Clinical trial results:
An Open-Label, Randomized, Crossover Trial utilizing a Single-Blinded Rater to evaluate APL-130277 compared to subcutaneous Apomorphine in Levodopa Responsive Subjects with Parkinson's Disease Complicated by Motor Fluctuations

Summary

EudraCT number	2016-003456-70
Trial protocol	GB DE AT ES IT
Global end of trial date	11 August 2021

Results information

Result version number	v2 (current)
This version publication date	15 June 2023
First version publication date	19 August 2022
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	CTH-302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03391882
WHO universal trial number (UTN)	-

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 Inc., 01 18665036351, clinicaltrialdisclosure@sunovion.com
Scientific contact	CNS Medical Director, Sunovion Pharmaceuticals Inc., 01 18665036351, 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	11 August 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 August 2021
Global end of trial reached?	Yes
Global end of trial date	11 August 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to demonstrate the efficacy of sublingual (sl) APL-130277 compared to subcutaneous (sc) apomorphine as a treatment of "OFF" episodes in subjects with Parkinson's Disease (PD) as measured by the change from pre-dose to 90 minutes post-dose in Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III score.

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	18 October 2018
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	Germany: 41
Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Spain: 31
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	France: 3
Worldwide total number of subjects	112
EEA total number of subjects	101

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)	52
From 65 to 84 years	60
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients with Parkinson’s disease (PD) complicated by motor fluctuations (‘OFF’ episodes) were recruited for this study Approval was obtained from the Enrollment Adjudication Committee and Sponsor prior to enrollment of each patient.

Pre-assignment

Screening details:

Screening assessments must be performed within 21 days before Titration Visit 1. If TV1 is required to occur more than 21 days after SV1, Medical Monitor approval is required. Subjects who fail screening process will be allowed to rescreen once if agreed by the Medical Monitor There were 113 subjects randomized, 112 dosed with study drug.

Period 1

Period 1 title	Part A - Titration Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	APL-SC

Arm description:

Part A - Titration Phase: APL (APL-130277) then SC (subcutaneous apomorphine); Did not continue in Part B - Treatment Phase.

Arm type	Experimental/Active comparator
Investigational medicinal product name	Subcutaneous Apomorphine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

2mg, 3mg, 4mg, 5/6mg

Investigational medicinal product name	APL-130277
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sublingual film
Routes of administration	Oral use

Dosage and administration details:

10/15 mg, 20mg, 25mg. 30mg

Arm title	SC-APL

Arm description:

Part A - Titration Phase: SC (subcutaneous apomorphine) then apomorphine hydrochloride APL (APL-130277); Did not continue in Part B - Treatment Phase.

Arm type	Experimental/Active comparator

No investigational medicinal product assigned in this arm

Arm title	APL-SC-APL-SC

Arm description:

Part A - Titration Phase: APL (APL-130277) then SC (subcutaneous apomorphine) into Part B - Treatment Phase: APL then SC

Arm type	Experimental/Active comparator

No investigational medicinal product assigned in this arm

Arm title	APL-SC-SC-APL
Arm description:	
Part A - Titration Phase: APL (APL-130277) then SC (subcutaneous apomorphine); Randomized into Part B - Treatment Phase: SC then APL	
Arm type	Experimental/Active comparator
No investigational medicinal product assigned in this arm	

Arm title	SC-APL-APL-SC
Arm description:	
Part A - Titration Phase: SC (subcutaneous apomorphine) then APL (APL-130277); Randomized into Part B - Treatment Phase: APL then SC	
Arm type	Experimental/Active comparator
No investigational medicinal product assigned in this arm	

Arm title	SC-APL-SC-APL
Arm description:	
Part A - Titration Phase: SC (subcutaneous apomorphine) then APL (APL-130277); Randomized into Part B - Treatment Phase: SC then APL	
Arm type	Experimental/Active comparator
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	APL-SC	SC-APL	APL-SC-APL-SC
Started	20	18	19
Safety Population Part A	20	18	19
Mod.Intent-to-Treat Population Part A	20	18	19
Completed	2	3	19
Not completed	18	15	0
Consent withdrawn by subject	3	2	-
Adverse event, non-fatal	3	6	-
EARLY TERM AT SPONSOR REQUEST	-	1	-
Lack of efficacy	12	6	-

Number of subjects in period 1	APL-SC-SC-APL	SC-APL-APL-SC	SC-APL-SC-APL
Started	18	18	19
Safety Population Part A	18	18	19
Mod.Intent-to-Treat Population Part A	18	18	19
Completed	18	18	19
Not completed	0	0	0
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	-	-
EARLY TERM AT SPONSOR REQUEST	-	-	-
Lack of efficacy	-	-	-

Period 2

Period 2 title	Post Part A / Pre Part B
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	APL-SC

Arm description:

Part A - Titration Phase: APL (APL-130277) then SC (subcutaneous apomorphine); Did not continue in Part B - Treatment Phase.

Arm type	Experimental/Active comparator

No investigational medicinal product assigned in this arm

Arm title	SC-APL

Arm description:

Part A - Titration Phase: SC (subcutaneous apomorphine) then apomorphine hydrochloride APL (APL-130277); Did not continue in Part B - Treatment Phase.

Arm type	Experimental/Active comparator

No investigational medicinal product assigned in this arm

Arm title	APL-SC-APL-SC

Arm description:

Part A - Titration Phase: APL (APL-130277) then SC (subcutaneous apomorphine) into Part B - Treatment Phase: APL then SC

Arm type	Experimental/Active comparator

No investigational medicinal product assigned in this arm

Arm title	APL-SC-SC-APL

Arm description:

Part A - Titration Phase: APL (APL-130277) then SC (subcutaneous apomorphine); Randomized into Part B - Treatment Phase: SC then APL

Arm type	Experimental/Active comparator

No investigational medicinal product assigned in this arm

Arm title	SC-APL-APL-SC

Arm description:

Part A - Titration Phase: SC (subcutaneous apomorphine) then APL (APL-130277); Randomized into Part B - Treatment Phase: APL then SC

Arm type	Experimental/Active comparator

No investigational medicinal product assigned in this arm

Arm title	SC-APL-SC-APL

Arm description:

Part A - Titration Phase: SC (subcutaneous apomorphine) then APL (APL-130277); Randomized into Part B - Treatment Phase: SC then APL

Arm type	Experimental/Active comparator

No investigational medicinal product assigned in this arm

Number of subjects in period 2	APL-SC	SC-APL	APL-SC-APL-SC
Started	2	3	19
Completed	0	0	19
Not completed	2	3	0
Lack of efficacy	1	3	-
Protocol deviation	1	-	-

Number of subjects in period 2	APL-SC-SC-APL	SC-APL-APL-SC	SC-APL-SC-APL
Started	18	18	19
Completed	18	18	19
Not completed	0	0	0
Lack of efficacy	-	-	-
Protocol deviation	-	-	-

Period 3

Period 3 title	Part B - Treatment Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	APL-SC-APL-SC

Arm description:

Part A - Titration Phase: APL (APL-130277) then SC (subcutaneous apomorphine) into Part B - Treatment Phase: APL then SC

Arm type	Experimental/Active comparator

No investigational medicinal product assigned in this arm

Arm title	APL-SC-SC-APL

Arm description:

Part A - Titration Phase: APL (APL-130277) then SC (subcutaneous apomorphine); Randomized into Part B - Treatment Phase: SC then APL

Arm type	Experimental/Active comparator

No investigational medicinal product assigned in this arm

Arm title	SC-APL-APL-SC

Arm description:

Part A - Titration Phase: SC (subcutaneous apomorphine) then APL (APL-130277); Randomized into Part B - Treatment Phase: APL then SC

Arm type	Experimental/Active comparator

No investigational medicinal product assigned in this arm

Arm title	SC-APL-SC-APL

Arm description:

Part A - Titration Phase: SC (subcutaneous apomorphine) then APL (APL-130277); Randomized into Part B - Treatment Phase: SC then APL

Arm type	Experimental/Active comparator
No investigational medicinal product assigned in this arm	

Number of subjects in period 3	APL-SC-APL-SC	APL-SC-SC-APL	SC-APL-APL-SC
Started	19	18	18
Safety Population Part B	19	18	18
Mod. Intent-to-Treat Population Part B	19	18	18
Completed	16	15	14
Not completed	3	3	4
Consent withdrawn by subject	2	2	1
Adverse event, non-fatal	1	1	3

Number of subjects in period 3	SC-APL-SC-APL
Started	19
Safety Population Part B	19
Mod. Intent-to-Treat Population Part B	19
Completed	15
Not completed	4
Consent withdrawn by subject	3
Adverse event, non-fatal	1

Baseline characteristics

Reporting groups	
Reporting group title	APL-SC
Reporting group description:	
Part A - Titration Phase: APL (APL-130277) then SC (subcutaneous apomorphine); Did not continue in Part B - Treatment Phase.	
Reporting group title	SC-APL
Reporting group description:	
Part A - Titration Phase: SC (subcutaneous apomorphine) then apomorphine hydrochloride APL (APL-130277); Did not continue in Part B - Treatment Phase.	
Reporting group title	APL-SC-APL-SC
Reporting group description:	
Part A - Titration Phase: APL (APL-130277) then SC (subcutaneous apomorphine) into Part B - Treatment Phase: APL then SC	
Reporting group title	APL-SC-SC-APL
Reporting group description:	
Part A - Titration Phase: APL (APL-130277) then SC (subcutaneous apomorphine); Randomized into Part B - Treatment Phase: SC then APL	
Reporting group title	SC-APL-APL-SC
Reporting group description:	
Part A - Titration Phase: SC (subcutaneous apomorphine) then APL (APL-130277); Randomized into Part B - Treatment Phase: APL then SC	
Reporting group title	SC-APL-SC-APL
Reporting group description:	
Part A - Titration Phase: SC (subcutaneous apomorphine) then APL (APL-130277); Randomized into Part B - Treatment Phase: SC then APL	

Reporting group values	APL-SC	SC-APL	APL-SC-APL-SC
Number of subjects	20	18	19
Age Categorical Units: Participants			
<=18 years	0	0	0
Between 18 and 65 years	9	8	8
>=65 years	11	10	11
Age Continuous Units: Years			
arithmetic mean	64.9	63.9	65.0
standard deviation	± 8.33	± 9.99	± 9.80
Gender, Male/Female Units: Participants			
Female	7	7	6
Male	13	11	13
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Black or African American	0	0	0
More than one race	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0

Unknown or Not Reported	0	0	0
White	20	18	19
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	3	1
Not Hispanic or Latino	19	15	18
Unknown or Not Reported	1	0	0
Country Units: Subjects			
Austria	1	0	2
Germany	6	2	8
Spain	7	8	4
France	1	1	0
United Kingdom	1	1	1
Italy	4	6	4
Apomorphine naive at screening Units: Subjects			
Not Naive	1	2	5
Yes Naive	19	16	14
Total Daily Levodopa Dose Category (mg) Units: Subjects			
< 900 mg	15	13	15
>= 900 mg	5	5	4
Parkinson's disease duration Group Units: Subjects			
<=10 years	17	14	11
>10 years	3	4	8
Baseline Height (cm) Units: cm			
arithmetic mean	168.05	165.62	171.91
standard deviation	± 12.626	± 12.348	± 10.260
Baseline Weight (kg) Units: kg			
arithmetic mean	74.25	70.91	78.45
standard deviation	± 16.151	± 18.624	± 21.893
Baseline BMI (kg/m^2) Units: kg/m^2			
arithmetic mean	26.19	25.60	26.36
standard deviation	± 4.436	± 4.813	± 5.866
Movement Disorders Society Unified Parkinson Part III Score assessed prior to levodopa dosing at SV2			
The summary score used here is Part III motor examination score. Each Part III item has a 0-4 rating, where 0=normal, 1=slight, 2=mild, 3= moderate, and 4=severe. Higher MDS-UPDRS scores reflect worse motor function. MDS-UPDRS III is a total of 18 questions with 33 individual items, each item ranges from 0-4. The MDS-UPDRS III motor score is the summation of all these 33 individual item scores, and hence ranges from 0-132. Score drops over time imply improvement in motor function (higher values represent a worse outcome). SV2= Screening Visit 2			
Units: Units on a scale			
arithmetic mean	53.6	50.6	50.3
standard deviation	± 13.11	± 14.74	± 12.18
Change in MDS-UPDRS Part III Score from Pre-dose to 30 minutes after			

levodopa dosing at SV2			
The summary score used here is Part III motor examination score. Each Part III item has a 0-4 rating, where 0=normal, 1=slight, 2=mild, 3= moderate, and 4=severe. Higher MDS-UPDRS scores reflect worse motor function. MDS-UPDRS III is a total of 18 questions with 33 individual items, each item ranges from 0-4. The MDS-UPDRS III motor score is the summation of all these 33 individual item scores, and hence ranges from 0-132. Score drops over time imply improvement in motor function (higher values represent a worse outcome). SV2= Screening Visit 2			
Units: Units on a scale			
arithmetic mean	-18.0	-16.2	-19.8
standard deviation	± 12.33	± 11.80	± 13.64

Reporting group values	APL-SC-SC-APL	SC-APL-APL-SC	SC-APL-SC-APL
Number of subjects	18	18	19
Age Categorical Units: Participants			
<=18 years	0	0	0
Between 18 and 65 years	10	9	8
>=65 years	8	9	11
Age Continuous Units: Years			
arithmetic mean	63.2	63.4	65.6
standard deviation	± 6.91	± 9.71	± 8.96
Gender, Male/Female Units: Participants			
Female	1	6	7
Male	17	12	12
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Black or African American	0	0	0
More than one race	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Unknown or Not Reported	0	0	0
White	18	18	19
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	2	1
Not Hispanic or Latino	16	16	18
Unknown or Not Reported	1	0	0
Country Units: Subjects			
Austria	1	1	0
Germany	10	5	10
Spain	3	5	4
France	0	0	1
United Kingdom	3	2	3
Italy	1	5	1
Apomorphine naive at screening Units: Subjects			
Not Naive	2	2	1
Yes Naive	16	16	18

Total Daily Levodopa Dose Category (mg) Units: Subjects			
< 900 mg	14	15	14
>= 900 mg	4	3	5
Parkinson's disease duration Group Units: Subjects			
<=10 years	12	10	11
>10 years	6	8	8
Baseline Height (cm) Units: cm			
arithmetic mean	174.78	170.94	171.16
standard deviation	± 6.632	± 9.795	± 9.929
Baseline Weight (kg) Units: kg			
arithmetic mean	80.31	83.26	77.14
standard deviation	± 11.691	± 24.383	± 15.284
Baseline BMI (kg/m^2) Units: kg/m^2			
arithmetic mean	26.34	28.12	26.30
standard deviation	± 4.013	± 6.100	± 4.912
Movement Disorders Society Unified Parkinson Part III Score assessed prior to levodopa dosing at SV2			
The summary score used here is Part III motor examination score. Each Part III item has a 0-4 rating, where 0=normal, 1=slight, 2=mild, 3= moderate, and 4=severe. Higher MDS-UPDRS scores reflect worse motor function. MDS-UPDRS III is a total of 18 questions with 33 individual items, each item ranges from 0-4. The MDS-UPDRS III motor score is the summation of all these 33 individual item scores, and hence ranges from 0-132. Score drops over time imply improvement in motor function (higher values represent a worse outcome). SV2= Screening Visit 2			
Units: Units on a scale			
arithmetic mean	50.1	53.3	48.6
standard deviation	± 10.33	± 15.20	± 13.36
Change in MDS-UPDRS Part III Score from Pre-dose to 30 minutes after levodopa dosing at SV2			
The summary score used here is Part III motor examination score. Each Part III item has a 0-4 rating, where 0=normal, 1=slight, 2=mild, 3= moderate, and 4=severe. Higher MDS-UPDRS scores reflect worse motor function. MDS-UPDRS III is a total of 18 questions with 33 individual items, each item ranges from 0-4. The MDS-UPDRS III motor score is the summation of all these 33 individual item scores, and hence ranges from 0-132. Score drops over time imply improvement in motor function (higher values represent a worse outcome). SV2= Screening Visit 2			
Units: Units on a scale			
arithmetic mean	-22.9	-21.9	-21.8
standard deviation	± 12.09	± 14.19	± 12.53

Reporting group values	Total		
Number of subjects	112		
Age Categorical Units: Participants			
<=18 years	0		
Between 18 and 65 years	52		
>=65 years	60		

Age Continuous Units: Years arithmetic mean standard deviation	 -		
Gender, Male/Female Units: Participants			
Female	34		
Male	78		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	0		
Black or African American	0		
More than one race	0		
Native Hawaiian or Other Pacific Islander	0		
Unknown or Not Reported	0		
White	112		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	8		
Not Hispanic or Latino	102		
Unknown or Not Reported	2		
Country Units: Subjects			
Austria	5		
Germany	41		
Spain	31		
France	3		
United Kingdom	11		
Italy	21		
Apomorphine naive at screening Units: Subjects			
Not Naive	13		
Yes Naive	99		
Total Daily Levodopa Dose Category (mg) Units: Subjects			
< 900 mg	86		
>= 900 mg	26		
Parkinson's disease duration Group Units: Subjects			
<=10 years	75		
>10 years	37		
Baseline Height (cm) Units: cm arithmetic mean standard deviation	 -		
Baseline Weight (kg) Units: kg arithmetic mean standard deviation	 -		

Baseline BMI (kg/m^2) Units: kg/m^2 arithmetic mean standard deviation	- 		
Movement Disorders Society Unified Parkinson Part III Score assessed prior to levodopa dosing at SV2			
The summary score used here is Part III motor examination score. Each Part III item has a 0-4 rating, where 0=normal, 1=slight, 2=mild, 3= moderate, and 4=severe. Higher MDS-UPDRS scores reflect worse motor function. MDS-UPDRS III is a total of 18 questions with 33 individual items, each item ranges from 0-4. The MDS-UPDRS III motor score is the summation of all these 33 individual item scores, and hence ranges from 0-132. Score drops over time imply improvement in motor function (higher values represent a worse outcome). SV2= Screening Visit 2			
Units: Units on a scale arithmetic mean standard deviation	- 		
Change in MDS-UPDRS Part III Score from Pre-dose to 30 minutes after levodopa dosing at SV2			
The summary score used here is Part III motor examination score. Each Part III item has a 0-4 rating, where 0=normal, 1=slight, 2=mild, 3= moderate, and 4=severe. Higher MDS-UPDRS scores reflect worse motor function. MDS-UPDRS III is a total of 18 questions with 33 individual items, each item ranges from 0-4. The MDS-UPDRS III motor score is the summation of all these 33 individual item scores, and hence ranges from 0-132. Score drops over time imply improvement in motor function (higher values represent a worse outcome). SV2= Screening Visit 2			
Units: Units on a scale arithmetic mean standard deviation	- 		

End points

End points reporting groups

Reporting group title	APL-SC
Reporting group description:	
Part A - Titration Phase: APL (APL-130277) then SC (subcutaneous apomorphine); Did not continue in Part B - Treatment Phase.	
Reporting group title	SC-APL
Reporting group description:	
Part A - Titration Phase: SC (subcutaneous apomorphine) then apomorphine hydrochloride APL (APL-130277); Did not continue in Part B - Treatment Phase.	
Reporting group title	APL-SC-APL-SC
Reporting group description:	
Part A - Titration Phase: APL (APL-130277) then SC (subcutaneous apomorphine) into Part B - Treatment Phase: APL then SC	
Reporting group title	APL-SC-SC-APL
Reporting group description:	
Part A - Titration Phase: APL (APL-130277) then SC (subcutaneous apomorphine); Randomized into Part B - Treatment Phase: SC then APL	
Reporting group title	SC-APL-APL-SC
Reporting group description:	
Part A - Titration Phase: SC (subcutaneous apomorphine) then APL (APL-130277); Randomized into Part B - Treatment Phase: APL then SC	
Reporting group title	SC-APL-SC-APL
Reporting group description:	
Part A - Titration Phase: SC (subcutaneous apomorphine) then APL (APL-130277); Randomized into Part B - Treatment Phase: SC then APL	
Reporting group title	APL-SC
Reporting group description:	
Part A - Titration Phase: APL (APL-130277) then SC (subcutaneous apomorphine); Did not continue in Part B - Treatment Phase.	
Reporting group title	SC-APL
Reporting group description:	
Part A - Titration Phase: SC (subcutaneous apomorphine) then apomorphine hydrochloride APL (APL-130277); Did not continue in Part B - Treatment Phase.	
Reporting group title	APL-SC-APL-SC
Reporting group description:	
Part A - Titration Phase: APL (APL-130277) then SC (subcutaneous apomorphine) into Part B - Treatment Phase: APL then SC	
Reporting group title	APL-SC-SC-APL
Reporting group description:	
Part A - Titration Phase: APL (APL-130277) then SC (subcutaneous apomorphine); Randomized into Part B - Treatment Phase: SC then APL	
Reporting group title	SC-APL-APL-SC
Reporting group description:	
Part A - Titration Phase: SC (subcutaneous apomorphine) then APL (APL-130277); Randomized into Part B - Treatment Phase: APL then SC	
Reporting group title	SC-APL-SC-APL
Reporting group description:	
Part A - Titration Phase: SC (subcutaneous apomorphine) then APL (APL-130277); Randomized into Part B - Treatment Phase: SC then APL	
Reporting group title	APL-SC-APL-SC
Reporting group description:	
Part A - Titration Phase: APL (APL-130277) then SC (subcutaneous apomorphine) into Part B - Treatment Phase: APL then SC	

Reporting group title	APL-SC-SC-APL
Reporting group description:	
Part A - Titration Phase: APL (APL-130277) then SC (subcutaneous apomorphine); Randomized into Part B - Treatment Phase: SC then APL	
Reporting group title	SC-APL-APL-SC
Reporting group description:	
Part A - Titration Phase: SC (subcutaneous apomorphine) then APL (APL-130277); Randomized into Part B - Treatment Phase: APL then SC	
Reporting group title	SC-APL-SC-APL
Reporting group description:	
Part A - Titration Phase: SC (subcutaneous apomorphine) then APL (APL-130277); Randomized into Part B - Treatment Phase: SC then APL	
Subject analysis set title	SC (subcutaneous apomorphine)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
subcutaneous apomorphine	
Subject analysis set title	APL (APL-130277)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
APL-130277	
Subject analysis set title	APL (APL-130227)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
APL-130227	
Subject analysis set title	Overall
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Overall	
Subject analysis set title	SC (subcutaneous apomorphine)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
subcutaneous apomorphine	
Subject analysis set title	APL (APL-130277)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
APL-130277	

Primary: Change from pre-dose to 90 mins. post-dose in Movement Disorders Society Unified Parkinson's Disease Rating Scale Part III score after 4 weeks of dosing in each crossover period (assessed by the blinded-rater in-clinic at Visit 3 and Visit 6 of PART B).

End point title	Change from pre-dose to 90 mins. post-dose in Movement Disorders Society Unified Parkinson's Disease Rating Scale Part III score after 4 weeks of dosing in each crossover period (assessed by the blinded-rater in-clinic at Visit 3 and Visit 6 of PART B).

End point description:

The Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) is a clinimetric assessment of subjective and objective symptoms and signs of Parkinson's disease created by the Movement Disorder Society. The summary score used in this study for the primary objective and primary efficacy endpoint is Part III motor examination score. Each Part III item has a 0-4 rating, where 0 = normal, 1 = slight, 2 = mild, 3 = moderate, and 4 = severe. Higher MDS-UPDRS scores reflect worse motor function. MDS-UPDRS III is a total of 18 questions with 33 individual items, each item ranges from 0-4. The MDS-UPDRS III motor score is the summation of all these 33 individual item scores, and hence ranges from 0-132. Score drops over time imply improvement in motor function (higher values represent a worse outcome).

End point type	Primary

End point timeframe:

Pre-dose to 90 minutes post-dose at Week 4 of each treatment period (Visit 3 and 6)

End point values	SC (subcutaneous apomorphine)	APL (APL-130277)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	61	62		
Units: Units on a scale				
least squares mean (confidence interval 95%)	-13.78 (-16.65 to -10.90)	-13.55 (-16.39 to -10.70)		

Statistical analyses

Statistical analysis title	primary outcome analysis
Comparison groups	SC (subcutaneous apomorphine) v APL (APL-130277)
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8944
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.16
upper limit	3.62
Variability estimate	Standard error of the mean
Dispersion value	1.722

Secondary: Durability of effect, defined as an Investigator confirmed full "ON" within 30 minutes post dose and at 90 minutes post-dose, after 4 weeks of dosing in each crossover period (assessed by the blinded-rater in-clinic at Visit 3 and Visit 6 of PART B).

End point title	Durability of effect, defined as an Investigator confirmed full "ON" within 30 minutes post dose and at 90 minutes post-dose, after 4 weeks of dosing in each crossover period (assessed by the blinded-rater in-clinic at Visit 3 and Visit 6 of PART B).

End point description:

Investigator will confirm whether subject is "OFF", Full "ON" or Partial "ON" , and note the time the subject changes from "OFF" to Partial "ON" or Full "ON". The Investigator will also record the subject "ON"/"OFF" status (binary variable, Yes / No) prior to performing each MDS-UPDRS Part III assessment. Durability of effect is defined as an Investigator confirmed full "ON" within 30 minutes post-dose and at 90 minutes post-dose, after 4 weeks of dosing in each PART B crossover period.
Response rate = % of subjects that achived full "ON" within the timeframe

End point type	Secondary

End point timeframe:

Within 30 minutes post-dose and at 90 minutes post-dose at Week 4 of each treatment period (Visit 3 and 6)

End point values	SC (subcutaneous apomorphine)	APL (APL-130227)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	61	62		
Units: Percentage of participants				
number (not applicable)	18.03	17.74		

Statistical analyses

Statistical analysis title	secondary outcome measure analysis
Comparison groups	SC (subcutaneous apomorphine) v APL (APL-130227)
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7777
Method	generalized linear random effects model
Parameter estimate	Odds ratio (OR)
Point estimate	1.129
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.484
upper limit	2.637

Secondary: Patient Global Impression of Change (PGI-C): Subject improvement of "OFF" episodes, defined as very much better, much better or a little better after 4 weeks of dosing in each crossover period (assessed in-clinic at Visit 3 and Visit 6 of PART B).

End point title	Patient Global Impression of Change (PGI-C): Subject improvement of "OFF" episodes, defined as very much better, much better or a little better after 4 weeks of dosing in each crossover period (assessed in-clinic at Visit 3 and Visit 6 of PART B).

End point description:

The PGI-C is the patient reported outcome counterpart to the Clinical Global Impressions scale, (CGI), which was published in 1976 by the National Institute of Mental Health (US). It consists of one item taken from the CGI and adapted to the patient. The PGI-C is based on a 7-point scale, where a lower score is associated with higher symptom improvement. The scale is:
Very much better
Much better
A little better
No change
A little worse

Much worse
Very much worse

Subject improvement of "OFF" episodes is defined as very much better, much better or a little better at Week 4 in each PART B crossover period.
Response rate= % of subjects who achieved improvement of "OFF" episodes

End point type	Secondary

End point timeframe:

At Week 4 of each treatment period (Visit 3 and 6, or Early Termination)

End point values	SC (subcutaneous apomorphine)	APL (APL-130277)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	71		
Units: Percentage of participants				
number (not applicable)	77.14	83.10		

Statistical analyses

Statistical analysis title	secondary outcome measure analysis
Comparison groups	SC (subcutaneous apomorphine) v APL (APL-130277)
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3922
Method	generalized linear random effects model
Parameter estimate	Odds ratio (OR)
Point estimate	1.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	3.53

Secondary: Subject preference for APL treatment as measured by the Subject Treatment Preference Questionnaire (TPQ), planned after the subject had completed both APL-130277 and sc apomorphine treatment regimens (assessed in-clinic at Visit 6 of PART B)

End point title	Subject preference for APL treatment as measured by the Subject Treatment Preference Questionnaire (TPQ), planned after the subject had completed both APL-130277 and sc apomorphine treatment regimens (assessed in-clinic at Visit 6 of PART B)

End point description:

The TPQ assessment of subject treatment preference was changed from being based on a visual analogue scale or VAS (Q9b)) to a 5-point Likert scale (Q9a). Subject reported preference for APL or SC

was based on question Q9a or Q9b combined. For Q9a, responses were dichotomized as follows for statistical analysis: preference for APL (responses of either definitely or somewhat prefer APL) versus no preference for APL (responses of no preference, or somewhat/definitely prefer sc apomorphine). The VAS score was similarly dichotomized as preference for APL (score of >0 to 50) versus no preference for APL (-50 to 0). If a subject responded to both Q9a and Q9b, then Q9a only was used.

End point type	Secondary

End point timeframe:

After 8 weeks of treatment (Visit 6)

End point values	Overall			
Subject group type	Subject analysis set			
Number of subjects analysed	72			
Units: % of participants				
number (confidence interval 95%)	72.2 (61.9 to 82.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Subject confirmed durability of effect, defined as subject confirmed full "ON" within 30 minutes post-dose and at 90 minutes post-dose, after 4 weeks of dosing in each crossover period (assessed in-clinic at Visit 3 and Visit 6 of PART B).

End point title	Subject confirmed durability of effect, defined as subject confirmed full "ON" within 30 minutes post-dose and at 90 minutes post-dose, after 4 weeks of dosing in each crossover period (assessed in-clinic at Visit 3 and Visit 6 of PART B).

End point description:

Patients will confirm whether he/she is "OFF", Full "ON" or Partial "ON", and the staff will ask the subject to notify the staff when he/she changes from "OFF" to Partial "ON" or Full "ON" (binary variable, Yes / No) . Subject confirmed durability of effect is defined as subject confirmed full "ON" within 30 minutes post-dose and at 90 minutes post-dose, after 4 weeks of dosing in each crossover period (assessed in-clinic at V3 and V6 of PART B).
Response rate = % subjects that achived full ON within the timeframe

End point type	Secondary

End point timeframe:

Week 4

End point values	SC (subcutaneous apomorphine)	APL (APL-130227)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	61	62		
Units: Percentage of participants				
number (not applicable)	14.75	19.36		

Statistical analyses

Statistical analysis title	secondary outcome measure analysis
Comparison groups	SC (subcutaneous apomorphine) v APL (APL-130227)
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1769
Method	generalized linear random effects model
Parameter estimate	Odds ratio (OR)
Point estimate	1.835
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.759
upper limit	4.438

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 10 weeks (from first dose of study drug to last study visit)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	Part A Dose Titration: SC (Subcutaneous Apomorphine)
Reporting group description: Part A Dose Titration: SC (Subcutaneous Apomorphine)	
Reporting group title	Part B Treatment: SC (Subcutaneous Apomorphine)
Reporting group description: Part B Treatment: SC (Subcutaneous Apomorphine)	
Reporting group title	Part B Treatment: APL (APL-130277)
Reporting group description: Part B Treatment: APL (APL-130277)	
Reporting group title	Part A Dose Titration: APL (APL-130277)
Reporting group description: Part A Dose Titration: APL (APL-130277)	

Serious adverse events	Part A Dose Titration: SC (Subcutaneous Apomorphine)	Part B Treatment: SC (Subcutaneous Apomorphine)	Part B Treatment: APL (APL-130277)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 97 (1.03%)	1 / 70 (1.43%)	1 / 71 (1.41%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Foot fracture			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 97 (0.00%)	1 / 70 (1.43%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Intestinal ischaemia			
alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	1 / 97 (1.03%)	0 / 70 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 97 (0.00%)	0 / 70 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part A Dose Titration: APL (APL-130277)		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 102 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Foot fracture			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Intestinal ischaemia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Part A Dose Titration: SC (Subcutaneous Apomorphine)	Part B Treatment: SC (Subcutaneous Apomorphine)	Part B Treatment: APL (APL-130277)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 97 (45.36%)	37 / 70 (52.86%)	23 / 71 (32.39%)
Injury, poisoning and procedural complications			
Fall			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 97 (1.03%)	1 / 70 (1.43%)	4 / 71 (5.63%)
occurrences (all)	1	3	5
Vascular disorders			
Orthostatic hypotension			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	5 / 97 (5.15%)	4 / 70 (5.71%)	3 / 71 (4.23%)
occurrences (all)	5	5	4
Nervous system disorders			
Dizziness			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	4 / 97 (4.12%)	3 / 70 (4.29%)	2 / 71 (2.82%)
occurrences (all)	4	3	2
Dyskinesia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	7 / 97 (7.22%)	14 / 70 (20.00%)	8 / 71 (11.27%)
occurrences (all)	13	20	11
Somnolence			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	13 / 97 (13.40%)	4 / 70 (5.71%)	3 / 71 (4.23%)
occurrences (all)	18	4	3
General disorders and administration site conditions			
Fatigue			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	10 / 97 (10.31%)	4 / 70 (5.71%)	4 / 71 (5.63%)
occurrences (all)	10	5	4
Injection site erythema			
alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	6 / 97 (6.19%)	5 / 70 (7.14%)	1 / 71 (1.41%)
occurrences (all)	9	5	1
Injection site haematoma			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	2 / 97 (2.06%)	19 / 70 (27.14%)	0 / 71 (0.00%)
occurrences (all)	2	23	0
Gastrointestinal disorders			
Nausea			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	22 / 97 (22.68%)	11 / 70 (15.71%)	10 / 71 (14.08%)
occurrences (all)	31	21	25
Respiratory, thoracic and mediastinal disorders			
Yawning			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	5 / 97 (5.15%)	1 / 70 (1.43%)	0 / 71 (0.00%)
occurrences (all)	8	1	0

Non-serious adverse events	Part A Dose Titration: APL (APL-130277)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 102 (50.98%)		
Injury, poisoning and procedural complications			
Fall			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences (all)	2		
Vascular disorders			
Orthostatic hypotension			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	4 / 102 (3.92%)		
occurrences (all)	5		
Nervous system disorders			
Dizziness			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	10 / 102 (9.80%)		
occurrences (all)	15		

Dyskinesia alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	8 / 102 (7.84%) 10		
Somnolence alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	9 / 102 (8.82%) 9		
General disorders and administration site conditions			
Fatigue alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	6 / 102 (5.88%) 6		
Injection site erythema alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	0 / 102 (0.00%) 0		
Injection site haematoma alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	0 / 102 (0.00%) 0		
Gastrointestinal disorders			
Nausea alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	32 / 102 (31.37%) 53		
Respiratory, thoracic and mediastinal disorders			
Yawning alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	3 / 102 (2.94%) 3		

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