration	Intranasal use

Dosage and administration details:

A dose of USL261 (5 mg midazolam [MDZ]) was delivered with a single actuation of the unit dose pump.

Number of subjects in period 1	USL261 TDP
Started	292
Completed	201
Not completed	91
Study/Site closure	6
Adverse Event	17
Caregiver no longer available	5
Logistical	6
Consent withdrawn by participant	8
Lost to follow-up	2
No treated seizure cluster episode	37

Protocol deviation	8
Noncompliance	2

Period 2

Period 2 title	CP
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

USL261 was not blinded for the TDP or for the second dose provided to some participants during the CP; however, blinding was considered important for safety and efficacy assessments for the first dose of the CP. The drug name did not appear on the label, and neither the investigator/study center staff nor the participant/caregiver knew the identity of the randomized medication.

Arms

Are arms mutually exclusive?	Yes
Arm title	USL261 CP

Arm description:

Participants completing TDP who received USL261 5 mg as randomized dose to treat a seizure cluster episode in the CP.

Arm type	Experimental
Investigational medicinal product name	USL261
Investigational medicinal product code	USL261
Other name	
Pharmaceutical forms	Nasal spray, solution
Routes of administration	Intranasal use

Dosage and administration details:

A dose of USL261 (5 mg MDZ) was delivered with a single actuation of the unit dose pump.

Arm title	Placebo CP

Arm description:

Participants completing TDP who received placebo as randomized dose to treat a seizure cluster episode in the CP.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray, solution
Routes of administration	Intranasal use

Dosage and administration details:

Matching placebo was administered.

Number of subjects in period 2	USL261 CP	Placebo CP
Started	134	67
Completed	133	67
Not completed	1	0
Consent withdrawn by participant	1	-

Baseline characteristics

Reporting groups	
Reporting group title	USL261 TDP
Reporting group description:	
Participants received at least 1 open-label USL261 5 mg dose in TDP.	

Reporting group values	USL261 TDP	Total	
Number of subjects	292	292	
Age categorical			
USL261 Test Dose: All participants receiving at least 1 dose of USL261 5 mg in TDP.			
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)	0	0	
Adolescents (12-17 years)	18	18	
Adults (18-64 years)	272	272	
From 65-84 years	2	2	
85 years and over	0	0	
Age continuous			
Units: years			
median	31.5		
full range (min-max)	12 to 65	-	
Gender categorical			
Units: Subjects			
Female	146	146	
Male	146	146	
Ethnicity			
Units: Subjects			
Hispanic or Latino	22	22	
Not Hispanic or Latino	270	270	
Race			
Units: Subjects			
White	275	275	
Asian	2	2	
American Indian or Alaska Native	2	2	
Black or African American	7	7	
Native Hawaiian or Other Pacific Islander	1	1	
Other	5	5	
Body mass index (BMI)			
Measure Analysis Population Description: Height not measurable in some participants. Number analyzed (n) = 287			
Units: kg/m2			
median	24.69		
full range (min-max)	15.8 to 48.5	-	

Number of seizure cluster episodes in 1 year before Visit 1 of the Study Units: seizure cluster episodes median full range (min-max)	 15.0 3 to 999	 -	
Number of years that participant has had seizure clusters prior to study			
Measure Analysis Population Description: Unknown or data entered as indefinite (eg >3) for some participants. n = 283			
Units: Years median full range (min-max)	 6.00 0.3 to 62.0	 -	
Typical number of seizures in seizure cluster episode			
Measure Analysis Population Description: Not reported for 1 participant. n = 291			
Units: seizures median full range (min-max)	 6.00 2.0 to 200.0	 -	
Typical duration of seizure cluster episode			
Measure Analysis Population Description: Non-numerical duration (eg "several" hours reported for some participants. n = 278			
Units: minutes median full range (min-max)	 67.50 2.5 to 4320.0	 -	

End points

End points reporting groups

Reporting group title	USL261 TDP
Reporting group description:	
Participants received at least 1 open-label USL261 5 mg dose in TDP.	
Reporting group title	USL261 CP
Reporting group description:	
Participants completing TDP who received USL261 5 mg as randomized dose to treat a seizure cluster episode in the CP.	
Reporting group title	Placebo CP
Reporting group description:	
Participants completing TDP who received placebo as randomized dose to treat a seizure cluster episode in the CP.	

Primary: Participants Who Met the Criteria for Treatment Success After Administration of the Double-blind Dose in the CP

End point title	Participants Who Met the Criteria for Treatment Success After Administration of the Double-blind Dose in the CP
End point description:	
Treatment Success is defined as achieving both of the following: 1) termination of seizure(s) within 10 minutes after double-blind study drug administration, and 2) no recurrence of seizure(s) beginning 10 minutes after study drug administration to 6 hours after study drug administration. Participants who received the open-label second dose within 6 hours of administration of the double-blind dose were analyzed as having had a seizure.	
End point type	Primary
End point timeframe:	
6 hours	

End point values	USL261 CP	Placebo CP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	67		
Units: Participants				
number (not applicable)	72	23		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	USL261 CP v Placebo CP

Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0109 [1]
Method	Fisher exact

Notes:

[1] - 2-sided p-value from Fisher’s exact test

Secondary: Participants With Seizure(s) >10 Minutes to 4 Hours After Administration of the Double-blind Dose

End point title	Participants With Seizure(s) >10 Minutes to 4 Hours After Administration of the Double-blind Dose

End point description:

Participants with recurrence of seizure(s) >10 minutes and up to 4 hours after administration of the double-blind dose in the CP. Participants who received the open-label second dose within 4 hours of administration of the double-blind dose were analyzed as having had a seizure.

End point type	Secondary

End point timeframe:

4 hours

End point values	USL261 CP	Placebo CP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	67		
Units: Participants				
number (not applicable)	51	40		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	USL261 CP v Placebo CP
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0043 [2]
Method	Fisher exact

Notes:

[2] - 2-sided

Secondary: Occurrence of Seizure With a Start Time >10 Minutes After Administration of the Double-blind Dose

End point title	Occurrence of Seizure With a Start Time >10 Minutes After Administration of the Double-blind Dose

End point description:

Occurrence of next seizure with a start time >10 minutes and up to 24 hours after administration of the double-blind dose in the CP. Participants who did not have another seizure before the end of the 24-hour observation period were censored at the end of the observation period. Participants administered the open-label second dose who did not have a seizure were censored at the time of the administration.

End point type	Secondary

End point timeframe:

24 hours

End point values	USL261 CP	Placebo CP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	67		
Units: Participants				
number (not applicable)	50	31		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo CP v USL261 CP
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0124
Method	Logrank

Secondary: Time to Next Seizure With a Start Time >10 Minutes After Administration of the Double-blind Dose

End point title	Time to Next Seizure With a Start Time >10 Minutes After Administration of the Double-blind Dose

End point description:

Time to next seizure with a start time >10 minutes and up to 24 hours after administration of the double-blind dose in the CP. Participants who did not have another seizure before the end of the 24-hour observation period were censored at the end of the observation period. Participants administered the open-label second dose who did not have a seizure were censored at the time of the administration.
99.99999=Not Available (NA)
For USL261 CP: Required data are NA since median was not estimable as probability of no seizures through 24 hours was above 50%. Upper bound of 95% CI was not estimable.
For Placebo CP: Required data are NA since upper bound of 95% CI was not estimable.

End point type	Secondary

End point timeframe:

24 hours

End point values	USL261 CP	Placebo CP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	67		
Units: Hours				
median (confidence interval 95%)	99.99999 (17.9 to 99.99999)	12.1 (2.2 to 99.99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Kaplan-Meier estimates.	
Comparison groups	USL261 CP v Placebo CP
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0124
Method	Logrank

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events (TEAEs) collected from administration of first open-label dose of USL261 5 mg in TDP until completion of the final study visit or 7 days after the last administration of study drug, whichever was later.

Adverse event reporting additional description:

Adverse events collected at each visit from participant and/or caregiver. TEAEs presented for TDP and CP separately. Due to the short systemic half-life of active (midazolam), TEAEs within 2 days after administration of first open-label USL261 5 mg dose presented for TDP, and within 2 days after administration of double-blind dose for CP.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	USL261 TDP

Reporting group description:

Participants who received at least 1 open-label USL261 5 mg dose in TDP

Reporting group title	USL261 CP, USL261 5 mg Only

Reporting group description:

Participants completing TDP who received USL261 5 mg as randomized dose to treat a seizure cluster episode in the CP

Reporting group title	USL261 CP, USL261 5 mg + 5 mg

Reporting group description:

Participants completing TDP who received USL261 5 mg as randomized dose to treat a seizure cluster episode and received an open-label USL261 5 mg dose in the CP

Reporting group title	Placebo CP, Placebo Only

Reporting group description:

Participants completing TDP who received Placebo as randomized dose to treat a seizure cluster episode in the CP

Reporting group title	Placebo CP, Placebo + USL261 5 mg

Reporting group description:

Participants completing TDP who received Placebo as randomized dose to treat a seizure cluster episode and received an open-label USL261 5 mg dose in the CP

Serious adverse events	USL261 TDP	USL261 CP, USL261 5 mg Only	USL261 CP, USL261 5 mg + 5 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 292 (0.68%)	0 / 91 (0.00%)	0 / 43 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Sedation			
subjects affected / exposed	1 / 292 (0.34%)	0 / 91 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Seizure cluster			
subjects affected / exposed	0 / 292 (0.00%)	0 / 91 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	1 / 292 (0.34%)	0 / 91 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo CP, Placebo Only	Placebo CP, Placebo + USL261 5 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 26 (0.00%)	1 / 41 (2.44%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Sedation			
subjects affected / exposed	0 / 26 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure cluster			
subjects affected / exposed	0 / 26 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	0 / 26 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	USL261 TDP	USL261 CP, USL261 5 mg Only	USL261 CP, USL261 5 mg + 5 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	78 / 292 (26.71%)	17 / 91 (18.68%)	10 / 43 (23.26%)
Nervous system disorders			

Headache			
subjects affected / exposed	1 / 292 (0.34%)	6 / 91 (6.59%)	1 / 43 (2.33%)
occurrences (all)	1	6	1
Somnolence			
subjects affected / exposed	28 / 292 (9.59%)	9 / 91 (9.89%)	4 / 43 (9.30%)
occurrences (all)	30	9	4
General disorders and administration site conditions			
Product taste abnormal			
subjects affected / exposed	17 / 292 (5.82%)	4 / 91 (4.40%)	0 / 43 (0.00%)
occurrences (all)	19	4	0
Eye disorders			
Lacrimation increased			
subjects affected / exposed	20 / 292 (6.85%)	1 / 91 (1.10%)	1 / 43 (2.33%)
occurrences (all)	26	1	1
Respiratory, thoracic and mediastinal disorders			
Nasal discomfort			
subjects affected / exposed	47 / 292 (16.10%)	5 / 91 (5.49%)	7 / 43 (16.28%)
occurrences (all)	61	5	8
Throat irritation			
subjects affected / exposed	15 / 292 (5.14%)	2 / 91 (2.20%)	3 / 43 (6.98%)
occurrences (all)	15	2	3

Non-serious adverse events	Placebo CP, Placebo Only	Placebo CP, Placebo + USL261 5 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 26 (11.54%)	7 / 41 (17.07%)	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 26 (0.00%)	0 / 41 (0.00%)	
occurrences (all)	0	0	
Somnolence			
subjects affected / exposed	1 / 26 (3.85%)	4 / 41 (9.76%)	
occurrences (all)	1	4	
General disorders and administration site conditions			
Product taste abnormal			
subjects affected / exposed	0 / 26 (0.00%)	0 / 41 (0.00%)	
occurrences (all)	0	0	

Eye disorders Lacrimation increased subjects affected / exposed occurrences (all)	 0 / 26 (0.00%) 0	 1 / 41 (2.44%) 1	
Respiratory, thoracic and mediastinal disorders Nasal discomfort subjects affected / exposed occurrences (all) Throat irritation subjects affected / exposed occurrences (all)	 2 / 26 (7.69%) 2 0 / 26 (0.00%) 0	 3 / 41 (7.32%) 3 1 / 41 (2.44%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 December 2012	Amendment 1: • To clarify the definition of recurrence of seizures; • To clarify efficacy versus safety objectives and to modify secondary and exploratory objectives; • To provide observation periods for the time to next seizure after study drug administration; • To clarify instructions for administering the second dose of study drug; • To clarify that medical history was to be taken at Visit 1 only; • To update the safety objectives and assessments to streamline the list of safety assessments; • To clarify inclusion and exclusion criteria; • To add test for phenobarbital in participants; • To clarify that the caregiver is to record the actual time of return to baseline activity; • To clarify requirement for training of the caregiver; • To remove the requirement to have a legally acceptable representative (LAR) co-sign the assent document with the participant; • Participant and caregiver satisfaction questionnaire, quality of life (QOL), and other health economic assessments at Visit 2 was moved from post-dose to before the administration of the first test dose; • To change the maximum amount of blood to be collected for PK analyses from 275 mL to 50 mL; • To update the permitted and prohibited medications and substances; • To include more information on the use of flumazenil in treating MDZ overdose per prescribing information of MDZ injection; • To clarify that adverse events (AEs) and serious adverse events (SAEs) were to be collected until 30 days after completing of the final study Visit; • To clarify statistical methodology; • To adjust time window for the occurrence of Visit 4 from 48 to 120 hours after study drug administration to 24 to 120 hours after study drug administration; • To add windows for completion of assessments at Visit 2 and change measurement of temperature to pre-dose only; • To allow extension of the Screening period; • To clarify instructions for repeating out-of-range vital signs.
20 October 2014	Amendment 2: • To modify the trial to utilize a group sequential design with 3 interim analyses and a maximum of approximately 240 participants who have completed the CP; • To remove the requirement for emergency rescue treatment with assisted breathing or intubation within 24 hours after study drug administration; • To decrease the lower age (from 14 to 12 years of age) and remove the upper age restriction from Inclusion Criterion 3; • To modify the definition of intermittent use of benzodiazepines to clarify that benzodiazepines are allowed provided they are typically used ≤ 3 days within a 7-day period; • To reduce the minimum observation time at the Test Dose Visit from 4 hours to 1 hour for all new test dosed participants after the originally planned 132 participants completed the CP; • To modify Exclusion Criterion 22 to clarify that a that a ≥ 40 mmHg decrease from baseline in systolic blood pressure (SBP) and a ≥ 30 mmHg decrease from baseline in diastolic blood pressure (DBP) during the observation period after administration of the USL261 test dose at Visit 2 were exclusionary; • To remove date and time of recognition of seizure cluster(s) eligible for treatment with study drug from the list of efficacy assessments; • To reduce the AE reporting time frame from 30 days after the last administration of study drug to 7 days after the last administration of study drug; • To clarify that participants who did not have sufficient available data to confirm whether they could be classified either as "Treatment Success" or as "Not a Treatment Success" were considered to have missing data; • To clarify that the PK profile after administration of any dose of USL261 would be evaluated, not just after 10 mg; • To update the statistical and PK analyses to provide additional detail on the planned analyses; • To clarify that participants who had not treated a seizure cluster meeting the study criteria within 6 months of randomization were to be discontinued from the study.

26 February 2015	Amendment 3: • To update the definition of modified Intent-to-Treat (mITT) to maintain the wording in the original protocol (include only those participants who received at least 1 dose of study drug during the CP and who had any post-treatment efficacy assessments); • To update the statistical analysis of the primary efficacy endpoint to maintain the analyses in the original protocol and add chi-squared test as a sensitivity analysis.
20 May 2015	Amendment 4: • To add the Brief Smell Identification Test (B-SIT) at US sites to assess the effects of USL261 on olfaction; • To update the procedures to be completed at Visits 1, 4, and on the monthly telephone follow-up calls between Visit 3 and Visit 4; • To update the introduction section to reflect current study status; • To clarify that the time between Visit 2 and Visit 3 may be extended, and that the extension must be approved by the Sponsor or Clinical Research Organization designee.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
22 February 2017	Due to business reasons, the study was stopped with a final sample size of 201 completed participants. Since the study was stopped prematurely, a conservative statistical approach was used for the final analysis.	-

Notes:

Limitations and caveats

None reported