



Clinical trial results:

An Open-Label, Phase 3 Study Examining the Long-Term Safety, Tolerability and Efficacy of APL-130277 in Levodopa Responsive Patients with Parkinson's Disease Complicated by Motor Fluctuations ("OFF" Episodes)

Summary

EudraCT number	2016-000637-43
Trial protocol	GB ES AT IT
Global end of trial date	08 November 2022

Results information

Result version number	v1 (current)
This version publication date	15 July 2023
First version publication date	15 July 2023
Summary attachment (see zip file)	results (cth-301-v5-A.pdf)

Trial information

Trial identification

Sponsor protocol code	CTH-301
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02542696
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, CNS Medical Director, 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	08 November 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 November 2022
Global end of trial reached?	Yes
Global end of trial date	08 November 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate the long-term safety and tolerability of APL-130277 in Subjects with Parkinson's disease (PD).

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	31 August 2015
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	Austria: 4
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	United Kingdom: 41
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	Italy: 19
Country: Number of subjects enrolled	United States: 391
Country: Number of subjects enrolled	Germany: 23
Worldwide total number of subjects	496
EEA total number of subjects	57

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)	239
From 65 to 84 years	257
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

informed consent must be obtained at an initial Screening Visit (SV1). If required by the Investigator, and following receipt of subject consent, the Investigator may review the subject's medical history, BMI, height, weight, vital signs, 12-Lead ECG (in triplicate) and perform a complete physical examination

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Titration

Arm description:

APL-130277 Titration Phase Only

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	Oral use

Dosage and administration details:
sublingual

Arm title	Titration+LTS
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Arm description:

APL-130277 Titration Phase + Long-Term Safety Phase

Arm type	experimental
No investigational medicinal product assigned in this arm	
Arm title	LTS (Long-Term Safety)

Arm description:

APL-130277 Long-Term Safety Phase Only

Arm type	experimental
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Titration	Titration+LTS	LTS (Long-Term Safety)
Started	70	379	47
Titration Full Analysis Population	70	379	0 ^[1]
LTS Phase Full Analysis Population	0	379	47
Completed	0	114	6
Not completed	70	265	41

Adverse event, serious fatal	1	4	3
STUDY TERMINATED BY SPONSOR	-	22	14
SUBJECT DECISION	-	2	-
DECREASED OFF TIME	-	1	-
Consent withdrawn by subject	17	76	11
PROGRESSION OF PARKINSON'S DISEASE	-	4	1
SITE UNABLE TO COMPLY WITH PROTOCOL	-	2	-
Adverse event, non-fatal	28	128	11
MEDICAL HISTORY	-	-	1
SPONSOR DECISION	-	3	-
ELIGIBILITY CRITERIA NOT MET	7	1	-
WITHDRAWN DURING TITRATION	1	-	-
Lost to follow-up	-	6	-
DID NOT MEET CRITERIA FOR CONTINUATION	-	1	-
Lack of efficacy	14	12	-
Protocol deviation	2	3	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: there were no subjects in this arm for this analysis

Baseline characteristics

Reporting groups

Reporting group title	Titration
Reporting group description: APL-130277 Titration Phase Only	
Reporting group title	Titration+LTS
Reporting group description: APL-130277 Titration Phase + Long-Term Safety Phase	
Reporting group title	LTS (Long-Term Safety)
Reporting group description: APL-130277 Long-Term Safety Phase Only	

Reporting group values	Titration	Titration+LTS	LTS (Long-Term Safety)
Number of subjects	70	379	47
Age Categorical Units: Participants			
Between 18 and 65 years	32	189	18
>=65 years	38	190	29
<=18 years	0	0	0
Age Continuous Units: Years			
arithmetic mean	65.3	64.1	65.7
standard deviation	± 9.40	± 8.69	± 7.79
Gender, Male/Female Units: Participants			
Female	27	124	12
Male	43	255	35
ON State Modified Hoehn and Yahr Score Units: Subjects			
0.0	0	2	0
1.0	2	10	0
1.5	1	8	0
2.0	40	203	0
2.5	8	45	0
3.0	11	31	0
4.0	0	1	0
Missing	8	79	47
Mini-Mental State Examination Total Score Units: Subjects			
<26	3	0	0
26	6	24	0
27	6	32	0
28	10	43	0
29	13	101	0
30	30	153	0
Missing	2	26	47

Age, Customized Units: Subjects			
<65 years	32	189	18
>=65 years and <75 years	26	147	24
>=75 years	12	43	5
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	4	33	2
Not Hispanic or Latino	66	346	45
Unknown or Not Reported	0	0	0
Country Units: Subjects			
AUT	0	0	4
CAN	1	6	0
DEU	0	0	23
ESP	0	2	9
GBR	6	31	4
ITA	0	12	7
United States	63	328	0
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	1	0
Asian	0	4	0
Black or African American	2	8	0
Native Hawaiian or Other Pacific Islander	0	1	0
Other	1	1	0
White	67	364	47
Baseline Height (cm) Units: cm			
arithmetic mean	170.31	172.39	171.48
standard deviation	± 9.849	± 9.761	± 9.457
Baseline Weight (kg) Units: kg			
arithmetic mean	77.62	82.97	82.24
standard deviation	± 16.643	± 18.760	± 20.893
Baseline BMI (kg/m^2) Units: kg/m^2			
arithmetic mean	26.506	27.851	27.781
standard deviation	± 4.1859	± 5.6788	± 5.9568
Screening MDS-UPDRS Part I Score Units: Score			
arithmetic mean	11.4	11.0	10.4
standard deviation	± 5.03	± 5.47	± 5.65
Screening MDS-UPDRS Part II Score Units: Score			
arithmetic mean	14.8	14.2	17.4
standard deviation	± 7.16	± 7.04	± 7.49
Baseline MDS-UPDRS Part III Score Units: Score			
arithmetic mean	999999	42.4	48.0
standard deviation	± 999999	± 15.06	± 12.06

Screening MDS-UPDRS Part III Score Units: Score arithmetic mean standard deviation	43.4 ± 17.12	41.8 ± 13.96	999999 ± 999999
Reporting group values	Total		
Number of subjects	496		
Age Categorical Units: Participants			
Between 18 and 65 years	239		
>=65 years	257		
<=18 years	0		
Age Continuous Units: Years arithmetic mean standard deviation	-		
Gender, Male/Female Units: Participants			
Female	163		
Male	333		
ON State Modified Hoehn and Yahr Score Units: Subjects			
0.0	2		
1.0	12		
1.5	9		
2.0	243		
2.5	53		
3.0	42		
4.0	1		
Missing	134		
Mini-Mental State Examination Total Score Units: Subjects			
<26	3		
26	30		
27	38		
28	53		
29	114		
30	183		
Missing	75		
Age, Customized Units: Subjects			
<65 years	239		
>=65 years and <75 years	197		
>=75 years	60		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	39		
Not Hispanic or Latino	457		
Unknown or Not Reported	0		
Country			

Units: Subjects			
AUT	4		
CAN	7		
DEU	23		
ESP	11		
GBR	41		
ITA	19		
United States	391		
Race/Ethnicity, Customized			
Units: Subjects			
American Indian or Alaska Native	1		
Asian	4		
Black or African American	10		
Native Hawaiian or Other Pacific Islander	1		
Other	2		
White	478		
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	-		
Screening MDS-UPDRS Part I Score			
Units: Score			
arithmetic mean			
standard deviation	-		
Screening MDS-UPDRS Part II Score			
Units: Score			
arithmetic mean			
standard deviation	-		
Baseline MDS-UPDRS Part III Score			
Units: Score			
arithmetic mean			
standard deviation	-		
Screening MDS-UPDRS Part III Score			
Units: Score			
arithmetic mean			
standard deviation	-		

Subject analysis sets

Subject analysis set title	APL-130277
Subject analysis set type	Full analysis
Subject analysis set description:	
APL-130277 Long Term Safety Phase	

[illegible]

Subject analysis set title	APL-103277
Subject analysis set type	Full analysis
Subject analysis set description: APL-103277 Long Term Safety Phase	
Subject analysis set title	APL-103277
Subject analysis set type	Full analysis
Subject analysis set description: APL-103277 Long Term Safety Phase	

Reporting group values	APL-130277	APL-130277	APL-130277
Number of subjects	426	167	80
Age Categorical Units: Participants			
Between 18 and 65 years			
>=65 years			
<=18 years			
Age Continuous Units: Years			
arithmetic mean			
standard deviation	±	±	±
Gender, Male/Female Units: Participants			
Female			
Male			
ON State Modified Hoehn and Yahr Score Units: Subjects			
0.0			
1.0			
1.5			
2.0			
2.5			
3.0			
4.0			
Missing			
Mini-Mental State Examination Total Score Units: Subjects			
<26			
26			
27			
28			
29			
30			
Missing			
Age, Customized Units: Subjects			
<65 years			
>=65 years and <75 years			
>=75 years			
Ethnicity (NIH/OMB) Units: Subjects			

Hispanic or Latino Not Hispanic or Latino Unknown or Not Reported			
Country Units: Subjects			
AUT CAN DEU ESP GBR ITA United States			
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native Asian Black or African American Native Hawaiian or Other Pacific Islander Other White			
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	±	±	±
Screening MDS-UPDRS Part I Score Units: Score arithmetic mean standard deviation	±	±	±
Screening MDS-UPDRS Part II Score Units: Score arithmetic mean standard deviation	±	±	±
Baseline MDS-UPDRS Part III Score Units: Score arithmetic mean standard deviation	±	±	±
Screening MDS-UPDRS Part III Score Units: Score arithmetic mean standard deviation	±	±	±
Reporting group values	APL-130277	APL-130277	APL-130277
Number of subjects	70	224	112

Age Categorical Units: Participants			
Between 18 and 65 years ≥65 years ≤18 years			
Age Continuous Units: Years arithmetic mean standard deviation	±	±	±
Gender, Male/Female Units: Participants			
Female Male			
ON State Modified Hoehn and Yahr Score Units: Subjects			
0.0 1.0 1.5 2.0 2.5 3.0 4.0 Missing			
Mini-Mental State Examination Total Score Units: Subjects			
<26 26 27 28 29 30 Missing			
Age, Customized Units: Subjects			
<65 years ≥65 years and <75 years ≥75 years			
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Unknown or Not Reported			
Country Units: Subjects			
AUT CAN DEU ESP GBR ITA			

United States			
Race/Ethnicity, Customized			
Units: Subjects			
American Indian or Alaska Native			
Asian			
Black or African American			
Native Hawaiian or Other Pacific Islander			
Other			
White			
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			
Screening MDS-UPDRS Part I Score			
Units: Score			
arithmetic mean	±	±	±
standard deviation			
Screening MDS-UPDRS Part II Score			
Units: Score			
arithmetic mean	±	±	±
standard deviation			
Baseline MDS-UPDRS Part III Score			
Units: Score			
arithmetic mean	±	±	±
standard deviation			
Screening MDS-UPDRS Part III Score			
Units: Score			
arithmetic mean	±	±	±
standard deviation			

Reporting group values	APL-130277	APL-103277	APL-103277
Number of subjects	90	223	222
Age Categorical			
Units: Participants			
Between 18 and 65 years			
>=65 years			
<=18 years			
Age Continuous			
Units: Years			
arithmetic mean	±	±	±
standard deviation			

Gender, Male/Female Units: Participants			
Female Male			
ON State Modified Hoehn and Yahr Score Units: Subjects			
0.0 1.0 1.5 2.0 2.5 3.0 4.0 Missing			
Mini-Mental State Examination Total Score Units: Subjects			
<26 26 27 28 29 30 Missing			
Age, Customized Units: Subjects			
<65 years ≥65 years and <75 years ≥75 years			
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Unknown or Not Reported			
Country Units: Subjects			
AUT CAN DEU ESP GBR ITA United States			
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native Asian Black or African American Native Hawaiian or Other Pacific Islander Other			

White			
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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	±	±	-22.1 ±
Screening MDS-UPDRS Part I Score Units: Score arithmetic mean standard deviation	±	±	±
Screening MDS-UPDRS Part II Score Units: Score arithmetic mean standard deviation	±	±	±
Baseline MDS-UPDRS Part III Score Units: Score arithmetic mean standard deviation	±	±	±
Screening MDS-UPDRS Part III Score Units: Score arithmetic mean standard deviation	±	±	-22.1 ±

Reporting group values	APL-103277	APL-103277	APL-103277
Number of subjects	221	48	111
Age Categorical Units: Participants			
Between 18 and 65 years ≥65 years ≤18 years			
Age Continuous Units: Years arithmetic mean standard deviation	±	±	±
Gender, Male/Female Units: Participants			
Female Male			
ON State Modified Hoehn and Yahr Score Units: Subjects			
0.0 1.0			

1.5 2.0 2.5 3.0 4.0 Missing			
Mini-Mental State Examination Total Score Units: Subjects			
<26 26 27 28 29 30 Missing			
Age, Customized Units: Subjects			
<65 years ≥65 years and <75 years ≥75 years			
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Unknown or Not Reported			
Country Units: Subjects			
AUT CAN DEU ESP GBR ITA United States			
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native Asian Black or African American Native Hawaiian or Other Pacific Islander Other White			
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	±	±	±
Screening MDS-UPDRS Part I Score Units: Score arithmetic mean standard deviation	±	±	±
Screening MDS-UPDRS Part II Score Units: Score arithmetic mean standard deviation	±	±	±
Baseline MDS-UPDRS Part III Score Units: Score arithmetic mean standard deviation	±	±	±
Screening MDS-UPDRS Part III Score Units: Score arithmetic mean standard deviation	±	±	±

Reporting group values	APL-103277	APL-103277	APL-103277
Number of subjects	110	112	54
Age Categorical Units: Participants			
Between 18 and 65 years >=65 years <=18 years			
Age Continuous Units: Years arithmetic mean standard deviation	±	±	±
Gender, Male/Female Units: Participants			
Female Male			
ON State Modified Hoehn and Yahr Score Units: Subjects			
0.0 1.0 1.5 2.0 2.5 3.0 4.0 Missing			
Mini-Mental State Examination Total Score Units: Subjects			
<26 26			

27			
28			
29			
30			
Missing			
Age, Customized			
Units: Subjects			
<65 years			
>=65 years and <75 years			
>=75 years			
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino			
Not Hispanic or Latino			
Unknown or Not Reported			
Country			
Units: Subjects			
AUT			
CAN			
DEU			
ESP			
GBR			
ITA			
United States			
Race/Ethnicity, Customized			
Units: Subjects			
American Indian or Alaska Native			
Asian			
Black or African American			
Native Hawaiian or Other Pacific Islander			
Other			
White			
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	±	±	±
Screening MDS-UPDRS Part I Score			
Units: Score			
arithmetic mean			
standard deviation	±	±	±
Screening MDS-UPDRS Part II Score			
Units: Score			
arithmetic mean			

standard deviation	±	±	±
Baseline MDS-UPDRS Part III Score Units: Score arithmetic mean standard deviation	±	±	±
Screening MDS-UPDRS Part III Score Units: Score arithmetic mean standard deviation	±	±	±

Reporting group values	APL-103277		
Number of subjects	90		
Age Categorical Units: Participants			
Between 18 and 65 years >=65 years <=18 years			
Age Continuous Units: Years arithmetic mean standard deviation	±		
Gender, Male/Female Units: Participants			
Female Male			
ON State Modified Hoehn and Yahr Score Units: Subjects			
0.0 1.0 1.5 2.0 2.5 3.0 4.0 Missing			
Mini-Mental State Examination Total Score Units: Subjects			
<26 26 27 28 29 30 Missing			
Age, Customized Units: Subjects			
<65 years >=65 years and <75 years >=75 years			
Ethnicity (NIH/OMB)			

Units: Subjects			
Hispanic or Latino			
Not Hispanic or Latino			
Unknown or Not Reported			
Country			
Units: Subjects			
AUT			
CAN			
DEU			
ESP			
GBR			
ITA			
United States			
Race/Ethnicity, Customized			
Units: Subjects			
American Indian or Alaska Native			
Asian			
Black or African American			
Native Hawaiian or Other Pacific Islander			
Other			
White			
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	±		
Screening MDS-UPDRS Part I Score			
Units: Score			
arithmetic mean			
standard deviation	±		
Screening MDS-UPDRS Part II Score			
Units: Score			
arithmetic mean			
standard deviation	±		
Baseline MDS-UPDRS Part III Score			
Units: Score			
arithmetic mean			
standard deviation	±		
Screening MDS-UPDRS Part III Score			
Units: Score			
arithmetic mean			
standard deviation	±		

End points

End points reporting groups

Reporting group title	Titration
Reporting group description: APL-130277 Titration Phase Only	
Reporting group title	Titration+LTS
Reporting group description: APL-130277 Titration Phase + Long-Term Safety Phase	
Reporting group title	LTS (Long-Term Safety)
Reporting group description: APL-130277 Long-Term Safety Phase Only	
Subject analysis set title	APL-130277
Subject analysis set type	Full analysis
Subject analysis set description: APL-130277 Long Term Safety Phase	
Subject analysis set title	APL-130277
Subject analysis set type	Full analysis
Subject analysis set description: APL-130277 Long Term Safety Phase	
Subject analysis set title	APL-130277
Subject analysis set type	Full analysis
Subject analysis set description: APL-130277 Long Term Safety Phase	
Subject analysis set title	APL-130277
Subject analysis set type	Full analysis
Subject analysis set description: APL-130277 Long Term Safety Phase	
Subject analysis set title	APL-130277
Subject analysis set type	Full analysis
Subject analysis set description: APL-130277 Long Term Safety Phase	
Subject analysis set title	APL-130277
Subject analysis set type	Full analysis
Subject analysis set description: APL-130277 Long Term Safety Phase	
Subject analysis set title	APL-130277
Subject analysis set type	Full analysis
Subject analysis set description: APL-130277 Long Term Safety Phase	
Subject analysis set title	APL-130277
Subject analysis set type	Full analysis
Subject analysis set description: APL-130277 Long Term Safety Phase	
Subject analysis set title	APL-130277
Subject analysis set type	Full analysis
Subject analysis set description: APL-130277 Long Term Safety Phase	
Subject analysis set title	APL-103277
Subject analysis set type	Full analysis
Subject analysis set description: APL-103277 Long Term Safety Phase	
Subject analysis set title	APL-103277
Subject analysis set type	Full analysis
Subject analysis set description: APL-103277 Long Term Safety Phase	
Subject analysis set title	APL-103277
Subject analysis set type	Full analysis

Subject analysis set description:

APL-103277 Long Term Safety Phase

Subject analysis set title	APL-103277
Subject analysis set type	Full analysis

Subject analysis set description:

APL-103277 Long Term Safety Phase

Subject analysis set title	APL-103277
Subject analysis set type	Full analysis

Subject analysis set description:

APL-103277 Long Term Safety Phase

Subject analysis set title	APL-103277
Subject analysis set type	Full analysis

Subject analysis set description:

APL-103277 Long Term Safety Phase

Subject analysis set title	APL-103277
Subject analysis set type	Full analysis

Subject analysis set description:

APL-103277 Long Term Safety Phase

Subject analysis set title	APL-103277
Subject analysis set type	Full analysis

Subject analysis set description:

APL-103277 Long Term Safety Phase

Subject analysis set title	APL-103277
Subject analysis set type	Full analysis

Subject analysis set description:

APL-103277 Long Term Safety Phase

Primary: Evaluation of safety and tolerability data collected, based on incidence of adverse events in the LTS phase

End point title	Evaluation of safety and tolerability data collected, based on incidence of adverse events in the LTS phase ^[1]
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End point description:

End point type	Primary
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End point timeframe:

up to approximately 3 years

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This outcome measure was not powered for statistical analysis.

End point values	APL-130277			
Subject group type	Subject analysis set			
Number of subjects analysed	426			
Units: participants	365			

Statistical analyses

No statistical analyses for this end point

Secondary: The percentage of instances where a full "ON" response was achieved within 30 minutes after self-administration of study medication at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase based on the home dosing diary entries.

End point title	The percentage of instances where a full "ON" response was achieved within 30 minutes after self-administration of study medication at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase based on the home dosing diary entries.
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End point description:

End point type	Secondary
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End point timeframe:

Week 48

End point values	APL-130277			
Subject group type	Subject analysis set			
Number of subjects analysed	70			
Units: mean percentage of instances				
arithmetic mean (standard deviation)	84.1 (± 30.74)			

Statistical analyses

No statistical analyses for this end point

Secondary: The percentage of instances where a full "ON" response was achieved within 30 minutes after self-administration of study medication at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase based on the home dosing diary entries.

End point title	The percentage of instances where a full "ON" response was achieved within 30 minutes after self-administration of study medication at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase based on the home dosing diary entries.
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End point description:

End point type	Secondary
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End point timeframe:

Week 36

End point values	APL-130277			
Subject group type	Subject analysis set			
Number of subjects analysed	80			
Units: mean percentage of instances				
arithmetic mean (standard deviation)	87.3 (\pm 28.70)			

Statistical analyses

No statistical analyses for this end point

Secondary: The percentage of instances where a full "ON" response was achieved within 30 minutes after self-administration of study medication at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase based on the home dosing diary entries.

End point title	The percentage of instances where a full "ON" response was achieved within 30 minutes after self-administration of study medication at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase based on the home dosing diary entries.
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End point description:

End point type	Secondary
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End point timeframe:

Week 24

End point values	APL-130277			
Subject group type	Subject analysis set			
Number of subjects analysed	167			
Units: mean percentage of instances				
arithmetic mean (standard deviation)	80.7 (\pm 32.55)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with a subject-rated full "ON" response within 30 minutes at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.

End point title	Percentage of subjects with a subject-rated full "ON" response within 30 minutes at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.
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End point description:

End point type	Secondary
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End point timeframe:

Week 24

End point values	APL-130277			
Subject group type	Subject analysis set			
Number of subjects analysed	224			
Units: percent of participants				
number (not applicable)	77.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from pre-dose in MDS-UPDRS Part III Motor Examination (MDS UPDRS MOTOR) score at 15, 30, 60, and 90 minutes after dosing at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.

End point title	Mean change from pre-dose in MDS-UPDRS Part III Motor Examination (MDS UPDRS MOTOR) score at 15, 30, 60, and 90 minutes after dosing at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.
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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. 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. Score drops over time imply improvement in motor function.

End point type	Secondary
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End point timeframe:

Week 24, 30 mins after dosing

End point values	APL-103277			
Subject group type	Subject analysis set			
Number of subjects analysed	222			
Units: Units on a scale				
arithmetic mean (standard deviation)	-22.1 (± 13.04)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from pre-dose in MDS-UPDRS Part III Motor Examination (MDS UPDRS MOTOR) score at 15, 30, 60, and 90 minutes after dosing at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.

End point title	Mean change from pre-dose in MDS-UPDRS Part III Motor Examination (MDS UPDRS MOTOR) score at 15, 30, 60, and 90
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minutes after dosing at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.

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. 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. Score drops over time imply improvement in motor function.

End point type Secondary

End point timeframe:

Week 24, 15 mins after dosing

End point values	APL-103277			
Subject group type	Subject analysis set			
Number of subjects analysed	223			
Units: Units on a scale				
arithmetic mean (standard deviation)	-14.2 (\pm 11.91)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with a subject-rated full "ON" response within 30 minutes at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.

End point title Percentage of subjects with a subject-rated full "ON" response within 30 minutes at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.

End point description:

End point type Secondary

End point timeframe:

Week 48

End point values	APL-130277			
Subject group type	Subject analysis set			
Number of subjects analysed	90			
Units: percent of participants				
number (not applicable)	84.4			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with a subject-rated full "ON" response within 30 minutes at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.

End point title	Percentage of subjects with a subject-rated full "ON" response within 30 minutes at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.
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End point description:

End point type	Secondary
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End point timeframe:

Week 36

End point values	APL-130277			
Subject group type	Subject analysis set			
Number of subjects analysed	112			
Units: percent of participants				
number (not applicable)	83.9			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from pre-dose in MDS-UPDRS Part III Motor Examination (MDS UPDRS MOTOR) score at 15, 30, 60, and 90 minutes after dosing at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.

End point title	Mean change from pre-dose in MDS-UPDRS Part III Motor Examination (MDS UPDRS MOTOR) score at 15, 30, 60, and 90 minutes after dosing at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.
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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. 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. Score drops over time imply improvement in motor function.

End point type	Secondary
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End point timeframe:

Week 24, 60 mins after dosing

End point values	APL-103277			
Subject group type	Subject analysis set			
Number of subjects analysed	221			
Units: Units on a scale				
arithmetic mean (standard deviation)	-21.0 (± 13.34)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from pre-dose in MDS-UPDRS Part III Motor Examination (MDS UPDRS MOTOR) score at 15, 30, 60, and 90 minutes after dosing at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.

End point title	Mean change from pre-dose in MDS-UPDRS Part III Motor Examination (MDS UPDRS MOTOR) score at 15, 30, 60, and 90 minutes after dosing at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.
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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. 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. Score drops over time imply improvement in motor function.

End point type	Secondary
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End point timeframe:

Week 36, 30 mins after dosing

End point values	APL-103277			
Subject group type	Subject analysis set			
Number of subjects analysed	110			
Units: Units on a scale				
arithmetic mean (standard deviation)	-22.3 (± 12.22)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from pre-dose in MDS-UPDRS Part III Motor Examination (MDS UPDRS MOTOR) score at 15, 30, 60, and 90 minutes after dosing at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.

End point title	Mean change from pre-dose in MDS-UPDRS Part III Motor Examination (MDS UPDRS MOTOR) score at 15, 30, 60, and 90 minutes after dosing at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.
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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. 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. Score drops over time imply improvement in motor function.

End point type	Secondary
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End point timeframe:

Week 36, 15 mins after dosing

End point values	APL-103277			
Subject group type	Subject analysis set			
Number of subjects analysed	111			
Units: Units on a scale				
arithmetic mean (standard deviation)	-11.7 (± 10.48)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from pre-dose in MDS-UPDRS Part III Motor Examination (MDS UPDRS MOTOR) score at 15, 30, 60, and 90 minutes after dosing at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.

End point title	Mean change from pre-dose in MDS-UPDRS Part III Motor Examination (MDS UPDRS MOTOR) score at 15, 30, 60, and 90 minutes after dosing at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.
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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. 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. Score drops over time imply improvement in motor function.

End point type	Secondary
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End point timeframe:

Week 24, 90 mins after dosing

End point values	APL-103277			
Subject group type	Subject analysis set			
Number of subjects analysed	48			
Units: Units on a scale				
arithmetic mean (standard deviation)	-16.9 (± 13.58)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from pre-dose in MDS-UPDRS Part III Motor Examination (MDS UPDRS MOTOR) score at 15, 30, 60, and 90 minutes after dosing at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.

