Clinical trial results:
A Phase 2, Randomized, Double-Blind, Placebo-Controlled, 3-Period Crossover, Positive Control, QT-Evaluation Study of APL-130277 in Patients with Parkinson's Disease Complicated by Motor Fluctuations ("OFF" Episodes)

Summary

EudraCT number	2016-001762-29
Trial protocol	IT
Global end of trial date	21 December 2017

Results information

Result version number	v1 (current)
This version publication date	06 January 2019
First version publication date	06 January 2019

Trial information

Trial identification

Sponsor protocol code	CTH-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03187301
WHO universal trial number (UTN)	-
Other trial identifiers	CTH-201: CTH-201

Notes:

Sponsors

Sponsor organisation name	Sunovion Pharmaceuticals Inc.
Sponsor organisation address	84 Waterford Drive, Marlboro, United States, 01752
Public contact	CNS Medical Director, SUNOVION PHARMACEUTICALS, +01 1-866-503-6351, ClinicalTrialDisclosure@sunovion.com
Scientific contact	CNS Medical Director, SUNOVION PHARMACEUTICALS, +01 1-866-503-6351, ClinicalTrialDisclosure@sunovion.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	21 December 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 December 2017
Global end of trial reached?	Yes
Global end of trial date	21 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate the effect of APL-130277 compared to placebo on QTc intervals in subjects with Parkinson’s disease (PD) complicated by motor fluctuations.

Protection of trial subjects:

The study was conducted according to the protocol, ICH Good Clinical Practice (GCP), ICH guidelines, and the ethical principles that have their origin in the Declaration of Helsinki

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 October 2016
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	Italy: 19
Country: Number of subjects enrolled	United States: 29
Worldwide total number of subjects	48
EEA total number of subjects	19

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)	26
From 65 to 84 years	21
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Patients with Parkinson's disease (PD) complicated by motor fluctuations ('OFF' episodes) were recruited in 13 study sites in Italy and the United States, starting April 2017. The study was completed in December 2017. Approval was obtained from the Enrollment Adjudication Committee and Sponsor prior to enrollment of each patient.

Pre-assignment

Screening details:

Dose Titration Phase: individual responses to single doses of APL 130277 were evaluated at 5 mg increments up to 40 mg and then 10 mg increments up to 60 mg until a full 'ON' was achieved. If tolerated, patients were titrated to a supratherapeutic dose (up to 60 mg) which was 1 or 2 levels above the initial dose producing an 'ON' response.

Period 1

Period 1 title	Period 1
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	APL-130277 (Titration)

Arm description:

Patients were titrated to an effective and tolerable dose of APL-130277. Patients were dosed with increasing doses of APL 130277 starting with 10 mg at Titration Visit (TV) 1 up to a maximum of 60 mg. Patients who did not achieve a complete and full 'ON' response with the 10 mg APL 130277 dose at TV1 restarted their normal PD medications and were asked to return to the clinic the next business day for TV2, to assess the next highest dose. The evaluation continued sequentially with 15 mg (TV2), 20 mg (TV3), 25 mg (TV4), 30 mg (TV5), 35 mg (TV6), 40 mg (TV7), 50 mg (TV8), and 60 mg (TV9) doses of APL-130277 until a full 'ON' state was achieved. If tolerated, patients were titrated to a supratherapeutic dose (up to 60 mg) which was 1 or 2 levels above the initial dose producing an 'ON' response. If the patient was unable to tolerate 1 or either of the 2 additional dose levels after reaching a full "ON" state patients were randomized to the previous tolerable dose.

Arm type	Experimental
Investigational medicinal product name	APL-130277
Investigational medicinal product code	
Other name	Apomorphine sublingual film
Pharmaceutical forms	Sublingual film
Routes of administration	Sublingual use

Dosage and administration details:

Patients received single doses of APL-130277 from 10 mg to 60 mg sequentially as required to elicit a full 'ON' response.

Number of subjects in period 1	APL-130277 (Titration)
Started	48
Completed	41
Not completed	7
Consent withdrawn by subject	1
Adverse event, non-fatal	5

reason unspecified	1

Period 2

Period 2 title	Period 2
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Arm title	Overall Crossover

Arm description:

Patients who successfully completed the Dose Titration Phase of the study were randomized to 1 of 6 treatment sequences in the single-dose Randomized Crossover Assessment Phase. Following confirmation by both the Investigator and the patient that the patient was in the 'OFF' state, the patient was dosed according to the patient's random treatment assignment with 1. APL-130277 at the dose determined in the Dose Titration Phase; OR 2. Matched placebo APL-130277; OR 3. A single 400 mg dose of moxifloxacin. Patients were randomized in equal numbers to 6 possible sequences of the above 3 study treatments determined by a 3-way balanced crossover design.

There was a 3-day washout period between treatment period dosing visits. Dosing of APL-130277 and placebo was double-blinded, and dosing of moxifloxacin was open-label.

Arm type	Experimental
Investigational medicinal product name	APL-130277
Investigational medicinal product code	
Other name	Apomorphine sublingual film
Pharmaceutical forms	Sublingual film
Routes of administration	Sublingual use

Dosage and administration details:

Patients received a single dose of APL-130277 in the relevant treatment period dosing visit.

Investigational medicinal product name	Moxifloxacin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients received a 400 mg dose of moxifloxacin in the relevant treatment period dosing visit.

Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sublingual film
Routes of administration	Sublingual use

Dosage and administration details:

Patients received a single dose of placebo in the relevant treatment period dosing visit.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: period one was the titration period to get to the baseline period (period 2)

Number of subjects in period 2[2][3]	Overall Crossover
Started	40
Completed	40

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The number of subjects in the baseline period, came from the titration period and that is where the 48 subjects came from - 48 were in tritration and 40 were in baseline

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 1. APL-130277 (Titration): Patients who completed the Dose Titration Phase in Period 1 (N=41) were eligible to proceed to randomization in the crossover phase (Period 2). One patient discontinued prior to receiving any study medication; therefore, a total of 40 patients were dosed with study medication in the crossover phase (Period 2) 2. Overall Crossover: Patients who completed the Dose Titration Phase in Period 1 were randomized to 1 of 6 treatment sequences to receive each of the treatments

Baseline characteristics

Reporting groups	
Reporting group title	Period 2
Reporting group description:	
Patients who successfully completed the Dose Titration Phase of the study were randomized to 1 of 6 treatment sequences in the single-dose Randomized Crossover Assessment Phase. Following confirmation by both the Investigator and the patient that the patient was in the 'OFF' state, the patient was dosed according to the patient's random treatment assignment with 1. APL-130277 at the dose determined in the Dose Titration Phase; OR 2. Matched placebo APL-130277; OR 3. A single 400 mg dose of moxifloxacin. Patients were randomized in equal numbers to 6 possible sequences of the above 3 study treatments determined by a 3-way balanced crossover design. There was a 3-day washout period between treatment period dosing visits. Dosing of APL-130277 and placebo was double-blinded, and dosing of moxifloxacin was open-label.	

Reporting group values	Period 2	Total	
Number of subjects	40	40	
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)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	25	25	
From 65-84 years	15	15	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	14	14	
Male	26	26	
Presence of a Rest Tremor at the Time of Diagnosis Units: Subjects			
yes	27	27	
no	13	13	
Type of 'OFF' Episodes Experienced Units: Subjects			
Morning akinesia	6	6	
Wearing-off	31	31	
Sudden-off	1	1	
Dose failure	1	1	
Delayed 'ON'	0	0	
Other	1	1	
Number of 'OFF' Episodes/Day Units: Subjects			
zero	1	1	
one	0	0	
two	3	3	

three	14	14	
four	12	12	
five	9	9	
six	1	1	
Time Since Diagnosis of PD			
Units: years			
arithmetic mean	8.30		
standard deviation	± 4.322	-	
Time Since Initiation of L-dopa Treatment			
Units: years			
arithmetic mean	6.20		
standard deviation	± 4.502	-	
Time Since Motor Fluctuations Started			
Units: years			
arithmetic mean	5.05		
standard deviation	± 3.811	-	
Typical Length of 'OFF' Episodes			
Units: hours			
arithmetic mean	1.30		
standard deviation	± 0.915	-	
Total Daily L-Dopa Dose			
Units: mg			
arithmetic mean	620.5		
standard deviation	± 273.05	-	

End points

End points reporting groups

Reporting group title	APL-130277 (Titration)

Reporting group description:

Patients were titrated to an effective and tolerable dose of APL-130277. Patients were dosed with increasing doses of APL 130277 starting with 10 mg at Titration Visit (TV) 1 up to a maximum of 60 mg. Patients who did not achieve a complete and full 'ON' response with the 10 mg APL 130277 dose at TV1 restarted their normal PD medications and were asked to return to the clinic the next business day for TV2, to assess the next highest dose. The evaluation continued sequentially with 15 mg (TV2), 20 mg (TV3), 25 mg (TV4), 30 mg (TV5), 35 mg (TV6), 40 mg (TV7), 50 mg (TV8), and 60 mg (TV9) doses of APL-130277 until a full 'ON' state was achieved. If tolerated, patients were titrated to a supratherapeutic dose (up to 60 mg) which was 1 or 2 levels above the initial dose producing an 'ON' response. If the patient was unable to tolerate 1 or either of the 2 additional dose levels after reaching a full "ON" state patients were randomized to the previous tolerable dose.

Reporting group title	Overall Crossover

Reporting group description:

Patients who successfully completed the Dose Titration Phase of the study were randomized to 1 of 6 treatment sequences in the single-dose Randomized Crossover Assessment Phase. Following confirmation by both the Investigator and the patient that the patient was in the 'OFF' state, the patient was dosed according to the patient's random treatment assignment with 1. APL-130277 at the dose determined in the Dose Titration Phase; OR 2. Matched placebo APL-130277; OR 3. A single 400 mg dose of moxifloxacin. Patients were randomized in equal numbers to 6 possible sequences of the above 3 study treatments determined by a 3-way balanced crossover design.

There was a 3-day washout period between treatment period dosing visits. Dosing of APL-130277 and placebo was double-blinded, and dosing of moxifloxacin was open-label.

Subject analysis set title	APL-130277 (Crossover)
Subject analysis set type	Full analysis

Subject analysis set description:

The ECG Population included all randomized patients who had evaluable baseline 12-lead ECG (Holter) data at P1V1 and at least one evaluable post-dose 12-lead ECG (Holter) assessment during the Randomized Crossover Assessment Phase.

Subject analysis set title	Placebo (Crossover)
Subject analysis set type	Full analysis

Subject analysis set description:

The ECG Population included all randomized patients who had evaluable baseline 12-lead ECG (Holter) data at P1V1 and at least one evaluable post-dose 12-lead ECG (Holter) assessment during the Randomized Crossover Assessment Phase.

Subject analysis set title	Moxifloxacin (Crossover)
Subject analysis set type	Full analysis

Subject analysis set description:

The ECG Population included all randomized patients who had evaluable baseline 12-lead ECG (Holter) data at P1V1 and at least one evaluable post-dose 12-lead ECG (Holter) assessment during the Randomized Crossover Assessment Phase.

Subject analysis set title	10 mg APL-130277 PK subset
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients who received a single dose of 10 mg APL-130277 (as determined in the Dose Titration Phase) in 1 of the 3 treatment period dosing visits during the Randomized Crossover Assessment Phase.

Subject analysis set title	15 mg APL-130277 PK subset
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients who received a single dose of 15 mg APL-130277 (as determined in the Dose Titration Phase) in 1 of the 3 treatment period dosing visits during the Randomized Crossover Assessment Phase.

Subject analysis set title	20 mg APL-130277 PK subset
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients who received a single dose of 20 mg APL-130277 (as determined in the Dose Titration Phase) in 1 of the 3 treatment period dosing visits during the Randomized Crossover Assessment Phase.

Subject analysis set title	25 mg APL-130277 PK subset
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients who received a single dose of 25 mg APL-130277 (as determined in the Dose Titration Phase) in 1 of the 3 treatment period dosing visits during the Randomized Crossover Assessment Phase.

Subject analysis set title	35 mg APL-130277 PK subset
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients who received a single dose of 35 mg APL-130277 (as determined in the Dose Titration Phase) in 1 of the 3 treatment period dosing visits during the Randomized Crossover Assessment Phase.

Subject analysis set title	50 mg APL-130277 PK subset
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients who received a single dose of 50 mg APL-130277 (as determined in the Dose Titration Phase) in 1 of the 3 treatment period dosing visits during the Randomized Crossover Assessment Phase.

Primary: Time-Matched Change From Baseline in QTc, Placebo-Adjusted and Corrected for Heart Rate Based on the Fridericia Correction Method (QTcF) Using Delta Delta Method (ΔΔQTcF): Comparison Between APL-130277 and Placebo (Central Tendency Analysis)

End point title	Time-Matched Change From Baseline in QTc, Placebo-Adjusted and Corrected for Heart Rate Based on the Fridericia Correction Method (QTcF) Using Delta Delta Method (ΔΔQTcF): Comparison Between APL-130277 and Placebo (Central Tendency Analysis)

End point description:

For the primary central tendency analysis, the changes from baseline (ΔQTcF) were compared between APL-130277 and placebo (ΔΔQTcF). Baseline was defined as the mean of the 9 ECGs (3 sets of triplicate ECGs) recorded at baseline (P1V1). In case any of the 9 ECGs were missing, the baseline was defined as the mean of the available baseline values. The post-dose ECGs were evaluated at 15, 30, 45 and 60 minutes (mins) and 2, 3 and 4 hours post-dose at each of the 3 treatment period dosing visits during the Randomized Crossover Assessment Phase. For each of the time points, an average value was calculated based on the 3 (or all available) ECGs. These average values were used in all change from baseline calculations.

End point type	Primary

End point timeframe:

Baseline to 15, 30, 45, 60 mins and 2, 3, and 4 hours post-dose for each of the 3 treatment period dosing visits.

End point values	APL-130277 (Crossover)	Placebo (Crossover)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	40		
Units: millisecond (msec)				
least squares mean (standard error)				
15 mins post-dose	0.2 (± 1.98)	-3.7 (± 1.97)		
30 mins post-dose	0.3 (± 1.98)	-2.7 (± 1.97)		
45 mins post-dose	0.0 (± 1.98)	-3.7 (± 1.97)		
60 mins post-dose	2.7 (± 1.98)	-3.5 (± 1.97)		
2 hours post-dose	1.8 (± 1.98)	-3.0 (± 1.97)		
3 hours post-dose	0.1 (± 1.98)	-1.6 (± 1.98)		

4 hours post-dose	-0.9 (± 1.98)	-0.2 (± 1.98)		

Statistical analyses

Statistical analysis title	comparison for 15 mins post-dose

Statistical analysis description:

comparison for 15 mins post-dose: time-matched, baseline-corrected comparison between APL-130277 and placebo using the ΔΔQTcF approach. The mixed model for repeated measurements (MMRM) included region, gender, planned sequence, period, treatment, time, and interaction between treatment and time as fixed factors, and baseline QTcF as a covariate. The patient nested within sequence was included as a random effect

Please note: crossover design - total subjects analyzed 40 not 80

Comparison groups	APL-130277 (Crossover) v Placebo (Crossover)
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Least Square (LS) Mean Difference (Param
Point estimate	4
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.5
upper limit	7.4
Variability estimate	Standard error of the mean
Dispersion value	2.11

Notes:

[1] - For each post-dose time point, change from baseline (ΔQTcF) was compared between APL-130277 and placebo (ΔΔQTcF). The hypothesis of no clinical difference was accepted, if all upper limits of the two-sided 90% confidence intervals (CIs) for APL-130277 versus placebo fell below 10 msec. In this case, it was concluded that APL-130277 did not prolong the QTc interval to a clinically significant degree.

Statistical analysis title	comparison for 30 mins post-dose

Statistical analysis description:

comparison for 30 mins post-dose: time-matched, baseline-corrected comparison between APL-130277 and placebo using the ΔΔQTcF approach. The MMRM included region, gender, planned sequence, period, treatment, time, and interaction between treatment and time as fixed factors, and baseline QTcF as a covariate. The patient nested within sequence was included as a random effect.
Please note: crossover design - total subjects analyzed 40 not 80

Comparison groups	APL-130277 (Crossover) v Placebo (Crossover)
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	LS Mean Difference (Parameter dispersion
Point estimate	3
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.5
upper limit	6.5

Variability estimate	Standard error of the mean
Dispersion value	2.11

Notes:

[2] - For each post-dose time point, change from baseline (ΔQTcF) was compared between APL-130277 and placebo (ΔΔQTcF). The hypothesis of no clinical difference was accepted, if all upper limits of the two-sided 90% CIs for APL-130277 versus placebo fell below 10 msec. In this case, it was concluded that APL-130277 did not prolong the QTc interval to a clinically significant degree.

Statistical analysis title	comparison for 45 mins post-dose

Statistical analysis description:

comparison for 45 mins post-dose: time-matched, baseline-corrected comparison between APL-130277 and placebo using the ΔΔQTcF approach. The MMRM included region, gender, planned sequence, period, treatment, time, and interaction between treatment and time as fixed factors, and baseline QTcF as a covariate. The patient nested within sequence was included as a random effect.
Please note: crossover design - total subjects analyzed 40 not 80

Comparison groups	APL-130277 (Crossover) v Placebo (Crossover)
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	: LS Mean Difference (Parameter dispers
Point estimate	3.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.2
upper limit	7.2
Variability estimate	Standard error of the mean
Dispersion value	2.11

Notes:

[3] - For each post-dose time point, change from baseline (ΔQTcF) was compared between APL-130277 and placebo (ΔΔQTcF). The hypothesis of no clinical difference was accepted, if all upper limits of the two-sided 90% CIs for APL-130277 versus placebo fell below 10 msec. In this case, it was concluded that APL-130277 did not prolong the QTc interval to a clinically significant degree.

Statistical analysis title	comparison for 60 mins post-dose

Statistical analysis description:

comparison for 60 mins post-dose: time-matched, baseline-corrected comparison between APL-130277 and placebo using the ΔΔQTcF approach. The MMRM included region, gender, planned sequence, period, treatment, time, and interaction between treatment and time as fixed factors, and baseline QTcF as a covariate. The patient nested within sequence was included as a random effect.
Please note: crossover design - total subjects analyzed 40 not 80

Comparison groups	APL-130277 (Crossover) v Placebo (Crossover)
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Parameter estimate	: LS Mean Difference (Parameter dispers
Point estimate	6.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	2.7
upper limit	9.7
Variability estimate	Standard error of the mean
Dispersion value	2.11

Notes:

[4] - For each post-dose time point, change from baseline (ΔQTcF) was compared between APL-130277 and placebo (ΔΔQTcF). The hypothesis of no clinical difference was accepted, if all upper limits of the two-sided 90% CIs for APL-130277 versus placebo fell below 10 msec. In this case, it was concluded that APL-130277 did not prolong the QTc interval to a clinically significant degree.

Statistical analysis title	comparison for 2 hours post-dose

Statistical analysis description:

comparison for2 hours post-dose: time-matched, baseline-corrected comparison between APL-130277 and placebo using the ΔΔQTcF approach. The MMRM included region, gender, planned sequence, period, treatment, time, and interaction between treatment and time as fixed factors, and baseline QTcF as a covariate. The patient nested within sequence was included as a random effect.

Comparison groups	APL-130277 (Crossover) v Placebo (Crossover)
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
Parameter estimate	: LS Mean Difference (Parameter dispers
Point estimate	4.8
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.3
upper limit	8.3
Variability estimate	Standard error of the mean
Dispersion value	2.11

Notes:

[5] - For each post-dose time point, change from baseline (ΔQTcF) was compared between APL-130277 and placebo (ΔΔQTcF). The hypothesis of no clinical difference was accepted, if all upper limits of the two-sided 90% CIs for APL-130277 versus placebo fell below 10 msec. In this case, it was concluded that APL-130277 did not prolong the QTc interval to a clinically significant degree.

Statistical analysis title	comparison for 3 hours post-dose

Statistical analysis description:

comparison for 3 hours post-dose: time-matched, baseline-corrected comparison between APL-130277 and placebo using the ΔΔQTcF approach. The MMRM included region, gender, planned sequence, period, treatment, time, and interaction between treatment and time as fixed factors, and baseline QTcF as a covariate. The patient nested within sequence was included as a random effect.
Please note: crossover design - total subjects analyzed 40 not 80

Comparison groups	Placebo (Crossover) v APL-130277 (Crossover)
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Parameter estimate	: LS Mean Difference (Parameter dispers
Point estimate	1.8
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.7
upper limit	5.3
Variability estimate	Standard error of the mean
Dispersion value	2.12

Notes:

[6] - For each post-dose time point, change from baseline (ΔQTcF) was compared between APL-130277 and placebo (ΔΔQTcF). The hypothesis of no clinical difference was accepted, if all upper limits of the two-sided 90% CIs for APL-130277 versus placebo fell below 10 msec. In this case, it was concluded that APL-130277 did not prolong the QTc interval to a clinically significant degree.

Statistical analysis title	comparison for 4 hours post-dose

Statistical analysis description:

comparison for 4 hours post-dose: time-matched, baseline-corrected comparison between APL-130277 and placebo using the ΔΔQTcF approach. The MMRM included region, gender, planned sequence, period, treatment, time, and interaction between treatment and time as fixed factors, and baseline QTcF as a covariate. The patient nested within sequence was included as a random effect.
Please note: crossover design - total subjects analyzed 40 not 80

Comparison groups	APL-130277 (Crossover) v Placebo (Crossover)
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
Parameter estimate	: LS Mean Difference (Parameter dispers
Point estimate	-0.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	-4.2
upper limit	2.8
Variability estimate	Standard error of the mean
Dispersion value	2.12

Notes:

[7] - For each post-dose time point, change from baseline (ΔQTcF) was compared between APL-130277 and placebo (ΔΔQTcF). The hypothesis of no clinical difference was accepted, if all upper limits of the two-sided 90% CIs for APL-130277 versus placebo fell below 10 msec. In this case, it was concluded that APL-130277 did not prolong the QTc interval to a clinically significant degree.

Primary: Time-Matched Change from Baseline in QTc, Placebo-Adjusted and Corrected for Heart Rate Based on QTcF Using ΔΔQTcF: Comparison Between Moxifloxacin and Placebo (Assay Sensitivity Analysis)

End point title	Time-Matched Change from Baseline in QTc, Placebo-Adjusted and Corrected for Heart Rate Based on QTcF Using ΔΔQTcF: Comparison Between Moxifloxacin and Placebo (Assay Sensitivity Analysis)

End point description:

For the assay sensitivity analysis in support of the primary central tendency analysis, the changes from baseline (ΔQTcF) were compared between moxifloxacin (positive control) and placebo (ΔΔQTcF). Baseline was defined as the mean of the 9 ECGs (3 sets of triplicate ECGs) recorded at baseline (P1V1). In case any of the 9 ECGs were missing, the baseline was defined as the mean of the available baseline values. The post-dose ECGs were evaluated at 60 mins and 2, 3 and 4 hours post-dose for each of the 3 treatment period dosing visits in the Randomized Crossover Assessment Phase. For each of the time points, an average value was calculated based on the 3 (or all available) ECGs. These average values were used in all change from baseline calculations.

End point type	Primary

End point timeframe:

Baseline to 60 mins and 2, 3, and 4 hours post-dose for each of the 3 treatment period dosing visits.

End point values	Placebo (Crossover)	Moxifloxacin (Crossover)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	40		
Units: msec				
least squares mean (standard error)				
60 mins post-dose	-3.5 (± 1.97)	6.5 (± 1.98)		
2 hours post-dose	-3.0 (± 1.97)	9.3 (± 1.99)		

3 hours post-dose	-1.6 (± 1.98)	9.3 (± 1.98)		
4 hours post-dose	-0.2 (± 1.98)	8.8 (± 1.98)		

Statistical analyses

Statistical analysis title	comparison for 60 mins post-dose

Statistical analysis description:

comparison for 60 mins post-dose: time-matched, baseline-corrected comparison between moxifloxacin and placebo using the ΔΔQTcF approach. The MMRM included region, gender, planned sequence, period, treatment, time, and interaction between treatment and time as fixed factors, and baseline QTcF as a covariate. The patient nested within sequence was included as a random effect.
Please note: crossover design - total subjects analyzed 40 not 80

Comparison groups	Placebo (Crossover) v Moxifloxacin (Crossover)
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
Parameter estimate	LS Mean Difference (Parameter dispersion
Point estimate	10
Confidence interval	
level	90 %
sides	2-sided
lower limit	5.3
upper limit	14.8
Variability estimate	Standard error of the mean
Dispersion value	2.11

Notes:

[8] - The hypothesis of assay sensitivit (difference in QTcF time between moxifloxacin and placebo) was evaluated by observing if any of the 4 post-dose evaluation time points had a one-sided (Bonferroni-corrected)95% lower confidence limit which was equal to, or exceeded, 5 msec. In this case, it was concluded that assay sensitivity(prolongation of QTcF time with moxifloxacin)was demonstrated. The Bonferroni-corrected CIs were calculated by using the two-sided coverage of 0.10/4 = 0.025 for the 4 CIs

Statistical analysis title	comparison for 2 hours post-dose

Statistical analysis description:

comparison for 2 hours post-dose: time-matched, baseline-corrected comparison between moxifloxacin and placebo using the ΔΔQTcF approach. The MMRM included region, gender, planned sequence, period, treatment, time, and interaction between treatment and time as fixed factors, and baseline QTcF as a covariate. The patient nested within sequence was included as a random effect.
Please note: crossover design - total subjects analyzed 40 not 80

Comparison groups	Placebo (Crossover) v Moxifloxacin (Crossover)
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	non-inferiority[9]
Parameter estimate	LS Mean Difference (Parameter dispersion
Point estimate	12.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	7.5
upper limit	17.1

Variability estimate	Standard error of the mean
Dispersion value	2.12

Notes:

[9] - The hypothesis of assay sensitivit (difference in QTcF time between moxifloxacin and placebo) was evaluated by observing if any of the 4 post-dose evaluation time points had a one-sided (Bonferroni-corrected)95% lower confidence limit which was equal to, or exceeded, 5 msec. In this case, it was concluded that assay sensitivity(prolongation of QTcF time with moxifloxacin)was demonstrated. The Bonferroni-corrected CIs were calculated by using the two-sided coverage of 0.10/4 = 0.025 for the 4 CIs

Statistical analysis title	comparison for 3 hours post-dose

Statistical analysis description:

comparison for 3 hours post-dose: time-matched, baseline-corrected comparison between moxifloxacin and placebo using the ΔΔQTcF approach. The MMRM included region, gender, planned sequence, period, treatment, time, and interaction between treatment and time as fixed factors, and baseline QTcF as a covariate. The patient nested within sequence was included as a random effect.
Please note: crossover design - total subjects analyzed 40 not 80

Comparison groups	Placebo (Crossover) v Moxifloxacin (Crossover)
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	non-inferiority[10]
Parameter estimate	LS Mean Difference (Parameter dispersion
Point estimate	10.9
Confidence interval	
level	90 %
sides	2-sided
lower limit	6.1
upper limit	15.7
Variability estimate	Standard error of the mean
Dispersion value	2.12

Notes:

[10] - The hypothesis of assay sensitivit (difference in QTcF time between moxifloxacin and placebo) was evaluated by observing if any of the 4 post-dose evaluation time points had a one-sided (Bonferroni-corrected)95% lower confidence limit which was equal to, or exceeded, 5 msec. In this case, it was concluded that assay sensitivity(prolongation of QTcF time with moxifloxacin)was demonstrated. The Bonferroni-corrected CIs were calculated by using the two-sided coverage of 0.10/4 = 0.025 for the 4 CIs

Statistical analysis title	comparison for 4 hours post-dose

Statistical analysis description:

comparison for 4 hours post-dose: time-matched, baseline-corrected comparison between moxifloxacin and placebo using the ΔΔQTcF approach. The MMRM included region, gender, planned sequence, period, treatment, time, and interaction between treatment and time as fixed factors, and baseline QTcF as a covariate. The patient nested within sequence was included as a random effect.
Please note: crossover design - total subjects analyzed 40 not 80

Comparison groups	Placebo (Crossover) v Moxifloxacin (Crossover)
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	non-inferiority[11]
Parameter estimate	LS Mean Difference (Parameter dispersion
Point estimate	9
Confidence interval	
level	90 %
sides	2-sided
lower limit	4.2
upper limit	13.8

Variability estimate	Standard error of the mean
Dispersion value	2.12

Notes:

[11] - The hypothesis of assay sensitivit (difference in QTcF time between moxifloxacin and placebo) was evaluated by observing if any of the 4 post-dose evaluation time points had a one-sided (Bonferroni-corrected)95% lower confidence limit which was equal to, or exceeded, 5 msec. In this case, it was concluded that assay sensitivity(prolongation of QTcF time with moxifloxacin)was demonstrated. The Bonferroni-corrected CIs were calculated by using the two-sided coverage of 0.10/4 = 0.025 for the 4 CIs

Secondary: Cmax of Apomorphine and Apomorphine Sulfate (Metabolite) Following the Administration of APL-130277

End point title	Cmax of Apomorphine and Apomorphine Sulfate (Metabolite) Following the Administration of APL-130277

End point description:

The maximum observed plasma concentration (Cmax) for apomorphine and apomorphine sulfate (metabolite) was determined in patients treated with APL-130277. Pharmacokinetic (PK) parameters were derived using a non-compartmental analysis method. Bioanalysis of apomorphine and apomorphine-sulfate plasma concentration were measured using a validated liquid chromatography-tandem mass spectrometry (LC/MS-MS) method. The calibration range was 0.0200 nanograms per milliliter (ng/mL) to 20.0 ng/mL apomorphine and 10.0 to 1000 ng/mL apomorphine sulfate (metabolite). PK assessments were performed at each period of the Randomized Crossover Assessment Phase (at P1V1, P2V2 and P3V3) and results are presented for each of the APL-130277 doses administered (as determined for each patient during the Dose Titration Phase).

End point type	Secondary

End point timeframe:

Blood samples for PK assessments were taken prior to dosing and at 0.5, 0.75, 1, 2, and 4 hours post-dose.

End point values	10 mg APL-130277 PK subset	15 mg APL-130277 PK subset	20 mg APL-130277 PK subset	25 mg APL-130277 PK subset
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	14	4	15	2
Units: ng/mL				
arithmetic mean (standard deviation)				
Apomorphine (n=14, 4, 15, 2, 3, 1)	5.14 (± 3.28)	6.57 (± 1.22)	4.23 (± 2.81)	4.16 (± 2.54)
Apomorphine sulfate (n=14, 4, 15, 2, 3, 1)	220 (± 77.4)	319 (± 97.7)	377 (± 82.0)	446 (± 46.7)

End point values	35 mg APL-130277 PK subset	50 mg APL-130277 PK subset		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	1		
Units: ng/mL				
arithmetic mean (standard deviation)				
Apomorphine (n=14, 4, 15, 2, 3, 1)	9.29 (± 9.97)	4.61 (± 999999)		
Apomorphine sulfate (n=14, 4, 15, 2, 3, 1)	458 (± 12.7)	1420 (± 999999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax of Apomorphine and Apomorphine Sulfate (Metabolite) Following the Administration of APL-130277

End point title	Tmax of Apomorphine and Apomorphine Sulfate (Metabolite) Following the Administration of APL-130277

End point description:

The time of maximum observed plasma concentration (Tmax) for apomorphine and apomorphine sulfate (metabolite) was determined in patients treated with APL-130277. PK parameters were derived using a non-compartmental analysis method. Bioanalysis of apomorphine and apomorphine-sulfate plasma concentration were measured using a validated LC/MS-MS method. The calibration range was 0.0200 ng/mL to 20.0 ng/mL apomorphine and 10.0 to 1000 ng/mL apomorphine sulfate. PK assessments were performed at each period of the Randomized Crossover Assessment Phase (at P1V1, P2V2 and P3V3) and results are presented for each of the APL-130277 doses administered (as determined for each patient during the Dose Titration Phase).

