Clinical trial results:
A randomised, double-blind, placebo-controlled, phase IIA study evaluating the efficacy and tolerability of IRL790 in Parkinson's disease dyskinesia

Summary

EudraCT number	2017-003458-18
Trial protocol	GB SE
Global end of trial date	12 June 2019

Results information

Result version number	v1 (current)
This version publication date	20 March 2020
First version publication date	20 March 2020

Trial information

Trial identification

Sponsor protocol code	IRL790C003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03368170
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Integrative Research Laboratories AB (IRLAB)
Sponsor organisation address	Arvid Wallgrens backe 20, Gothenburg, Sweden, 413 46
Public contact	Clinical Trials Information, Integrative Research Laboratories AB (IRLAB), +46 (0)707601691, joakim.tedroff@irlab.se
Scientific contact	Clinical Trials Information, Integrative Research Laboratories AB (IRLAB), +46 (0)707601691, 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	14 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 June 2019
Global end of trial reached?	Yes
Global end of trial date	12 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of IRL790 in Parkinson's disease dyskinesia

Protection of trial subjects:

This study was conducted in compliance with International Conference for Harmonisation Good Clinical Practice (ICH GCP) guidelines and with the ethical principles originating in the Declaration of Helsinki. Written informed consent was obtained from all study subjects before any study related procedures were performed. A Data Safety Monitoring Board (DSMB) were used for this study, responsible for reviewing and commenting on the cumulative safety data.

Background therapy:

Patients included in the study had to be on stable anti-Parkinson treatment for at least 30 days prior screening and during the study.

Evidence for comparator: -

Actual start date of recruitment	01 November 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 15
Country: Number of subjects enrolled	United Kingdom: 60
Worldwide total number of subjects	75
EEA total number of subjects	75

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)	28

From 65 to 84 years	47
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment period 13 months (12 Apr 18 - 9 May 19). First patient first visit: 12 April 2019. Last patient last visit: 12 June 2019.
Participating countries: UK and Sweden.
A total of 75 subjects were randomized study (39 on active study drug and 36 on placebo). 72 subjects completed the study (37 on active study drug and 35 on placebo).

Pre-assignment

Screening details:

The screening period was up to 4 weeks and the treatment period was 4 weeks followed by a follow-up visit 5-8 days after end of treatment. A total of 108 subjects were enrolled in the study and a total of 75 subjects were randomized in the study.

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, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Mesdopetam

Arm description:

Mesdopetam (IRL790). Capsule 2.5 mg. Oral administration b.i.d.

Arm type	Experimental
Investigational medicinal product name	Mesdopetam
Investigational medicinal product code	IRL790
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

This was a randomized, placebo-controlled study with the patients taking the study drug for 4 weeks at home. Mesdopetam was taken twice daily (5 mg, 7.5 mg or 10 mg b.i.d.) as adjunctive treatment to the patients' regular and stable antiparkinsonian medication. The first two weeks of treatment allowed for per patient titration of study medication to the highest tolerated per patient dose for an additional two weeks.
Capsules were to be swallowed intact together with 200 mL of tap water in the morning and in the afternoon approximately 8 hours apart of each administration day.
Formulation details: 2.5 mg free base equivalent: White hard Hydroxypropyl Methylcellulose (HPMC) capsule, coni snap size 3, colour with containing IRL790 X 1/2 L-tartrate.

Arm title	Placebo

Arm description:

Placebo comparator. Matching placebo capsule. Oral administration b.i.d.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

This was a randomized, placebo-controlled study with the patients taking the study drug for 4 weeks at home. Placebo capsules were taken twice daily (b.i.d.) as adjunctive treatment to the patients' regular

and stable antiparkinsonian medication. The first two weeks of treatment allowed for per patient titration of study medication to the highest number of placebo capsules (1 capsule x 4) per patient tolerated dose for an additional two weeks.
Capsules were to be swallowed intact together with 200 mL of tap water in the morning and in the afternoon approximately 8 hours apart of each administration day.
Formulation details: White hard Hydroxypropyl Methylcellulose (HPMC) capsule, coni snap size 3, colour white containing starch.

Number of subjects in period 1	Mesdopetam	Placebo
Started	39	36
Completed	37	35
Not completed	2	1
Adverse event, non-fatal	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Mesdopetam
Reporting group description:	
Mesdopetam (IRL790). Capsule 2.5 mg. Oral administration b.i.d.	
Reporting group title	Placebo
Reporting group description:	
Placebo comparator. Matching placebo capsule. Oral administration b.i.d.	

Reporting group values	Mesdopetam	Placebo	Total
Number of subjects	39	36	75
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)	15	13	28
From 65-84 years	24	23	47
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	65.5	67.7	
standard deviation	± 8.9	± 7.7	-
Gender categorical Units: Subjects			
Female	20	13	33
Male	19	23	42
Ethnicity Units: Subjects			
Hispanic or Latino	0	1	1
Not Hispanic or Latino	39	35	74
Race Units: Subjects			
Asian	1	0	1
White	38	35	73
Unknown or not reported	0	1	1
Body Mass Index (BMI) Units: units on a scale			
arithmetic mean	26.6	25.3	
standard deviation	± 7.2	± 4.2	-
Height Units: centimeter			
arithmetic mean	166.7	169	

standard deviation	± 10.3	± 9.4	-
Years with Parkinson's disease Units: Years			
arithmetic mean	10.7	10.7	
standard deviation	± 5.9	± 4.3	-

End points

End points reporting groups

Reporting group title	Mesdopetam
Reporting group description:	
Mesdopetam (IRL790). Capsule 2.5 mg. Oral administration b.i.d.	
Reporting group title	Placebo
Reporting group description:	
Placebo comparator. Matching placebo capsule. Oral administration b.i.d.	

Primary: The change from baseline to day 28 of treatment (Visit 4) in the sum of the items comprising the Unified Dyskinesia Rating Scale (UDysRS).

End point title	The change from baseline to day 28 of treatment (Visit 4) in the sum of the items comprising the Unified Dyskinesia Rating Scale (UDysRS).
End point description:	
The UDysRS is administered to assess dyskinesia. The scoring range is 0-104, where higher score means more dyskinesia.	
End point type	Primary
End point timeframe:	
The change from baseline to day 28 of treatment (Visit 4).	

End point values	Mesdopetam	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	34		
Units: Score on a scale				
least squares mean (confidence interval 95%)	-4.2 (-7.3 to -1.0)	-7.0 (-10.3 to -3.8)		

Statistical analyses

Statistical analysis title	Total UDysRS score
Statistical analysis description:	
Absolute change from baseline to end of treatment.	
Comparison groups	Mesdopetam v Placebo
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	7.5

Secondary: Change in MDS-UPDRS sum score of questions 4.1 (Time spent with dyskinesias) and 4.2 (Functional impact of dyskinesias) in part IV from baseline to visit 4.

End point title	Change in MDS-UPDRS sum score of questions 4.1 (Time spent with dyskinesias) and 4.2 (Functional impact of dyskinesias) in part IV from baseline to visit 4.

End point description:

Maximum score is 8, where a higher score means more dyskinesia.

End point type	Secondary

End point timeframe:

Change from baseline to visit 4.

End point values	Mesdopetam	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	35		
Units: Score on a scale				
least squares mean (confidence interval 95%)	-1.3 (-1.8 to 0.8)	-0.6 (-1.1 to 0.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in MDS-UPDRS sum score of parts II+III (Motor aspects of Experiences of Daily living + Motor Examination) from baseline to visit 4.

End point title	Change in MDS-UPDRS sum score of parts II+III (Motor aspects of Experiences of Daily living + Motor Examination) from baseline to visit 4.

End point description:

Minimum value is 0 and maximum value is 124. Higher score mean a worse outcome.

End point type	Secondary

End point timeframe:

Change from baseline to visit 4.

End point values	Mesdopetam	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	35		
Units: score on a scale				
least squares mean (confidence interval 95%)	-3.0 (-6.5 to 0.6)	-2.2 (-5.9 to 1.4)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in "ON"-time with troublesome dyskinesia as assessed by patient completed 24-hour diaries, from run-in to visit 4.

End point title	Change in "ON"-time with troublesome dyskinesia as assessed by patient completed 24-hour diaries, from run-in to visit 4.

End point description:

This is a self administered diary where patients assess their motor state every half hour during 24 hours.

End point type	Other pre-specified

End point timeframe:

Change in from run-in to visit 4.

End point values	Mesdopetam	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	34		
Units: Daily hours				
least squares mean (confidence interval 95%)	-3.3 (-4.3 to 2.4)	-1.7 (-2.8 to 0.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 5 weeks (from the randomization visit to the follow up visit)	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0
Reporting groups	
Reporting group title	Mesdopetam
Reporting group description: mesdopetam (IRL790). Capsule 2.5 mg, oral administration b.i.d.	
Reporting group title	Placebo
Reporting group description: placebo comparator. Identical capsule, oral administration b.i.d.	

Serious adverse events	Mesdopetam	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 39 (0.00%)	0 / 36 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Mesdopetam	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 39 (74.36%)	28 / 36 (77.78%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	4 / 39 (10.26%)	3 / 36 (8.33%)	
occurrences (all)	5	7	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 39 (5.13%)	3 / 36 (8.33%)	
occurrences (all)	2	3	
Dyskinesia			

subjects affected / exposed	4 / 39 (10.26%)	2 / 36 (5.56%)	
occurrences (all)	4	3	
Freezing phenomenon			
subjects affected / exposed	1 / 39 (2.56%)	4 / 36 (11.11%)	
occurrences (all)	1	4	
Gait disturbance			
subjects affected / exposed	0 / 39 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Headache			
subjects affected / exposed	5 / 39 (12.82%)	5 / 36 (13.89%)	
occurrences (all)	6	5	
On and off phenomenon			
subjects affected / exposed	2 / 39 (5.13%)	1 / 36 (2.78%)	
occurrences (all)	2	2	
Parkinsonism	Additional description: In the mesdopetam group, 7 of the parkinsonism adverse events occurred during the titration phase (i.e. the first 2 weeks of study treatment) and only 2 of the parkinsonism event during steady state (i.e. the last two weeks of study treatment.		
subjects affected / exposed	9 / 39 (23.08%)	3 / 36 (8.33%)	
occurrences (all)	9	3	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 39 (5.13%)	9 / 36 (25.00%)	
occurrences (all)	2	9	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 39 (0.00%)	4 / 36 (11.11%)	
occurrences (all)	0	4	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 39 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 39 (5.13%)	2 / 36 (5.56%)	
occurrences (all)	2	2	
Sleep disorder			

subjects affected / exposed	3 / 39 (7.69%)	2 / 36 (5.56%)	
occurrences (all)	3	2	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	0 / 39 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
muscoloskeletal stiffness			
subjects affected / exposed	1 / 39 (2.56%)	3 / 36 (8.33%)	
occurrences (all)	1	4	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	2 / 39 (5.13%)	2 / 36 (5.56%)	
occurrences (all)	2	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 October 2017	Version 2. Updates to section 6.4 "Blinding and randomization".
14 November 2017	Version 3. Updates to sections "synopsis & schedule of assessments", 8.2.2.4 "MDS-UPDRS", 6.4 "Blinding & randomization", 8.2.2.5.1 "Rush filming protocol", 4.3 "Inclusion/Exclusion criteria", 1.3 "summary of risk management". 2.2 "Secondary objectives", 3.1 "Study design", 7.2 + 7.6 (Visit descriptions), 8.2.2.6 "PKG", 11.7 "Efficacy endpoints", 1.1.2 "Efficacy", abbreviations and contact details to statistics and IRS.
11 June 2018	Version 4. Updates to sections 8.1.1 "Ethnic origin", 8.1.5 "ECG", 11.4 "Ethnicity", 9 "statistical analysis" and change of statistician.
24 July 2018	Version 5. Updates to sections 7.8 (updated visit description) and 5.2 "non-permitted concomitant medications".
14 January 2019	Version 6. Updates to sections 4 "Inclusion/Exclusion criteria", 7.3 "Contraception methods", 4.1 "re-screening clarification" and addition of CTC as Swedish CRO.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Technical difficulties in administration of UDysRS objective score. A post-hoc analysis was performed on 41 rush films and showed that 24% of the patients were NOT in ON-phase during the UDysRS part III+IV dyskinesia assessment.

Notes: