



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 suprathreshold 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 suprathreshold 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 titration 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 standard deviation | 8.30 ± 4.322 | - | |
| Time Since Initiation of L-dopa Treatment Units: years arithmetic mean standard deviation | 6.20 ± 4.502 | - | |
| Time Since Motor Fluctuations Started Units: years arithmetic mean standard deviation | 5.05 ± 3.811 | - | |
| Typical Length of 'OFF' Episodes Units: hours arithmetic mean standard deviation | 1.30 ± 0.915 | - | |
| Total Daily L-Dopa Dose Units: mg arithmetic mean standard deviation | 620.5 ± 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 ($\Delta\Delta$ QTcF): 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 ($\Delta\Delta$ QTcF): Comparison Between APL-130277 and Placebo (Central Tendency Analysis) |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

For the primary central tendency analysis, the changes from baseline (Δ QTcF) were compared between APL-130277 and placebo ($\Delta\Delta$ QTcF). 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 (\pm 1.98) | -3.7 (\pm 1.97) | | |
| 30 mins post-dose | 0.3 (\pm 1.98) | -2.7 (\pm 1.97) | | |
| 45 mins post-dose | 0.0 (\pm 1.98) | -3.7 (\pm 1.97) | | |
| 60 mins post-dose | 2.7 (\pm 1.98) | -3.5 (\pm 1.97) | | |
| 2 hours post-dose | 1.8 (\pm 1.98) | -3.0 (\pm 1.97) | | |
| 3 hours post-dose | 0.1 (\pm 1.98) | -1.6 (\pm 1.98) | | |

| | | | | |
|-------------------|--------------------|--------------------|--|--|
| 4 hours post-dose | -0.9 (\pm 1.98) | -0.2 (\pm 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 $\Delta\Delta$ QTcF 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 (Δ QTcF) was compared between APL-130277 and placebo ($\Delta\Delta$ QTcF). 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 $\Delta\Delta$ QTcF 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 (Δ QTcF) was compared between APL-130277 and placebo ($\Delta\Delta$ QTcF). 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 $\Delta\Delta$ QTcF 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 (Δ QTcF) was compared between APL-130277 and placebo ($\Delta\Delta$ QTcF). 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 $\Delta\Delta$ QTcF 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 (Δ QTcF) was compared between APL-130277 and placebo ($\Delta\Delta$ QTcF). 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 for 2 hours post-dose: time-matched, baseline-corrected comparison between APL-130277 and placebo using the $\Delta\Delta$ QTcF 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 (Δ QTcF) was compared between APL-130277 and placebo ($\Delta\Delta$ QTcF). 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 $\Delta\Delta$ QTcF 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 (Δ QTcF) was compared between APL-130277 and placebo ($\Delta\Delta$ QTcF). 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 $\Delta\Delta\text{QTcF}$ 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 ($\Delta\Delta\text{QTcF}$). 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 $\Delta\Delta\text{QTcF}$: 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 $\Delta\Delta\text{QTcF}$: 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 ($\Delta\Delta\text{QTcF}$). 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 (\pm 1.98) | 9.3 (\pm 1.98) | | |
| 4 hours post-dose | -0.2 (\pm 1.98) | 8.8 (\pm 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 $\Delta\Delta$ QTcF 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 sensitivity (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 $\Delta\Delta$ QTcF 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 sensitivity (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 $\Delta\Delta\text{QTcF}$ 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 sensitivity (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 $\Delta\Delta\text{QTcF}$ 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 sensitivity (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 $\Delta\Delta$ QTcB 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 $\Delta\Delta\text{QTcB}$ 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 $\Delta\Delta\text{QTcB}$ 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 $\Delta\Delta\text{QTcB}$ 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 $\Delta\Delta\text{QTcB}$ 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 $\Delta\Delta\text{QTcB}$ 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 $\Delta\Delta\text{QTcB}$ 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

| 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 (\pm 1.31) | 2.1 (\pm 1.30) | 0.1 (\pm 1.31) | |
| 30 mins post-dose | 1.5 (\pm 1.31) | 2.1 (\pm 1.30) | 0.5 (\pm 1.31) | |
| 45 mins post-dose | 0.1 (\pm 1.31) | 0.8 (\pm 1.30) | 3.6 (\pm 1.31) | |
| 60 mins post-dose | -3.0 (\pm 1.31) | 0.1 (\pm 1.30) | 1.8 (\pm 1.31) | |
| 2 hours post-dose | 3.3 (\pm 1.31) | 2.8 (\pm 1.30) | 1.5 (\pm 1.32) | |
| 3 hours post-dose | 7.6 (\pm 1.31) | 4.6 (\pm 1.31) | 3.3 (\pm 1.31) | |
| 4 hours post-dose | 9.5 (\pm 1.31) | 6.2 (\pm 1.31) | 2.9 (\pm 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 (\pm 1.72) | -1.9 (\pm 1.71) | -1.1 (\pm 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

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

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

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

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

| | | | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|
| Vertigo subjects affected / exposed occurrences (all) | 0 / 40 (0.00%) 0 | | |
| Eye disorders Blepharospasm 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 | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 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