End point type	Secondary

End point timeframe:

Blood samples for PK assessments were taken prior to dosing and at 0.5, 0.75, 1, 2, and 4 hours post-dose.

End point values	10 mg APL-130277 PK subset	15 mg APL-130277 PK subset	20 mg APL-130277 PK subset	25 mg APL-130277 PK subset
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	14	4	15	2
Units: hours				
median (full range (min-max))				
Apomorphine (n=14,4,15,2,3,1)	0.75 (0.50 to 1.02)	0.75 (0.50 to 0.75)	1.00 (0.50 to 2.07)	1.50 (1.00 to 2.00)
Apomorphine sulfate (n=14,4,15,2,3,1)	2.00 (1.00 to 4.00)	1.52 (0.75 to 2.17)	2.00 (0.50 to 2.07)	1.50 (1.00 to 2.00)

End point values	35 mg APL-130277 PK subset	50 mg APL-130277 PK subset		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	1		
Units: hours				
median (full range (min-max))				
Apomorphine (n=14,4,15,2,3,1)	0.58 (0.50 to 0.88)	0.78 (0.78 to 999999)		
Apomorphine sulfate (n=14,4,15,2,3,1)	2.13 (1.00 to 4.08)	0.52 (0.52 to 999999)		

Statistical analyses

No statistical analyses for this end point

Secondary: AUClast of Apomorphine and Apomorphine Sulfate (Metabolite) Following the Administration of APL-130277

End point title	AUClast of Apomorphine and Apomorphine Sulfate (Metabolite) Following the Administration of APL-130277

End point description:

The area under the concentration-time curve from time of dosing to the last measurable point (AUClast) for apomorphine and apomorphine sulfate (metabolite) was determined in patients treated with APL-130277. PK parameters were derived using a non-compartmental analysis method. Bioanalysis of apomorphine and apomorphine-sulfate plasma concentration were measured using a validated LC/MS-MS method. The calibration range was 0.0200 ng/mL to 20.0 ng/mL apomorphine and 10.0 to 1000 ng/mL apomorphine sulfate. PK assessments were performed at each period of the Randomized Crossover Assessment Phase (at P1V1, P2V2 and P3V3) and results are presented for each of the APL-130277 doses administered (as determined for each patient during the Dose Titration Phase).

End point type	Secondary

End point timeframe:

Blood samples for PK assessments were taken prior to dosing and at 0.5, 0.75, 1, 2, and 4 hours post-dose.

End point values	10 mg APL-130277 PK subset	15 mg APL-130277 PK subset	20 mg APL-130277 PK subset	25 mg APL-130277 PK subset
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	14	4	15	2
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Apomorphine (n=14,4,15,2,3,1)	7.70 (± 4.15)	9.39 (± 3.31)	7.55 (± 3.81)	7.84 (± 0.975)
Apomorphine sulfate (n=14,4,15,2,3,1)	558 (± 161)	734 (± 155)	861 (± 147)	870 (± 108)

End point values	35 mg APL-130277 PK subset	50 mg APL-130277 PK subset		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	1		
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Apomorphine (n=14,4,15,2,3,1)	12.1 (± 6.63)	10.9 (± 999999)		
Apomorphine sulfate (n=14,4,15,2,3,1)	979 (± 127)	1980 (± 999999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients with Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Patients with Treatment-Emergent Adverse Events (TEAEs)

End point description:

AE definition: any untoward medical occurrence in a clinical trial participant. Serious AE definition: an AE that is fatal, life threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in permanent (persistent) disability/incapacity, is a congenital anomaly/birth defect or is an important medical event. Severity of AEs were classified as: mild: causes no limitation of usual activities, moderate: causes some limitation of usual activities; or severe: prevents or severely limits usual activities. The investigator assessed AEs for relatedness to study medication. TEAEs were defined as all AEs that started on or after the first dose of study medication (APL-130277, moxifloxacin or placebo). Results are presented for TEAEs during the Randomized Crossover Assessment Phase.

End point type	Secondary

End point timeframe:

From first dose of study medication up to last study visit for Randomized Crossover Assessment Phase.

End point values	APL-130277 (Crossover)	Placebo (Crossover)	Moxifloxacin (Crossover)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	40	40	40	
Units: participants				
Any TEAE	13	6	4	
Drug-related TEAE	12	2	0	
Severe TEAE	1	0	0	
Serious TEAE	0	0	0	
TEAE leading to study treatment discontinuation	0	0	0	
TEAE leading to death	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: ECG Assessments: Mean Change from Baseline to Post-Baseline Value for QTcB Interval During Randomized Crossover Assessment Phase

End point title	ECG Assessments: Mean Change from Baseline to Post-Baseline Value for QTcB Interval During Randomized Crossover Assessment Phase

End point description:

QTcB was defined as QT interval corrected with Bazett's method. QT was defined as time between start of Q wave and end of T wave. QTcB was determined during continuous 12-lead ECG (Holter) monitoring at each of the 3 treatment period dosing visits at pre-specified timepoints post-dose. Baseline was defined as the mean of the 9 ECGs (3 sets of triplicate ECGs) recorded at baseline (pre-dose P1V1). In case any of the 9 ECGs were missing, the baseline was defined as the mean of the available baseline values. The post-dose ECGs were evaluated at 15, 30, 45 and 60 mins and 2, 3 and 4 hours post-dose at each of the 3 treatment period dosing visits during the Randomized Crossover Assessment Phase. For each of the time points, an average value was calculated based on the 3 (or all available) ECGs. Results are presented for the mean change from baseline at each pre-specified post-dose timepoint.

End point type	Secondary

End point timeframe:

Baseline and at 15, 30, 45, 60 minutes and 2, 3, and 4 hours post-dose for each of the 3 treatment period dosing visits during the Randomized Crossover Assessment Phase.

End point values	APL-130277 (Crossover)	Placebo (Crossover)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	40		
Units: msec				
least squares mean (standard error)				
15 mins post-dose	2.7 (± 2.24)	-1.7 (± 2.22)		
30 mins post-dose	1.9 (± 2.24)	-0.7 (± 2.22)		
45 mins post-dose	0.1 (± 2.24)	-3.2 (± 2.22)		
60 mins post-dose	-0.1 (± 2.24)	-3.3 (± 2.22)		
2 hours post-dose	4.7 (± 2.24)	-0.4 (± 2.22)		
3 hours post-dose	7.2 (± 2.24)	2.7 (± 2.24)		
4 hours post-dose	8.1 (± 2.24)	5.5 (± 2.24)		

Statistical analyses

Statistical analysis title	comparison for 15 mins post-dose:

Statistical analysis description:

comparison for 15 mins post-dose: time-matched, baseline-corrected comparison between APL-130277 and placebo using the ΔΔQTcB approach. The MMRM included region, gender, planned sequence, period, treatment, time, and interaction between treatment and time as fixed factors, and baseline QTcB as a covariate. The patient nested within sequence was included as a random effect.

Comparison groups	APL-130277 (Crossover) v Placebo (Crossover)
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Least Square (LS) Mean Difference (Param
Point estimate	4.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.3
upper limit	8.6
Variability estimate	Standard error of the mean
Dispersion value	2.54

Statistical analysis title	comparison for 30 mins post-dose:
Statistical analysis description:	
comparison for 30 mins post-dose: time-matched, baseline-corrected comparison between APL-130277 and placebo using the ΔΔQTcB approach. The MMRM included region, gender, planned sequence, period, treatment, time, and interaction between treatment and time as fixed factors, and baseline QTcB as a covariate. The patient nested within sequence was included as a random effect.	
Comparison groups	APL-130277 (Crossover) v Placebo (Crossover)
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Least Square (LS) Mean Difference (Param
Point estimate	2.5
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.6
upper limit	6.7
Variability estimate	Standard error of the mean
Dispersion value	2.54

Statistical analysis title	comparison for 45 mins post-dose:
Statistical analysis description:	
comparison for 45 mins post-dose: time-matched, baseline-corrected comparison between APL-130277 and placebo using the ΔΔQTcB approach. The MMRM included region, gender, planned sequence, period, treatment, time, and interaction between treatment and time as fixed factors, and baseline QTcB as a covariate. The patient nested within sequence was included as a random effect.	
Comparison groups	APL-130277 (Crossover) v Placebo (Crossover)
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Least Square (LS) Mean Difference (Param
Point estimate	3.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.9
upper limit	7.4
Variability estimate	Standard error of the mean
Dispersion value	2.54

Statistical analysis title	comparison for 60 mins post-dose:
Statistical analysis description:	
comparison for 60 mins post-dose: time-matched, baseline-corrected comparison between APL-130277 and placebo using the ΔΔQTcB approach. The MMRM included region, gender, planned sequence, period, treatment, time, and interaction between treatment and time as fixed factors, and baseline QTcB as a	

covariate. The patient nested within sequence was included as a random effect.

Comparison groups	APL-130277 (Crossover) v Placebo (Crossover)
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Least Square (LS) Mean Difference (Param
Point estimate	3.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.9
upper limit	7.5
Variability estimate	Standard error of the mean
Dispersion value	2.54

Statistical analysis title	comparison for 2 hours post-dose:

Statistical analysis description:

comparison for 2 hours post-dose: time-matched, baseline-corrected comparison between APL-130277 and placebo using the ΔΔQTcB approach. The MMRM included region, gender, planned sequence, period, treatment, time, and interaction between treatment and time as fixed factors, and baseline QTcB as a covariate. The patient nested within sequence was included as a random effect.

Comparison groups	APL-130277 (Crossover) v Placebo (Crossover)
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Least Square (LS) Mean Difference (Param
Point estimate	5
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.8
upper limit	9.2
Variability estimate	Standard error of the mean
Dispersion value	2.54

Statistical analysis title	comparison for 3 hours post-dose:

Statistical analysis description:

comparison for 3 hours post-dose: time-matched, baseline-corrected comparison between APL-130277 and placebo using the ΔΔQTcB approach. The MMRM included region, gender, planned sequence, period, treatment, time, and interaction between treatment and time as fixed factors, and baseline QTcB as a covariate. The patient nested within sequence was included as a random effect.

Comparison groups	APL-130277 (Crossover) v Placebo (Crossover)

Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Least Square (LS) Mean Difference (Param
Point estimate	4.6
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.4
upper limit	8.8
Variability estimate	Standard error of the mean
Dispersion value	2.55

Statistical analysis title	comparison for 4 hours post-dose:

Statistical analysis description:

comparison for 4 hours post-dose: time-matched, baseline-corrected comparison between APL-130277 and placebo using the ΔΔQTcB approach. The MMRM included region, gender, planned sequence, period, treatment, time, and interaction between treatment and time as fixed factors, and baseline QTcB as a covariate. The patient nested within sequence was included as a random effect.

Comparison groups	APL-130277 (Crossover) v Placebo (Crossover)
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Least Square (LS) Mean Difference (Param
Point estimate	2.6
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.6
upper limit	6.9
Variability estimate	Standard error of the mean
Dispersion value	2.56

Secondary: ECG Assessments: Mean Change from Baseline to Post-Baseline Value for Heart Rate During Randomized Crossover Assessment Phase

End point title	ECG Assessments: Mean Change from Baseline to Post-Baseline Value for Heart Rate During Randomized Crossover Assessment Phase

End point description:

Heart rate was determined during continuous 12-lead ECG (Holter) monitoring at each of the 3 treatment period dosing visits at pre-specified timepoints post-dose. Baseline was defined as the mean of the 9 ECGs (3 sets of triplicate ECGs) recorded at baseline (pre-dose P1V1). In case any of the 9 ECGs were missing, the baseline was defined as the mean of the available baseline values. The post-dose ECGs were evaluated at 15, 30, 45 and 60 mins and 2, 3 and 4 hours post-dose at each of the 3 treatment period dosing visits during the Randomized Crossover Assessment Phase. For each of the time points, an average value was calculated based on the 3 (or all available) ECGs. Results are presented for the mean change from baseline at each pre-specified post-dose timepoint.

End point type	Secondary

End point timeframe:

Baseline and at 15, 30, 45, 60 minutes and 2, 3, and 4 hours post-dose for each of the 3 treatment

period dosing visits during the Randomized Crossover Assessment Phase.

End point values	APL-130277 (Crossover)	Placebo (Crossover)	Moxifloxacin (Crossover)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	40	40	40	
Units: beats per minute				
least squares mean (standard error)				
15 mins post-dose	2.5 (± 1.31)	2.1 (± 1.30)	0.1 (± 1.31)	
30 mins post-dose	1.5 (± 1.31)	2.1 (± 1.30)	0.5 (± 1.31)	
45 mins post-dose	0.1 (± 1.31)	0.8 (± 1.30)	3.6 (± 1.31)	
60 mins post-dose	-3.0 (± 1.31)	0.1 (± 1.30)	1.8 (± 1.31)	
2 hours post-dose	3.3 (± 1.31)	2.8 (± 1.30)	1.5 (± 1.32)	
3 hours post-dose	7.6 (± 1.31)	4.6 (± 1.31)	3.3 (± 1.31)	
4 hours post-dose	9.5 (± 1.31)	6.2 (± 1.31)	2.9 (± 1.31)	

Statistical analyses

No statistical analyses for this end point

Secondary: ECG Assessments: Mean Change from Baseline to Post-Baseline Value for PR Interval During Randomized Crossover Assessment Phase

End point title	ECG Assessments: Mean Change from Baseline to Post-Baseline Value for PR Interval During Randomized Crossover Assessment Phase

End point description:

PR interval was defined as time from the onset of the P wave to the start of the QRS complex. PR interval was determined during continuous 12-lead ECG (Holter) monitoring at each of the 3 treatment period dosing visits at pre-specified timepoints post-dose. Baseline was defined as the mean of the 9 ECGs (3 sets of triplicate ECGs) recorded at baseline (pre-dose P1V1). In case any of the 9 ECGs were missing, the baseline was defined as the mean of the available baseline values. The post-dose ECGs were evaluated at 15, 30, 45 and 60 mins and 2, 3 and 4 hours post-dose at each of the 3 treatment period dosing visits during the Randomized Crossover Assessment Phase. For each of the time points, an average value was calculated based on the 3 (or all available) ECGs. Results are presented for the mean change from baseline at each pre-specified post-dose timepoint.

End point type	Secondary

End point timeframe:

Baseline (pre-dose P1V1) and at 15, 30, 45, 60 minutes and 2, 3, and 4 hours post-dose for each of the 3 treatment period dosing visits during the Randomized Crossover Assessment Phase.

End point values	APL-130277 (Crossover)	Placebo (Crossover)	Moxifloxacin (Crossover)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	40	40	40	
Units: msec				
least squares mean (standard error)				
15 mins post-dose	0.4 (± 1.72)	-1.9 (± 1.71)	-1.1 (± 1.72)	

30 mins post-dose	-1.6 (± 1.73)	-0.2 (± 1.71)	-0.2 (± 1.72)	
45 mins post-dose	1.2 (± 1.72)	0.1 (± 1.71)	-1.1 (± 1.72)	
60 min post-dose	2.5 (± 1.72)	-0.3 (± 1.71)	1.5 (± 1.72)	
2 hours post-dose	-0.2 (± 1.72)	-1.7 (± 1.71)	-0.1 (± 1.73)	
3 hours post-dose	-1.5 (± 1.73)	-2.2 (± 1.72)	1.6 (± 1.72)	
4 hours post-dose	-3.7 (± 1.73)	-3.1 (± 1.72)	0.8 (± 1.72)	

Statistical analyses

No statistical analyses for this end point

Secondary: ECG Assessments: Mean Change from Baseline to Post-Baseline Value for QRS Interval During Randomized Crossover Assessment Phase

End point title	ECG Assessments: Mean Change from Baseline to Post-Baseline Value for QRS Interval During Randomized Crossover Assessment Phase

End point description:

QRS interval was defined as the time of QRS complex (Q, R, and S waves). QRS interval was determined during continuous 12-lead ECG (Holter) monitoring at each of the 3 treatment period dosing visits at pre-specified timepoints post-dose. Baseline was defined as the mean of the 9 ECGs (3 sets of triplicate ECGs) recorded at baseline (pre-dose P1V1). In case any of the 9 ECGs were missing, the baseline was defined as the mean of the available baseline values. The post-dose ECGs were evaluated at 15, 30, 45 and 60 mins and 2, 3 and 4 hours post-dose at each of the 3 treatment period dosing visits during the Randomized Crossover Assessment Phase. For each of the time points, an average value was calculated based on the 3 (or all available) ECGs. Results are presented for the mean change from baseline at each pre-specified post-dose timepoint.

End point type	Secondary

End point timeframe:

Baseline and at 15, 30, 45, 60 minutes and 2, 3, and 4 hours post-dose for each of the 3 treatment period dosing visits during the Randomized Crossover Assessment Phase.

End point values	APL-130277 (Crossover)	Placebo (Crossover)	Moxifloxacin (Crossover)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	40	40	40	
Units: msec				
least squares mean (standard error)				
15 mins post-dose	-0.7 (± 0.94)	-1.2 (± 0.93)	-0.7 (± 0.94)	
30 mins post-dose	-0.4 (± 0.94)	-0.9 (± 0.93)	-0.1 (± 0.94)	
45 mins post-dose	-1.2 (± 0.94)	-0.1 (± 0.93)	-0.9 (± 0.94)	
60 mins post-dose	-0.8 (± 0.94)	-1.4 (± 0.93)	-0.4 (± 0.94)	
2 hours post-dose	1.1 (± 0.94)	-1.3 (± 0.93)	-1.1 (± 0.95)	
3 hours post-dose	-0.2 (± 0.94)	-0.9 (± 0.94)	-1.0 (± 0.94)	
4 hours post-dose	0.5 (± 0.94)	-0.6 (± 0.94)	0.4 (± 0.94)	

Statistical analyses

No statistical analyses for this end point

Secondary: ECG Assessments: Mean Change from Baseline to Post-Baseline Value for Uncorrected QT Interval during Randomized Crossover Assessment Phase

End point title	ECG Assessments: Mean Change from Baseline to Post-Baseline Value for Uncorrected QT Interval during Randomized Crossover Assessment Phase

End point description:

Uncorrected QT interval was defined as time between start of Q wave and end of T wave. QT interval was determined during continuous 12-lead ECG (Holter) monitoring at each of the 3 treatment period dosing visits at pre-specified timepoints post-dose. Baseline was defined as the mean of the 9 ECGs (3 sets of triplicate ECGs) recorded at baseline (pre-dose P1V1). In case any of the 9 ECGs were missing, the baseline was defined as the mean of the available baseline values. The post-dose ECGs were evaluated at 15, 30, 45 and 60 mins and 2, 3 and 4 hours post-dose at each of the 3 treatment period dosing visits during the Randomized Crossover Assessment Phase. For each of the time points, an average value was calculated based on the 3 (or all available) ECGs. Results are presented for the mean change from baseline at each pre-specified post-dose timepoint.

End point type	Secondary

End point timeframe:

Baseline and at 15, 30, 45, 60 minutes and 2, 3, and 4 hours post-dose for each of the 3 treatment period dosing visits during the Randomized Crossover Assessment Phase.

End point values	APL-130277 (Crossover)	Placebo (Crossover)	Moxifloxacin (Crossover)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	40	40	40	
Units: msec				
least squares mean (standard error)				
15 mins post-dose	-3.9 (± 3.05)	-7.1 (± 3.02)	-2.7 (± 3.04)	
30 mins post-dose	-2.2 (± 3.05)	-6.1 (± 3.02)	-0.7 (± 3.04)	
45 mins post-dose	0.3 (± 3.05)	-4.2 (± 3.02)	-2.2 (± 3.04)	
60 mins post-dose	8.3 (± 3.05)	-3.5 (± 3.02)	3.5 (± 3.04)	
2 hours post-dose	-2.6 (± 3.05)	-7.6 (± 3.02)	6.2 (± 3.07)	
3 hours post-dose	-12.0 (± 3.05)	-8.9 (± 3.04)	3.0 (± 3.04)	
4 hours post-dose	-16.4 (± 3.05)	-10.1 (± 3.05)	2.8 (± 3.04)	

Statistical analyses

No statistical analyses for this end point

Secondary: Median Time to 'ON' During the Dose Titration Phase

End point title	Median Time to 'ON' During the Dose Titration Phase

End point description:

The time to 'ON' was calculated as minutes from the time when the patient received APL-130277 until the time the patient turned fully 'ON', as assessed by the Investigator. Data was censored at 90 minutes.
The median time to a full 'ON' response during the Dose Titration Phase following the highest tolerated APL-130277 dose level (indicated as Day 2) and the lowest APL-130277 dose resulting in a full 'ON' (indicated as Day 1) are presented. The median time to 'ON' on Day 1 and Day 2 was calculated using the Kaplan-Meier method.

End point type	Secondary

End point timeframe:

Time of dosing up to 90 minutes post-dose during the Dose Titration Phase.

End point values	APL-130277 (Titration)			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: mins				
median (inter-quartile range (Q1-Q3))				
Day 1	30 (22 to 45)			
Day 2	30 (22 to 60)			

Statistical analyses

No statistical analyses for this end point

Secondary: Median Duration of 'ON' During the Dose Titration Phase

End point title	Median Duration of 'ON' During the Dose Titration Phase

End point description:

The duration of 'ON' was calculated as minutes from the time when the patient turned fully 'ON' until the time when the patient turned 'OFF', as assessed by the Investigator. If the patient did not turn fully 'ON' within 90 minutes the duration of 'ON' was defined as zero minutes. If the patient turned fully 'ON' and did not turn 'OFF' by 90 minutes, the data was censored at 90 minutes minus the time when the patient turned fully 'ON'.
The median duration of a full 'ON' response during the Dose Titration Phase following the highest tolerated APL-130277 dose level (indicated as Day 2) and the lowest APL-130277 dose resulting in a full 'ON' (indicated as Day 1) are presented. The median duration of 'ON' on Day 1 and Day 2 was calculated using the Kaplan-Meier method.

End point type	Secondary

End point timeframe:

Time of dosing up to 90 minutes post-dose during the Dose Titration Phase.

End point values	APL-130277 (Titration)			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: mins				
median (inter-quartile range (Q1-Q3))				
Day 1	999999 (0 to 999999)			
Day 2	999999 (0 to 999999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Pre-Dose to Post-Baseline Value in the Movement Disorders Society Unified Parkinson's Disease Rating Scale Part III Motor Examination (MDS-UPDRS Part III) Score During the Dose Titration Phase

End point title	Mean Change from Pre-Dose to Post-Baseline Value in the Movement Disorders Society Unified Parkinson's Disease Rating Scale Part III Motor Examination (MDS-UPDRS Part III) Score During the Dose Titration Phase

End point description:

The Motor Function section (Part III) of the MDS-UPDRS was administered by the Investigator, and included 33 scores based on 18-items, each anchored with 5 responses: 0 = normal, 1 = slight, 2 = mild, 3 = moderate, and 4 = severe. The scale range was from 0 to 132, with a lower score indicating better motor function and a higher score indicating more severe motor symptoms.
The least squares mean change in the MDS-UPDRS Part III score from pre-dose to 30, 60 and 90 minutes post-dose during the Dose Titration Phase at the highest tolerated APL-130277 dose level (indicated as Day 2) and the lowest APL-130277 dose resulting in a full 'ON' (indicated as Day 1) are presented.

End point type	Secondary

End point timeframe:

Baseline (pre-dose) and at 30, 60 and 90 minutes after dosing during the Dose Titration Phase.

End point values	APL-130277 (Titration)			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Points on a scale				
least squares mean (standard error)				
30 mins post-dose (day 1)	-21.1 (± 1.79)			
30 mins post-dose (day 2)	-26.7 (± 1.78)			
60 mins post-dose (day 1)	-26.3 (± 1.46)			
60 mins post-dose (day 2)	-31.3 (± 1.72)			
90 mins post-dose (day 1)	-25.2 (± 1.43)			
90 mins post-dose (day 2)	-28.9 (± 1.68)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Dose Titration Phase (up to 28 days): all AEs that started on/after the first dose of APL-130277 but before the first dose of study medication during the Randomized Crossover Assessment Phase.

Randomized Crossover Assessment Phase (up to 18 days): all

Adverse event reporting additional description:

All AEs were collected for each patient. Patients were queried in a non-leading manner, without specific prompting. TEAEs are presented for the Dose Titration Phase (APl-130277 [titration]) and for the Randomized Crossover Assessment Phase (APL-130277 [crossover], Placebo [crossover] and Moxifloxacin [crossover]).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	APL-13077 (titration)
Reporting group description: -	
Reporting group title	APL-13077 (Crossover)
Reporting group description: -	
Reporting group title	Placebo (crossover)
Reporting group description: -	
Reporting group title	Moxifloxacom (crossover)

Reporting group description: -

Serious adverse events	APL-13077 (titration)	APL-13077 (Crossover)	Placebo (crossover)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 48 (0.00%)	0 / 40 (0.00%)	0 / 40 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Moxifloxacom (crossover)		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 40 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	APL-13077 (titration)	APL-13077 (Crossover)	Placebo (crossover)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 48 (85.42%)	13 / 40 (32.50%)	6 / 40 (15.00%)
Vascular disorders			
Hypotension			
subjects affected / exposed	4 / 48 (8.33%)	1 / 40 (2.50%)	0 / 40 (0.00%)
occurrences (all)	5	1	0
Hypertension			
subjects affected / exposed	0 / 48 (0.00%)	0 / 40 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	2
Hot flush			
subjects affected / exposed	1 / 48 (2.08%)	1 / 40 (2.50%)	0 / 40 (0.00%)
occurrences (all)	1	1	0
Orthostatic hypertension			
subjects affected / exposed	1 / 48 (2.08%)	0 / 40 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Orthostatic hypotension			
subjects affected / exposed	2 / 48 (4.17%)	1 / 40 (2.50%)	0 / 40 (0.00%)
occurrences (all)	5	2	0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 48 (2.08%)	0 / 40 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Malaise			
subjects affected / exposed	1 / 48 (2.08%)	0 / 40 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Spontaneous penile erection			
subjects affected / exposed	1 / 48 (2.08%)	1 / 40 (2.50%)	0 / 40 (0.00%)
occurrences (all)	2	1	0
Respiratory, thoracic and mediastinal disorders			
Yawning			
subjects affected / exposed	2 / 48 (4.17%)	0 / 40 (0.00%)	0 / 40 (0.00%)
occurrences (all)	3	0	0
Psychiatric disorders			

Agitation			
subjects affected / exposed	0 / 48 (0.00%)	1 / 40 (2.50%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 48 (2.08%)	0 / 40 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Blood pressure systolic decreased			
subjects affected / exposed	2 / 48 (4.17%)	1 / 40 (2.50%)	0 / 40 (0.00%)
occurrences (all)	2	1	0
Weight decreased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 40 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 48 (2.08%)	0 / 40 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Contusion			
subjects affected / exposed	1 / 48 (2.08%)	0 / 40 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Bundle branch block left			
subjects affected / exposed	0 / 48 (0.00%)	1 / 40 (2.50%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Nodal arrhythmia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 40 (2.50%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Bundle branch block right			
subjects affected / exposed	1 / 48 (2.08%)	0 / 40 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Somnolence			
subjects affected / exposed	12 / 48 (25.00%)	6 / 40 (15.00%)	2 / 40 (5.00%)
occurrences (all)	20	6	2
Dizziness			

subjects affected / exposed	8 / 48 (16.67%)	0 / 40 (0.00%)	0 / 40 (0.00%)
occurrences (all)	8	0	0
Dyskinesia			
subjects affected / exposed	2 / 48 (4.17%)	1 / 40 (2.50%)	0 / 40 (0.00%)
occurrences (all)	2	1	0
Headache			
subjects affected / exposed	3 / 48 (6.25%)	0 / 40 (0.00%)	0 / 40 (0.00%)
occurrences (all)	3	0	0
Tremor			
subjects affected / exposed	1 / 48 (2.08%)	0 / 40 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Sinus headache			
subjects affected / exposed	0 / 48 (0.00%)	0 / 40 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 48 (4.17%)	0 / 40 (0.00%)	0 / 40 (0.00%)
occurrences (all)	2	0	0
Eye disorders			
Biepharospasm			
subjects affected / exposed	1 / 48 (2.08%)	0 / 40 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	27 / 48 (56.25%)	4 / 40 (10.00%)	0 / 40 (0.00%)
occurrences (all)	35	4	0
Vomiting			
subjects affected / exposed	9 / 48 (18.75%)	2 / 40 (5.00%)	0 / 40 (0.00%)
occurrences (all)	9	2	0
Diarrhoea			
subjects affected / exposed	0 / 48 (0.00%)	1 / 40 (2.50%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Eructation			
subjects affected / exposed	1 / 48 (2.08%)	0 / 40 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal reflux disease			

subjects affected / exposed	1 / 48 (2.08%)	0 / 40 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Glossodynia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 40 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	7 / 48 (14.58%)	1 / 40 (2.50%)	0 / 40 (0.00%)
occurrences (all)	7	1	0
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	0 / 48 (0.00%)	0 / 40 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Infections and infestations			
Infected cyst			
subjects affected / exposed	0 / 48 (0.00%)	0 / 40 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Urinary tract infection			
subjects affected / exposed	1 / 48 (2.08%)	0 / 40 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Moxifloxacom (crossover)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 40 (10.00%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Hot flush			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Orthostatic hypertension			

subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Orthostatic hypotension			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	3		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Malaise			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Spontaneous penile erection			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Yawning			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Blood pressure systolic decreased			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			

Fall subjects affected / exposed occurrences (all) Contusion subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0 0 / 40 (0.00%) 0		
Cardiac disorders Bundle branch block left subjects affected / exposed occurrences (all) Nodal arrhythmia subjects affected / exposed occurrences (all) Bundle branch block right subjects affected / exposed occurrences (all)	 0 / 40 (0.00%) 0 0 / 40 (0.00%) 0 0 / 40 (0.00%) 0		
Nervous system disorders Somnolence subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Dyskinesia subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Tremor subjects affected / exposed occurrences (all) Sinus headache subjects affected / exposed occurrences (all)	 1 / 40 (2.50%) 1 0 / 40 (0.00%) 0 0 / 40 (0.00%) 0 0 / 40 (0.00%) 0 0 / 40 (0.00%) 0 0 / 40 (0.00%) 0		
Ear and labyrinth disorders			

Vertigo subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Eye disorders Biepharospasm subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Eructation subjects affected / exposed occurrences (all) Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) Glossodynia subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0 0 / 40 (0.00%) 0 0 / 40 (0.00%) 0 0 / 40 (0.00%) 0 0 / 40 (0.00%) 0 0 / 40 (0.00%) 0		
Skin and subcutaneous tissue disorders Hyperhidrosis subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Musculoskeletal and connective tissue disorders Neck pain subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Infections and infestations			

Infected cyst subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		

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