End point title	Mean change from pre-dose in MDS-UPDRS Part III Motor Examination (MDS UPDRS MOTOR) score at 15, 30, 60, and 90 minutes after dosing at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.
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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. 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. Score drops over time imply improvement in motor function.

End point type	Secondary
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End point timeframe:

Week 36, 60 mins after dosing

End point values	APL-103277			
Subject group type	Subject analysis set			
Number of subjects analysed	112			
Units: Units on a scale				
arithmetic mean (standard deviation)	-21.3 (± 13.54)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from pre-dose in MDS-UPDRS Part III Motor Examination (MDS UPDRS MOTOR) score at 15, 30, 60, and 90 minutes after dosing at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.

End point title	Mean change from pre-dose in MDS-UPDRS Part III Motor Examination (MDS UPDRS MOTOR) score at 15, 30, 60, and 90 minutes after dosing at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.
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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. 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. Score

drops over time imply improvement in motor function.

End point type	Secondary
End point timeframe:	
Week 36, 90 mins after dosing	

End point values	APL-103277			
Subject group type	Subject analysis set			
Number of subjects analysed	54			
Units: Units on a scale				
arithmetic mean (standard deviation)	-13.3 (± 13.11)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from pre-dose in MDS-UPDRS Part III Motor Examination (MDS UPDRS MOTOR) score at 15, 30, 60, and 90 minutes after dosing at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.

End point title	Mean change from pre-dose in MDS-UPDRS Part III Motor Examination (MDS UPDRS MOTOR) score at 15, 30, 60, and 90 minutes after dosing at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.
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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. 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. Score drops over time imply improvement in motor function.

End point type	Secondary
End point timeframe:	
Week 48, 60 mins after dosing	

End point values	APL-103277			
Subject group type	Subject analysis set			
Number of subjects analysed	90			
Units: Units on a scale				
arithmetic mean (standard deviation)	-22.3 (± 13.35)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from pre-dose in MDS-UPDRS Part III Motor Examination (MDS UPDRS MOTOR) score at 15, 30, 60, and 90 minutes after dosing at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.

End point title	Mean change from pre-dose in MDS-UPDRS Part III Motor Examination (MDS UPDRS MOTOR) score at 15, 30, 60, and 90 minutes after dosing at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.
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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. 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. Score drops over time imply improvement in motor function.

End point type	Secondary
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End point timeframe:

Week 48, 30 mins after dosing

End point values	APL-103277			
Subject group type	Subject analysis set			
Number of subjects analysed	90			
Units: Units on a scale				
arithmetic mean (standard deviation)	-23.2 (± 12.44)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from pre-dose in MDS-UPDRS Part III Motor Examination (MDS UPDRS MOTOR) score at 15, 30, 60, and 90 minutes after dosing at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.

End point title	Mean change from pre-dose in MDS-UPDRS Part III Motor Examination (MDS UPDRS MOTOR) score at 15, 30, 60, and 90 minutes after dosing at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.
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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. 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. Score drops over time imply improvement in motor function.

End point type	Secondary
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End point timeframe:

Week 48, 15 mins after dosing

End point values	APL-103277			
Subject group type	Subject analysis set			
Number of subjects analysed	90			
Units: Units on a scale				
arithmetic mean (standard deviation)	-13.3 (\pm 10.17)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from pre-dose in MDS-UPDRS Part III Motor Examination (MDS UPDRS MOTOR) score at 15, 30, 60, and 90 minutes after dosing at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.

End point title	Mean change from pre-dose in MDS-UPDRS Part III Motor Examination (MDS UPDRS MOTOR) score at 15, 30, 60, and 90 minutes after dosing at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.
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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. 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. Score drops over time imply improvement in motor function.

End point type	Secondary
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End point timeframe:

Week 48, 90 mins after dosing

End point values	APL-103277			
Subject group type	Subject analysis set			
Number of subjects analysed	48			
Units: Units on a scale				
arithmetic mean (standard deviation)	-16.6 (\pm 10.93)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 22 weeks for titration phase

Up to approximately 3 years for Long Term Safety Phase

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.1
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Reporting groups

Reporting group title	LTS (Long-Term Safety)
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Reporting group description:

APL-130277 Long-Term Safety Phase

Reporting group title	Titration
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Reporting group description:

APL-130277 Titration Phase

Serious adverse events	LTS (Long-Term Safety)	Titration	
Total subjects affected by serious adverse events			
subjects affected / exposed	58 / 426 (13.62%)	6 / 449 (1.34%)	
number of deaths (all causes)	7	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	2 / 426 (0.47%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone cancer			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioblastoma			
subjects affected / exposed	0 / 426 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Hodgkin's lymphoma			

subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer stage II			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	2 / 426 (0.47%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 426 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drowning			
subjects affected / exposed	1 / 426 (0.23%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
General physical health deterioration			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural thickening			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary arterial hypertension			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	2 / 426 (0.47%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary embolism			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Adjustment disorder with mixed anxiety and depressed mood			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dopamine dysregulation syndrome			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Substance-induced psychotic disorder			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Carbon dioxide increased			

subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adjacent segment degeneration			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	5 / 426 (1.17%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fractured sacrum			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			

subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	2 / 426 (0.47%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sternal fracture			
subjects affected / exposed	0 / 426 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon injury			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arrhythmia			

subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	3 / 426 (0.70%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	3 / 426 (0.70%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 426 (0.47%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sinus node dysfunction			

subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradyarrhythmia			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 426 (0.23%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Myelopathy			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autonomic nervous system imbalance			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	2 / 426 (0.47%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			

subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paresis			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 426 (0.47%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haematoma			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinson's disease			
subjects affected / exposed	2 / 426 (0.47%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Iron deficiency anaemia			

subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal artery occlusion			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lip blister			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotid gland enlargement			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	2 / 426 (0.47%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			

Hepatitis toxic			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Nail fold inflammation			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Obstructive uropathy			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis haemorrhagic			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus bladder			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder neck obstruction			
subjects affected / exposed	0 / 426 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthropathy			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	3 / 426 (0.70%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	2 / 426 (0.47%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations Abscess limb subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 426 (0.23%) 0 / 1 0 / 0	0 / 449 (0.00%) 0 / 0 0 / 0	
Cellulitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 426 (0.47%) 0 / 3 0 / 0	0 / 449 (0.00%) 0 / 0 0 / 0	
Corona virus infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 426 (0.47%) 0 / 2 0 / 0	0 / 449 (0.00%) 0 / 0 0 / 0	
Kidney infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 426 (0.23%) 0 / 1 0 / 0	0 / 449 (0.00%) 0 / 0 0 / 0	
Oral candidiasis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 426 (0.23%) 0 / 1 0 / 0	0 / 449 (0.00%) 0 / 0 0 / 0	
Osteomyelitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 426 (0.23%) 0 / 1 0 / 0	0 / 449 (0.00%) 0 / 0 0 / 0	
Pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	5 / 426 (1.17%) 0 / 5 0 / 2	0 / 449 (0.00%) 0 / 0 0 / 0	
Psoas abscess subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 426 (0.23%) 0 / 1 0 / 0	0 / 449 (0.00%) 0 / 0 0 / 0	
Sepsis			

subjects affected / exposed	2 / 426 (0.47%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	4 / 426 (0.94%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 426 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	LTS (Long-Term Safety)	Titration	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	233 / 426 (54.69%)	153 / 449 (34.08%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	40 / 426 (9.39%)	4 / 449 (0.89%)	
occurrences (all)	59	4	
Nervous system disorders			
Dizziness			
subjects affected / exposed	27 / 426 (6.34%)	27 / 449 (6.01%)	
occurrences (all)	35	35	
Dyskinesia			
subjects affected / exposed	24 / 426 (5.63%)	12 / 449 (2.67%)	
occurrences (all)	33	14	
Headache			
subjects affected / exposed	14 / 426 (3.29%)	23 / 449 (5.12%)	
occurrences (all)	15	28	
Somnolence			
subjects affected / exposed	32 / 426 (7.51%)	30 / 449 (6.68%)	
occurrences (all)	34	47	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	22 / 426 (5.16%)	18 / 449 (4.01%)	
occurrences (all)	23	25	
Gastrointestinal disorders			
Lip swelling			
subjects affected / exposed	27 / 426 (6.34%)	0 / 449 (0.00%)	
occurrences (all)	36	0	
Mouth ulceration			
subjects affected / exposed	25 / 426 (5.87%)	3 / 449 (0.67%)	
occurrences (all)	34	3	
Nausea			
subjects affected / exposed	91 / 426 (21.36%)	67 / 449 (14.92%)	
occurrences (all)	122	75	
Oral mucosal erythema			

subjects affected / exposed	30 / 426 (7.04%)	17 / 449 (3.79%)	
occurrences (all)	40	20	
Stomatitis			
subjects affected / exposed	23 / 426 (5.40%)	2 / 449 (0.45%)	
occurrences (all)	37	2	
Respiratory, thoracic and mediastinal disorders			
Yawning			
subjects affected / exposed	23 / 426 (5.40%)	43 / 449 (9.58%)	
occurrences (all)	30	69	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 May 2017	Amendment 3
25 February 2019	Amendment 4

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported