Clinical trial results:
A randomized, double-blind, placebo-controlled, multi-centre phase IIa study evaluating the safety and tolerability of IRL752 in patients with Parkinson's Disease Dementia.

Summary

EudraCT number	2017-001673-17
Trial protocol	SE FI
Global end of trial date	25 May 2018

Results information

Result version number	v1 (current)
This version publication date	14 June 2019
First version publication date	14 June 2019

Trial information

Trial identification

Sponsor protocol code	IRL752C002

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Integrative Research Laboratories AB
Sponsor organisation address	Arvid Wallgrens Backe 20, Göteborg, Sweden, SE-413 46
Public contact	Joakim Tedroff, Integrative Research Laboratories AB, 0046 707 60 16 91, joakim.tedroff@irlab.se
Scientific contact	Joakim Tedroff, Integrative Research Laboratories AB, 0046 707 60 16 91, joakim.tedroff@irlab.se

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	25 June 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 May 2018
Global end of trial reached?	Yes
Global end of trial date	25 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of IRL752 after repeated dosing in patients with Parkinson's Disease Dementia (PDD).

Protection of trial subjects:

The ICF included information that data would be recorded, collected and processed and could be transferred to European Economic Area (EEA) or non-EEA countries. In accordance with the EU Data Protection Directive (95/46/EC), the data would not identify any patients taking part in the study.
The potential study patient (and/or LAR, as applicable) and his/her caregiver were informed that by signing the ICF he/she/they approved that authorized representatives from Sponsor and CTC Clinical Trial Consultant AB (CTC), the concerned IEC and CA had direct access to his/her medical records for verification of clinical study procedures. An authorization from the hospital for access to medical records by the Monitor was available, as required by local legislation.
The patient had the right to request access to his/her personal data for rectification of any data that was not correct and/or complete.
The Investigator filed a Patient Identification List, which included sufficient information to link records, i.e. the eCRF and clinical records. This list will be preserved for possible future inspections/audits but has not been made available to the Sponsor except for monitoring or auditing purposes.

Background therapy:

Patients included in the study had to be on stable anti-Parkinson treatment for at least 30 days prior to inclusion and during the study. Treatment with Selegiline was not allowed. Concomitant treatment with pro-cognitive treatments such as Ach esterase inhibitors and Memantine were allowed.

Evidence for comparator:

N/A (placebo)

Actual start date of recruitment	20 September 2017
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	Sweden: 31
Country: Number of subjects enrolled	Finland: 1
Worldwide total number of subjects	32
EEA total number of subjects	32

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)	1
From 65 to 84 years	31
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from the out-patient population at the study sites. Potentially eligible patients interested in taking part of the study could also be referred from other clinics.

Pre-assignment

Screening details:

Patients were screened (Visit 1; Screening Visit) for eligibility according to study-specific inclusion/exclusion criteria within 7-21 days before start of Investigational Medicinal Product administration.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

This was a double-blind study and the allocation of treatments was not disclosed until clean file had been declared and the database had been locked. Capsules of IRL752 and placebo were of identical appearance.

Arms

Are arms mutually exclusive?	Yes
Arm title	IRL752

Arm description:

25 subjects were treated with IRL752 (50 mg hard HPMC capsules).

Arm type	Experimental
Investigational medicinal product name	IRL752 50mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

IRL752 capsules, 50 mg: White hard hydroxypropylmethyl cellulose (HPMC) capsule for oral administration coni snap size 3.
The starting dose of IMP was 100 mg TID. Dose adjustments could be made during the first 14 days, at the discretion of the treating physician, according to the following:
- Visit 3 (Day 4): the dose could be increased to 150 mg TID, maintained at 100 mg TID, or reduced to 50 mg TID.
- Visit 4 (Day 8): the dose could be increased up to 200 mg TID, maintained or reduced to any previous dose level.
- Visit 5 (Day 11): the dose could be increased up to 250 mg TID, maintained or reduced to any previous dose level.
The minimum dose was 50 mg (1 capsule) TID and the maximum dose was 250 mg (5 capsules) TID.
The fixed IRL752 dose level for the remaining 14 days of treatment was determined on Day 14 (Visit 6) for each patient (50-250 mg TID).

Arm title	Placebo

Arm description:

7 subjects were treated with placebo (hard HPMC capsules identical in appearance to IRL752 capsules).

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

White hard HPMC capsule for oral administration coni snap size 3 with a matching total weight as for the IRL752 50 mg capsules.
The starting dose of IMP was 100 mg TID. Dose adjustments could be made during the first 14 days, at the discretion of the treating physician, according to the following:
- Visit 3 (Day 4): the dose could be increased to 150 mg TID, maintained at 100 mg TID, or reduced to 50 mg TID.
- Visit 4 (Day 8): the dose could be increased up to 200 mg TID, maintained or reduced to any previous dose level.
- Visit 5 (Day 11): the dose could be increased up to 250 mg TID, maintained or reduced to any previous dose level.
The minimum dose was 50 mg (1 capsule) TID and the maximum dose was 250 mg (5 capsules) TID.
The fixed IRL752 dose level for the remaining 14 days of treatment was determined on Day 14 (Visit 6) for each patient (50-250 mg TID).

Number of subjects in period 1	IRL752	Placebo
Started	25	7
Completed	23	6
Not completed	2	1
Adverse event, serious fatal	1	1
Consent withdrawn by subject	1	-

Baseline characteristics

Reporting groups	
Reporting group title	IRL752
Reporting group description:	
25 subjects were treated with IRL752 (50 mg hard HPMC capsules).	
Reporting group title	Placebo
Reporting group description:	
7 subjects were treated with placebo (hard HPMC capsules identical in appearance to IRL752 capsules).	

Reporting group values	IRL752	Placebo	Total
Number of subjects	25	7	32
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	1	0	1
From 65-84 years	24	7	31
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	71.8	72.7	
standard deviation	± 3.89	± 5.59	-
Gender categorical Units: Subjects			
Female	2	2	4
Male	23	5	28
Race Units: Subjects			
White	25	7	32

End points

End points reporting groups

Reporting group title	IRL752
Reporting group description:	
25 subjects were treated with IRL752 (50 mg hard HPMC capsules).	
Reporting group title	Placebo
Reporting group description:	
7 subjects were treated with placebo (hard HPMC capsules identical in appearance to IRL752 capsules).	

Primary: Adverse Events

End point title	Adverse Events[1]
End point description:	
Adverse Events were spontaneously reported by the patients, observed or elicited based on non-leading questions by the Investigator or medical personnel.	
End point type	Primary
End point timeframe:	
From signing the ICF (V1; Screening) until the follow-up assessment (V9; Follow-up). AEs occurring after first administration of IMP (TEAEs) are presented below.	

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: Descriptive statistics.

End point values	IRL752	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25[2]	7		
Units: Number of AEs				
Titration	32	1		
Steady state	24	3		

Notes:

[2] - Titration: N=25
Steady state: N=23

Statistical analyses

No statistical analyses for this end point

Primary: Physical examination

End point title	Physical examination[3]
End point description:	
Physical examination findings were categorized as Normal, Abnormal not clinically significant (NCS), and Abnormal clinically significant (CS). One abnormal finding (pneumonia) assessed as clinically significant but not related to study treatment was reported for patient #1022 on Visit 8 (Day 29). The event was reported as an AE. No other clinically significant findings were reported.	
End point type	Primary
End point timeframe:	
From Visit 1 (Screening) to Visit 9 (Follow-up).	

Notes:

[3] - 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: Descriptive statistics.

End point values	IRL752	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	7		
Units: No of clinical significant (CS) values				
Abdomen (liver and spleen) - Abnormal CS	0	0		
Cardiovascular - Abnormal CS	0	0		
Ears - Abnormal CS	0	0		
Extremities - Abnormal CS	0	0		
Eyes - Abnormal CS	0	0		
Head - Abnormal CS	0	0		
Lungs - Abnormal CS	1	0		
Lymph nodes - Abnormal CS	0	0		
Neurological - Abnormal CS	0	0		
Nose - Abnormal CS	0	0		
Skin - Abnormal CS	0	0		
Throat - Abnormal CS	0	0		
Thyroid - Abnormal CS	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: ECG

End point title	ECG[4]

End point description:

Single 12-lead ECGs were recorded in supine position after 5 min of rest. The parameters PQ, QRS, QT, and QTcF intervals were recorded.

There were no clinically relevant mean changes over time with regards to any of the ECG parameters evaluated and no individual abnormal values assessed as clinically significant.

End point type	Primary

End point timeframe:

From Visit 1 (Screening) to Visit 8 (Follow-up).

Notes:

[4] - 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: Descriptive statistics.

End point values	IRL752	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	7		
Units: No of clinically significant (CS) values				
Visit 1, Screening - Abnormal CS	0	0		

Visit 6, Day 14 - Abnormal CS	0	0		
Visit 7, Day 28 - Abnormal CS	0	0		
Visit 9, Follow-up - Abnormal CS	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Vital signs - Systolic blood pressure

End point title	Vital signs - Systolic blood pressure[5]

End point description:

Systolic/diastolic blood pressure and pulse were measured in the supine position after 5 min of rest.

There were no clinically relevant mean changes over time with regards to any of the vital signs parameters evaluated and no individual abnormal values assessed as clinically significant.

End point type	Primary

End point timeframe:

From Visit 1 (Screening) to Visit 8 (Follow-up).

Notes:

[5] - 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: Descriptive statistics.

End point values	IRL752	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25[6]	7[7]		
Units: mmHg				
arithmetic mean (standard deviation)				
Visit 1, Screening	134.5 (± 19.5)	119.6 (± 13.6)		
Visit 6, Day 14	131.4 (± 17.6)	124.0 (± 15.1)		
Visit 8, Day 29	132.9 (± 23.7)	112.0 (± 8.6)		
Visit 9, Follow-up	137.1 (± 22.3)	125.5 (± 25.0)		

Notes:

[6] - Screening: N=25
Visit 6: N=23
Visit 8: N=23
Visit 9: N=24
[7] - Screening: N=7
Visit 6: N=7
Visit 8: N=6
Visit 9: N=6

Statistical analyses

No statistical analyses for this end point

Primary: Safety laboratory measurements

End point title	Safety laboratory measurements[8]

End point description:

Venous blood samples for analysis of clinical chemistry, haematology and coagulation parameters and urine samples were collected and analysed.

End point type	Primary

End point timeframe:

From Visit 1 (Screening) to Visit 8 (Follow-up).

Notes:

[8] - 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: Descriptive statistics.

End point values	IRL752	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	7		
Units: No of clinically significant (CS) values				
Clinical chemistry	13	0		
Haematology	0	0		
Coagulation	0	0		
Urine	1	0		

Statistical analyses

No statistical analyses for this end point

Primary: Vital signs - Diastolic blood pressure

End point title	Vital signs - Diastolic blood pressure[9]

End point description:

Systolic/diastolic blood pressure and pulse were measured in the supine position after 5 min of rest.

There were no clinically relevant mean changes over time with regards to any of the vital signs parameters evaluated and no individual abnormal values assessed as clinically significant.

End point type	Primary

End point timeframe:

From Visit 1 (Screening) to Visit 8 (Follow-up).

Notes:

[9] - 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: Descriptive statistics.

End point values	IRL752	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25[10]	7[11]		
Units: mmHg				
arithmetic mean (standard deviation)				
Visit 1, Screening	77.0 (± 9.6)	70.9 (± 6.0)		
Visit 6, Day 14	75.4 (± 8.7)	70.4 (± 9.4)		
Visit 8, Day 29	78.2 (± 9.8)	65.8 (± 5.9)		
Visit 9, Follow-up	78.9 (± 11.6)	72.8 (± 14.0)		

Notes:

[10] - Screening: N=25
Visit 6: N=23
Visit 8: N=23
Visit 9: N=24

[11] - Screening: N=7
Visit 6: N=7
Visit 8: N=6
Visit 9: N=6

Statistical analyses

No statistical analyses for this end point

Primary: Vital signs - Pulse

End point title	Vital signs - Pulse[12]

End point description:

Systolic/diastolic blood pressure and pulse were measured in the supine position after 5 min of rest.

There were no clinically relevant mean changes over time with regards to any of the vital signs parameters evaluated and no individual abnormal values assessed as clinically significant.

End point type	Primary

End point timeframe:

From Visit 1 (Screening) to Visit 8 (Follow-up).

Notes:

[12] - 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: Descriptive statistics.

End point values	IRL752	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25[13]	7[14]		
Units: beats/min				
arithmetic mean (standard deviation)				
Visit 1, Screening	63.8 (± 7.5)	62.9 (± 5.6)		
Visit 6, Day 14	67.2 (± 11.3)	66.1 (± 11.9)		
Visit 8, Day 29	61.3 (± 8.5)	62.5 (± 11.7)		
Visit 9, Follow-up	64.0 (± 12.4)	63.3 (± 10.3)		

Notes:

[13] - Visit 1: N=25
Visit 6: N=23
Visit 8: N=23
Visit 9: N=24
[14] - Visit 1: N=7
Visit 6: N=7
Visit 8: N=6
Visit 9: N=6

Statistical analyses

No statistical analyses for this end point

Secondary: Unified Parkinson’s Disease Rating Scale (UPDRS)

End point title	Unified Parkinson’s Disease Rating Scale (UPDRS)

End point description:

The objective was to evaluate the effects of IRL752 on symptoms of PD assessed with Unified Parkinson’s Disease Rating Scale (UPDRS) part 1-4, as compared to placebo. Data based on FAS

End point type	Secondary

End point timeframe:

From baseline to end of treatment.

End point values	IRL752	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[15]	7[16]		
Units: Score				
arithmetic mean (standard deviation)				
1. Mention, Behavior and Mood - Day 1	5.8 (± 1.7)	5.6 (± 2.3)		
1. Mention, Behavior and Mood - Day 28	5.2 (± 2.1)	5.0 (± 3.0)		
2. Activities of daily living - Day 1	15.8 (± 6.7)	20.6 (± 6.8)		
2. Activities of daily living - Day 28	15.7 (± 5.9)	20.0 (± 7.3)		
3. Motor examination - Day 1	30.3 (± 11.1)	31.3 (± 13.5)		
3. Motor examination - Day 28	29.7 (± 11.8)	28.2 (± 15.3)		
4. Complication of therapy - Day 1	4.5 (± 2.2)	5.1 (± 3.4)		
4. Complication of therapy - Day 28	4.4 (± 2.9)	4.5 (± 3.5)		

Notes:

[15] - Day 1: 24
Day 28: 23
[16] - Day 1: 7
Day 28: 6

Statistical analyses

No statistical analyses for this end point

Secondary: Timed Up and Go (TUG)

End point title	Timed Up and Go (TUG)

End point description:

The objective was to evaluate the effects of IRL752 on postural control and walking speed assessed with Timed Up and Go (TUG) test, as compared to placebo. Data based on FAS population.

End point type	Secondary

End point timeframe:

From baseline to end of treatment.

End point values	IRL752	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[17]	7[18]		
Units: seconds				
arithmetic mean (standard deviation)				
Day 1	15.7 (± 17.2)	13.6 (± 4.5)		
Day 28	19.1 (± 40.2)	10.9 (± 1.9)		

Notes:

[17] - Day 1: 24
Day 28:23
[18] - Day 1: 7
Day 28:6

Statistical analyses

No statistical analyses for this end point

Secondary: Freezing of Gait Questionnaire (FOGQ)

End point title	Freezing of Gait Questionnaire (FOGQ)

End point description:

The objective was to evaluate the effects of IRL752 on freezing of gait assessed with the Freezing of Gait Questionnaire (FOGQ), as compared to placebo. Data based on FAS population.

End point type	Secondary

End point timeframe:

From baseline to end of treatment.

End point values	IRL752	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[19]	7[20]		
Units: score				
arithmetic mean (standard deviation)				
Day 1	8.7 (± 6.2)	14.3 (± 4.8)		
Day 28	7.8 (± 5.1)	13.8 (± 2.9)		

Notes:

[19] - Day 1: 24
Day 28: 23
[20] - Day 1: 7
Day 28: 6

Statistical analyses

No statistical analyses for this end point

Secondary: CANTAB - Motor Screening: Mean Latency

End point title	CANTAB - Motor Screening: Mean Latency

End point description:

The objective was to evaluate the effects of IRL752 on cognitive functions assessed with the Cambridge Neuropsychological Test Automated Battery (CANTAB), as compared to placebo, including:
- Motor Screening task
- Reaction Time (RTI) task
- Spatial Working Memory (SWM) task
- Planning and executive function test, One Touch Stockings of Cambridge (OTS)
Data based on FAS population.

Motor Screening - Mean Latency: The mean latency from the display of a stimulus to a correct response to that stimulus during assessment trials.

End point type	Secondary

End point timeframe:

From baseline to end of treatment.

End point values	IRL752	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23[21]	7[22]		
Units: msec				
arithmetic mean (standard deviation)				
Screening	1413.6 (± 647.1)	1128.1 (± 258.8)		
Day 1	1382.8 (± 664.9)	1235.6 (± 295.7)		
Day 28	1392.4 (± 708.7)	1012.8 (± 254.2)		

Notes:

[21] - Screening: 23
Day 1: 24
Day 28: 22
[22] - Screening: 7
Day 1: 7
Day 28: 6

Statistical analyses

No statistical analyses for this end point

Secondary: CANTAB - Motor Screening: Incorrect responses

End point title	CANTAB - Motor Screening: Incorrect responses

End point description:

The objective was to evaluate the effects of IRL752 on cognitive functions assessed with the Cambridge Neuropsychological Test Automated Battery (CANTAB), as compared to placebo, including:
- Motor Screening task
- Reaction Time (RTI) task
- Spatial Working Memory (SWM) task
- Planning and executive function test, One Touch Stockings of Cambridge (OTS)

Motor Screening - Incorrect responses: The total number of assessment trials on which the subject failed to make a correct response.

Data based on FAS population.

End point type	Secondary

End point timeframe:

From baseline to end of treatment.

End point values	IRL752	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23[23]	7[24]		
Units: number of assessment trials				
arithmetic mean (standard deviation)				
Screening	0.1 (± 0.5)	0.0 (± 0.0)		
Day 1	0.5 (± 1.1)	0.0 (± 0.0)		
Day 28	0.3 (± 1.3)	0.0 (± 0.0)		

Notes:

[23] - Screening: 23
Day 1: 24
Day 28: 22

[24] - Screening: 7
Day 1: 7
Day 28: 6

Statistical analyses

No statistical analyses for this end point

Secondary: CANTAB - Motor Screening: Correct responses

End point title	CANTAB - Motor Screening: Correct responses

End point description:

The objective was to evaluate the effects of IRL752 on cognitive functions assessed with the Cambridge Neuropsychological Test Automated Battery (CANTAB), as compared to placebo, including:
- Motor Screening task
- Reaction Time (RTI) task
- Spatial Working Memory (SWM) task
- Planning and executive function test, One Touch Stockings of Cambridge (OTS)

Motor Screening - Correct responses: The total number of assessment trials on which the subject made a correct response.

Data based on FAS population.

End point type	Secondary

End point timeframe:

From baseline to end of treatment.

End point values	IRL752	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23[25]	7[26]		
Units: number of assessment trials				
arithmetic mean (standard deviation)				
Screening	9.9 (± 0.5)	10.0 (± 0.0)		
Day 1	9.5 (± 1.1)	10.0 (± 0.0)		
Day 28	9.7 (± 1.3)	10.0 (± 0.0)		

Notes:

[25] - Screening: 23
Day 1: 24
Day 28: 22

[26] - Screening: 7
Day 1: 7
Day 28: 6

Statistical analyses

No statistical analyses for this end point

Secondary: CANTAB - RTI: Reaction time

End point title	CANTAB - RTI: Reaction time

End point description:

The objective was to evaluate the effects of IRL752 on cognitive functions assessed with the Cambridge Neuropsychological Test Automated Battery (CANTAB), as compared to placebo, including:

- Motor Screening task
- Reaction Time (RTI) task
- Spatial Working Memory (SWM) task
- Planning and executive function test, One Touch Stockings of Cambridge (OTS)
Data based on FAS population.

End point type	Secondary

End point timeframe:

From baseline to end of treatment.

End point values	IRL752	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21[27]	7[28]		
Units: msec				
arithmetic mean (standard deviation)				
Reaction Time: Screening	645.4 (± 328.1)	636.7 (± 154.5)		
Reaction Time: Day 1	750.0 (± 532.4)	579.2 (± 134.5)		
Reaction Time: Day 28	651.7 (± 308.0)	572.4 (± 122.2)		
Movement Time: Screening	540.9 (± 369.5)	567.2 (± 328.8)		
Movement Time: Day 1	762.5 (± 666.4)	463.1 (± 159.9)		
Movement Time: Day 28	621.5 (± 517.5)	466.6 (± 198.4)		

Notes:

[27] - Screening: 21
Reaction Time Day 1: 23
Reaction Time Day 28: 21
[28] - Screening: 7
Day 1: 7
Day 28: 6

Statistical analyses

No statistical analyses for this end point

Secondary: CANTAB - Spatial Working Memory (SWM): Total errors

End point title	CANTAB - Spatial Working Memory (SWM): Total errors

End point description:

The objective was to evaluate the effects of IRL752 on cognitive functions assessed with the Cambridge Neuropsychological Test Automated Battery (CANTAB), as compared to placebo, including:
- Motor Screening task
- Reaction Time (RTI) task
- Spatial Working Memory (SWM) task
- Planning and executive function test, One Touch Stockings of Cambridge (OTS)
Data based on FAS population.

End point type	Secondary

End point timeframe:

From baseline to end of treatment.

End point values	IRL752	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22[29]	7[30]		
Units: score				
arithmetic mean (standard deviation)				
Screening	31.4 (± 13.2)	26.7 (± 5.2)		
Day 1	28.3 (± 8.2)	28.0 (± 4.4)		
Day 28	27.7 (± 9.3)	30.8 (± 10.1)		

Notes:

[29] - Screening: 22
Day 1: 23
Day 28: 20
[30] - Screening: 7
Day 1: 7
Day 28: 6

Statistical analyses

No statistical analyses for this end point

Secondary: CANTAB - Spatial Working Memory (SWM): Within errors

End point title	CANTAB - Spatial Working Memory (SWM): Within errors

End point description:

The objective was to evaluate the effects of IRL752 on cognitive functions assessed with the Cambridge Neuropsychological Test Automated Battery (CANTAB), as compared to placebo, including:
- Motor Screening task
- Reaction Time (RTI) task
- Spatial Working Memory (SWM) task
- Planning and executive function test, One Touch Stockings of Cambridge (OTS)

SWM within errors: The number of times a subject revisits a box already shown to be empty during the same search.

Data based on FAS population.

End point type	Secondary

End point timeframe:

From baseline to end of treatment.

End point values	IRL752	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22[31]	7[32]		
Units: score				
arithmetic mean (standard deviation)				
Screening	6.7 (± 9.6)	3.9 (± 4.5)		
Day 1	4.3 (± 6.7)	3.7 (± 3.6)		
Day 28	3.9 (± 8.8)	5.5 (± 5.8)		

Notes:

[31] - Screening: 22
Day 1: 23
Day 28: 20
[32] - Screening: 7
Day 1: 7
Day 28: 6

Statistical analyses

No statistical analyses for this end point

Secondary: CANTAB - Spatial Working Memory (SWM): Between errors

End point title	CANTAB - Spatial Working Memory (SWM): Between errors

End point description:

The objective was to evaluate the effects of IRL752 on cognitive functions assessed with the Cambridge Neuropsychological Test Automated Battery (CANTAB), as compared to placebo, including:
- Motor Screening task
- Reaction Time (RTI) task
- Spatial Working Memory (SWM) task
- Planning and executive function test, One Touch Stockings of Cambridge (OTS)

SWM Between errors: The number of times the subject incorrectly revisits a box in which a token has previously been found.

Data based on FAS population.

End point type	Secondary

End point timeframe:

From baseline to end of treatment.

End point values	IRL752	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22[33]	7[34]		
Units: score				
arithmetic mean (standard deviation)				
Screening	29.0 (± 10.7)	26.0 (± 5.2)		
Day 1	27.1 (± 7.2)	27.3 (± 4.4)		
Day 28	26.7 (± 7.2)	29.7 (± 8.9)		

Notes:

[33] - Screening: 22
Day 1: 23
Day 28: 20
[34] - Screening: 7
Day 1: 7
Day 28: 6

Statistical analyses

No statistical analyses for this end point

Secondary: CANTAB - Spatial Working Memory (SWM): Strategy

End point title	CANTAB - Spatial Working Memory (SWM): Strategy

End point description:

The objective was to evaluate the effects of IRL752 on cognitive functions assessed with the Cambridge Neuropsychological Test Automated Battery (CANTAB), as compared to placebo, including:
- Motor Screening task
- Reaction Time (RTI) task
- Spatial Working Memory (SWM) task
- Planning and executive function test, One Touch Stockings of Cambridge (OTS)

SWM Strategy: The number of times a subject begins a new search pattern from the same box they started with previously.

Data based on FAS population.

End point type	Secondary

End point timeframe:

From baseline to end of treatment.

End point values	IRL752	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22[35]	7[36]		
Units: score				
arithmetic mean (standard deviation)				
Screening	9.5 (± 1.9)	9.3 (± 0.8)		
Day 1	9.4 (± 1.5)	10.3 (± 1.1)		
Day 28	9.6 (± 1.5)	9.8 (± 1.0)		

Notes:

[35] - Screening: 22
Day 1: 23
Day 28: 20
[36] - Screening: 7
Day 1: 7
Day 28: 6

Statistical analyses

No statistical analyses for this end point

Secondary: CANTAB - One Touch Stockings (OTS): First choice accuracy

End point title	CANTAB - One Touch Stockings (OTS): First choice accuracy

End point description:

The objective was to evaluate the effects of IRL752 on cognitive functions assessed with the Cambridge Neuropsychological Test Automated Battery (CANTAB), as compared to placebo, including:
- Motor Screening task
- Reaction Time (RTI) task
- Spatial Working Memory (SWM) task
- Planning and executive function test, One Touch Stockings of Cambridge (OTS)

OTS First choice accuracy: The total number of assessed trials where the subject choose the correct answer on the first attempt.

Data based on FAS population.

End point type	Secondary

End point timeframe:

From baseline to end of treatment.

End point values	IRL752	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[37]	6[38]		
Units: score				
arithmetic mean (standard deviation)				
Screening	4.2 (± 2.9)	4.3 (± 1.4)		
Day 1	3.9 (± 4.0)	3.0 (± 1.1)		
Day 28	4.9 (± 3.0)	3.2 (± 1.1)		

Notes:

[37] - Screening: 20
Day 1: 23
Day 28: 20
[38] - Screening: 6
Day 1: 6
Day 28: 5

Statistical analyses

No statistical analyses for this end point

Secondary: CANTAB - One Touch Stockings: Median Latency Correct

End point title	CANTAB - One Touch Stockings: Median Latency Correct

End point description:

The objective was to evaluate the effects of IRL752 on cognitive functions assessed with the Cambridge Neuropsychological Test Automated Battery (CANTAB), as compared to placebo, including:
- Motor Screening task
- Reaction Time (RTI) task
- Spatial Working Memory (SWM) task
- Planning and executive function test, One Touch Stockings of Cambridge (OTS)

OTS Median Latency Correct: The median latency, measured from the appearance of the stocking balls until the correct box choice was made by the subject.

Data based on FAS population.

End point type	Secondary

End point timeframe:

From baseline to end of treatment.

End point values	IRL752	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[39]	6[40]		
Units: score				
arithmetic mean (standard deviation)				
Screening	46399.0 (± 35576.8)	47776.5 (± 56226.5)		
Day 1	47512.7 (± 35512.9)	57887.8 (± 63752.6)		
Day 28	43590.2 (± 38919.0)	60184.4 (± 59576.5)		

Notes:

[39] - Screening: 20
Day 1: 23
Day 28: 20
[40] - Screening: 6
Day 1: 6
Day 28: 5

Statistical analyses

No statistical analyses for this end point

Secondary: Neuropsychiatric Inventory-12 (NPI-12)

End point title	Neuropsychiatric Inventory-12 (NPI-12)

End point description:

The objective was to evaluate the effects of IRL752 on neuropsychiatric symptoms assessed with Neuropsychiatric Inventory-12 (NPI-12), as compared to placebo.

The NPI-12 is a clinical instrument for assessing behavioural and psychological symptoms in dementia in 12 domains [13]. It is based on an interview with the primary caregiver. Each NPI domain is scored by the caregiver based on a standardized interview administered by the clinician. Each domain is scored for frequency, severity and associated caregiver distress. A higher score represents a higher severity or caregiver distress.

Data based on FAS population.

End point type	Secondary

End point timeframe:

From baseline (screening) to end of treatment.

End point values	IRL752	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[41]	7[42]		
Units: score				
arithmetic mean (standard deviation)				
Caregiver distress: Screening	7.9 (± 5.5)	11.3 (± 8.0)		
Caregiver distress: Day 29	6.4 (± 5.8)	7.2 (± 7.9)		
Severity: Screening	16.3 (± 10.1)	12.3 (± 8.3)		
Severity: Day 29	14.5 (± 13.1)	10.3 (± 15.7)		

Notes:

[41] - Screening: 24
Day 29: 23
[42] - Screening: 7
Day 29: 6

Statistical analyses

No statistical analyses for this end point

Secondary: Clinician's Interview-Based Impression of Change Plus caregiver input (CIBIC-Plus)

End point title	Clinician's Interview-Based Impression of Change Plus caregiver input (CIBIC-Plus)

End point description:

The objective was to evaluate the effects of IRL752 on global function assessed with Clinician's Interview-Based Impression of Change Plus caregiver input (CIBIC-Plus), as compared to placebo.

The CIBIC-Plus is a validated clinical instrument used to measure change in global function through an interview with patients and their caregivers. Patients are assessed on a 7-point scale, "1=Very much improved" to "7=Marked worsening", based on information from four major categories: General, Mental/Cognitive State, Behaviour, and ADLs.

Data based on FAS population.

End point type	Secondary

End point timeframe:

At end of treatment.

End point values	IRL752	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	6		
Units: Number of observations				
Subject's interview: 2. Much improved	0	1		
Subject's interview: 3. Minimally improved	5	1		
Subject's interview: 4. No change	11	4		
Subject's interview: 5. Minimal worsening	4	0		
Subject's interview: 6. Moderate worsening	3	0		
Informant's interview: 2. Much improved	1	0		
Informant's interview: 3. Minimally improved	4	2		
Informant's interview: 4. No change	12	4		
Informant's interview: 5. Minimal worsening	4	0		
Informant's interview: 6. Moderate worsening	1	0		
Informant's interview: 7. Marked worsening	1	0		
Overall score: 3. Minimally improved	5	2		
Overall score: 4. No change	14	4		
Overall score: 5. Minimal worsening	3	0		
Overall score: 6. Moderate worsening	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: EEG

End point title	EEG

End point description:

The objective was to evaluate the effects of IRL752 on electroencephalography (EEG) pattern changes as compared to placebo.

Resting EEG recordings were captured with no less than 5 min of technically satisfactory, artefact free recording. EEGs were captured at Baseline (Visit 2) and at end of treatment (Visit 7).

Data based on FAS population.

End point type	Secondary

End point timeframe:

From baseline to end of treatment.

End point values	IRL752	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[43]	7[44]		
Units: Ach index				
arithmetic mean (standard deviation)				
Day 1	78.1 (± 18.3)	79.0 (± 10.4)		
Day 28	77.7 (± 18.3)	82.7 (± 9.4)		

Notes:

[43] - Day 1: 24
Day 28: 23
[44] - Day 1: 7
Day 28: 6

Statistical analyses

No statistical analyses for this end point

Secondary: Exposure of IRL752

End point title	Exposure of IRL752[45]

End point description:

The objective was to examine the exposure of IRL752 in patients with PDD.

Venous blood samples (approximately 5 mL) for the determination of concentrations of IRL752 in plasma were collected at specified time-points.

End point type	Secondary

End point timeframe:

From baseline to end of treatment.

Notes:

[45] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Exposure is not applicable for the placebo group.

End point values	IRL752			
Subject group type	Reporting group			
Number of subjects analysed	24[46]			
Units: nM				
arithmetic mean (standard deviation)				
Day 1: Pre-dose	0 (± 0)			
Day 1: 2 hours	1380 (± 568.8)			
Day 14: Pre-dose	1822 (± 916.8)			
Day 14: 2 hours	4275 (± 1717)			
Day 28: Pre-dose	1515 (± 517.5)			
Day 28: 2 hours	3969 (± 1354)			

Notes:

[46] - Day 1: 24
Day 14: 23
Day 28: 23

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From signing the ICF (Visit 1; Screening) until the follow-up assessment (Visit 8). AEs occurring after first administration of IMP (TEAEs) is presented below.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	IRL752 Steady state
Reporting group description: 25 patients were treated with IRL752.	
Reporting group title	Placebo Steady state
Reporting group description: 7 patients were treated with placebo.	
Reporting group title	IRL752 Titration
Reporting group description: 25 patients were treated with IRL752.	
Reporting group title	Placebo Titration
Reporting group description: 7 patients were treated with placebo.	

Serious adverse events	IRL752 Steady state	Placebo Steady state	IRL752 Titration
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 23 (0.00%)	1 / 7 (14.29%)	1 / 25 (4.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Collum fracture			
subjects affected / exposed	0 / 23 (0.00%)	1 / 7 (14.29%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Freeze x 3 during night			
subjects affected / exposed	0 / 23 (0.00%)	0 / 7 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			

Confused			
subjects affected / exposed	0 / 23 (0.00%)	0 / 7 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infection			
subjects affected / exposed	0 / 23 (0.00%)	0 / 7 (0.00%)	1 / 25 (4.00%)
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	Placebo Titration		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 7 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Collum fracture			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Freeze x 3 during night			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confused			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infection			
subjects affected / exposed	0 / 7 (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: 0 %

Non-serious adverse events	IRL752 Steady state	Placebo Steady state	IRL752 Titration
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 23 (47.83%)	1 / 7 (14.29%)	16 / 25 (64.00%)
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 23 (4.35%)	0 / 7 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Oedema peripheral			
subjects affected / exposed	1 / 23 (4.35%)	0 / 7 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 7 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 7 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	0 / 23 (0.00%)	0 / 7 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 23 (4.35%)	0 / 7 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Confusional state			
subjects affected / exposed	0 / 23 (0.00%)	0 / 7 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Depression			
subjects affected / exposed	0 / 23 (0.00%)	0 / 7 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Hallucination			
subjects affected / exposed	1 / 23 (4.35%)	0 / 7 (0.00%)	1 / 25 (4.00%)
occurrences (all)	1	0	1
Irritability			

subjects affected / exposed	1 / 23 (4.35%)	0 / 7 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 23 (4.35%)	0 / 7 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Hepatic enzyme increased			
subjects affected / exposed	3 / 23 (13.04%)	0 / 7 (0.00%)	0 / 25 (0.00%)
occurrences (all)	3	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 23 (8.70%)	0 / 7 (0.00%)	0 / 25 (0.00%)
occurrences (all)	3	0	0
Cardiac disorders			
Atrioventricular block			
subjects affected / exposed	0 / 23 (0.00%)	1 / 7 (14.29%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 23 (0.00%)	0 / 7 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Cognitive disorder			
subjects affected / exposed	2 / 23 (8.70%)	0 / 7 (0.00%)	1 / 25 (4.00%)
occurrences (all)	2	0	1
Dizziness			
subjects affected / exposed	0 / 23 (0.00%)	0 / 7 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	0 / 23 (0.00%)	0 / 7 (0.00%)	3 / 25 (12.00%)
occurrences (all)	0	0	3
Parkinsonism			
subjects affected / exposed	0 / 23 (0.00%)	0 / 7 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Tremor			
subjects affected / exposed	0 / 23 (0.00%)	0 / 7 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2

Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 23 (4.35%)	0 / 7 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Xerophthalmia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 7 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 7 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Abdominal pain upper			
subjects affected / exposed	0 / 23 (0.00%)	0 / 7 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2
Constipation			
subjects affected / exposed	1 / 23 (4.35%)	0 / 7 (0.00%)	1 / 25 (4.00%)
occurrences (all)	1	0	1
Dry mouth			
subjects affected / exposed	0 / 23 (0.00%)	1 / 7 (14.29%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Gastritis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 7 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 23 (0.00%)	0 / 7 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Proctalgia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 7 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	0 / 23 (0.00%)	0 / 7 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 7 (0.00%)	1 / 25 (4.00%)
occurrences (all)	1	0	1

Skin reaction			
subjects affected / exposed	0 / 23 (0.00%)	0 / 7 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Musculoskeletal stiffness			
subjects affected / exposed	0 / 23 (0.00%)	0 / 7 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	0 / 23 (0.00%)	0 / 7 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2
Posture abnormal			
subjects affected / exposed	1 / 23 (4.35%)	0 / 7 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 7 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	0 / 23 (0.00%)	0 / 7 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 7 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 7 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	1 / 23 (4.35%)	0 / 7 (0.00%)	1 / 25 (4.00%)
occurrences (all)	1	0	1
Viral infection			
subjects affected / exposed	0 / 23 (0.00%)	0 / 7 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1

Non-serious adverse events	Placebo Titration		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 7 (14.29%)		

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Oedema peripheral			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Confusional state			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hallucination			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Irritability			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Investigations			
Blood alkaline phosphatase increased			

subjects affected / exposed occurrences (all) Hepatic enzyme increased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0 0 / 7 (0.00%) 0		
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	 0 / 7 (0.00%) 0		
Cardiac disorders Atrioventricular block subjects affected / exposed occurrences (all)	 0 / 7 (0.00%) 0		
Nervous system disorders Balance disorder subjects affected / exposed occurrences (all) Cognitive disorder subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Parkinsonism subjects affected / exposed occurrences (all) Tremor subjects affected / exposed occurrences (all)	 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	 0 / 7 (0.00%) 0		

Eye disorders			
Xerophthalmia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Dry mouth			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Gastritis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Proctalgia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Toothache			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Skin reaction			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue			

disorders			
Musculoskeletal stiffness			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Posture abnormal			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Pneumonia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Viral infection			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported