Clinical trial results:
A Phase 3, Long-term, Open-label Study of Istradefylline in Subjects with Moderate to Severe Parkinson's Disease

Summary

EudraCT number	2015-003887-34
Trial protocol	DE CZ PL IT
Global end of trial date	20 December 2017

Results information

Result version number	v1 (current)
This version publication date	03 January 2019
First version publication date	03 January 2019

Trial information

Trial identification

Sponsor protocol code	6002-018

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02610231
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Kyowa Kirin Pharmaceutical Development, Inc
Sponsor organisation address	212 Carnegie Center, Princeton, United States, 08540
Public contact	Clinical Trial Help Desk, Kyowa Kirin Pharmaceutical Development, Inc., 6002014helpdesk@kyowakirin.com
Scientific contact	Clinical Trial Help Desk, Kyowa Kirin Pharmaceutical Development, Inc., 6002014helpdesk@kyowakirin.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 February 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 December 2017
Global end of trial reached?	Yes
Global end of trial date	20 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term safety and tolerability of oral istradefylline 20 to 40 mg/d as treatment for subjects with moderate to severe Parkinson's Disease (PD).

Protection of trial subjects:

The Principal Investigators were responsible for the conduct and administration of the study in accordance with the protocol and ICH E6-GCP (CPMP/ICH/135/95) guidelines, for collecting, recording, and reporting the data accurately and properly as well as compliance with 21CFR Parts 11, 50,54,56 and 312 and the applicable country -specific requirements and in accordance with the ethical principles enunciated in the Declaration of Helsinki adopted by the 18th World Medical Association (WMA) General Assembly in Helsinki, Finland (June 1964); and amended most recently in 2013 (ninth revision). The Principal Investigator at each center was also responsible for contacts with study center management, the IEC/IRB, and with local non-regulatory bodies. Agreement of the Investigator to conduct and administer this study in accordance with the protocol was documented in separate study agreements with the Sponsor and other forms as required by national authorities in the country where the study center was located. The Informed Consent Form (ICF) incorporated the required elements for informed consent, including the possible treatment risks and necessary documentation as required by the Declaration of Helsinki, 21 CFR Part 50, and the ICH-GCP (CPMP/ICH/135/95) guidelines. The ICF also contained any additional information required by local laws relating to IRB/IEC review. The ICF was approved by the IRB/IEC and the Sponsor. The subject's willingness to participate in the study was documented in writing (signed and dated by the subject [or by the subject's legally acceptable representative] and by the person who conducted the informed consent discussion). The Investigators kept the original consent forms and copies were given to the subjects. No procedures were to take place until ICF was signed.

Background therapy:

The study was an open-label, phase 3 continuation of study 6002-014 for the long term extension of treatment up to 52 weeks. Subjects must have completed 12 weeks of double blind treatment and a 30 day follow up period prior to enrollment in 6002-018.

Evidence for comparator: -

Actual start date of recruitment	18 February 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 49
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	United States: 79
Country: Number of subjects enrolled	Serbia: 18
Country: Number of subjects enrolled	Israel: 16

Country: Number of subjects enrolled	Italy: 18
Country: Number of subjects enrolled	Czech Republic: 41
Worldwide total number of subjects	239
EEA total number of subjects	120

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)	109
From 65 to 84 years	129
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Recruitment opened in February 2016 and closed 16 November 2016.

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects that met all the inclusion/exclusion criteria as per the protocol, were eligible for entry into the trial. A total of 243 subjects were enrolled (screened) of which 4 failed. 239 subjects were therefore enrolled into the trial.

Period 1

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

Arms

Arm title	Overall Trial

Arm description:

Open label study therefore all subjects were treated with istradefylline at a starting dose of 20 mg/d with an option for a dose adjustment to 40 mg/d at week 12 based on the Investigator's judgement of each subject's response and tolerability.

Arm type	Experimental
Investigational medicinal product name	Istradefylline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were treated with istradefylline at a starting dose of 20 mg/d with an option for a dose adjustment to 40 mg/d at week 12 based on the Investigator's judgement of each subject's response and tolerability. If deemed necessary, one unscheduled dose adjustment dose adjustment visit between weeks 2 and 12 was allowed in accordance with the Investigator's clinical judgement. Subject's who had a dose adjustment to 40mg/d could have their their dose decreased to 20mg/d by the investigator at a second unscheduled dose adjustment visit if there were tolerability issues. The istradefylline dose was to remain fixed between weeks 26 and 52. Consultation with the Sponsors Medical Monitor was required prior to any unscheduled dose adjustment visits. Study drug was to be taken in the morning for the duration of study participation on an outpatient basis. Study drug could be taken with or without food.

Number of subjects in period 1	Overall Trial
Started	239
Week 12	219
Week 26	198
Completed	179
Not completed	60
Adverse event, serious fatal	5
Consent withdrawn by subject	27

Physician decision	1
Adverse event, non-fatal	20
Unknown	3
Non-compliance	2
Surgery	2

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	239	239	
Age categorical			
Due to change in German Privacy Law the age for two subjects was not entered. The age of these subjects were estimated in the enrolled reporting table but have been added as unknown to the age categorical table.			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	108	108	
From 65-84 years	128	128	
85 years and over	1	1	
Unknown (age not collected)	2	2	
Age continuous			
Due to change in German Privacy Law the age for two subjects was not entered. The age of these subjects were estimated in the enrolled reporting table but have been added as unknown to the age continuous table.			
Units: years			
arithmetic mean	65.0		
standard deviation	± 8.95	-	
Gender categorical			
Units: Subjects			
Female	87	87	
Male	152	152	

Subject analysis sets

Subject analysis set title	Efficacy analysis
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Efficacy analyses were based on the Intent to treat population, defined as all subjects who had both a valid baseline and at least one valid post-baseline efficacy assessment.

Subject analysis set title	Safety Evaluation
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety analysis was based on the safety analysis set. All continuous safety data that was collected in the study was summarized using descriptive statistics at each assessment time based on actual values and change from baseline values.

Reporting group values	Efficacy analysis	Safety Evaluation	
Number of subjects	238	239	
Age categorical			
Due to change in German Privacy Law the age for two subjects was not entered. The age of these subjects were estimated in the enrolled reporting table but have been added as unknown to the age categorical table.			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	107	108	
From 65-84 years	128	128	
85 years and over	1	1	
Unknown (age not collected)	2	2	
Age continuous			
Due to change in German Privacy Law the age for two subjects was not entered. The age of these subjects were estimated in the enrolled reporting table but have been added as unknown to the age continuous table.			
Units: years			
arithmetic mean	65	65	
standard deviation	± 8.96	± 8.95	
Gender categorical			
Units: Subjects			
Female	86	87	
Male	152	152	

End points

End points reporting groups

Reporting group title	Overall Trial

Reporting group description:

Open label study therefore all subjects were treated with istradefylline at a starting dose of 20 mg/d with an option for a dose adjustment to 40 mg/d at week 12 based on the Investigator's judgement of each subject's response and tolerability.

Subject analysis set title	Efficacy analysis
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Efficacy analyses were based on the Intent to treat population, defined as all subjects who had both a valid baseline and at least one valid post-baseline efficacy assessment.

Subject analysis set title	Safety Evaluation
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety analysis was based on the safety analysis set. All continuous safety data that was collected in the study was summarized using descriptive statistics at each assessment time based on actual values and change from baseline values.

Primary: Safety Analysis based on the Safety Analysis Set.

End point title	Safety Analysis based on the Safety Analysis Set.[1]

End point description:

All continuous safety data collected in this study was categorised using descriptive statistics at each assessment time based on actual values and change from baseline values.

End point type	Primary

End point timeframe:

From the time ICF was signed through to 30 days post last dose administration.

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: Statistical Analysis was performed using descriptive statistics (number of subjects, mean, standard deviation, median, minimum and maximum) for continuous variables and frequency distributions and percentages for discrete (or any categorical) variables were utilized.

End point values	Overall Trial	Safety Evaluation		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	239	239		
Units: Adverse events				
Subjects with any TEAE	141	141		
Subjects with any serious TEAE	30	30		
Subjects with any TEAE leading to discontinuation	25	25		
Subjects with any related TEAE	78	78		
Subjects with any severe TEAE	27	27		
Subjects who died	5	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy Analysis based on the PGI-I scores at end of study (Week 52) as a percentage

End point title	Efficacy Analysis based on the PGI-I scores at end of study (Week 52) as a percentage

End point description:

The percentage of subjects showing improvement (moderate and mild) at week 52.

End point type	Secondary

End point timeframe:

From baseline to week 52 (end of study)

End point values	Efficacy analysis			
Subject group type	Subject analysis set			
Number of subjects analysed	187			
Units: percentage				
number (not applicable)				
Overall Condition	40.7			
Fatigue	21.4			
Sleep	19.8			
Motivation to get things done	24.1			
Key Symptom	39			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time the subject signs the ICF and until 30 days after last dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Safety Evaluation

Reporting group description:

All safety analyses was based on the safety analyses set. All continuous safety data collected in this study was summarized using descriptive statistics at each assessment time based on actual values and changes from baseline values. Baseline was defined as the last non missing value obtained prior to first treatment. Continuous variables were summarized using n, mean, SD, median,minimum, and maximum values. Categorical variables were summarized using the number and percentage of subjects in each category. All out of normal range results and clinically significant changes in any safety variable were flagged in the subject data listings.

Serious adverse events	Safety Evaluation		
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 239 (12.55%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	5		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	1 / 1		
Acute pulmonary oedema			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Panic attack			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Confusional state			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Protein total decreased			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood creatinine increased			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Limb amputation			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Procedural pain			

subjects affected / exposed	2 / 239 (0.84%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pubis fracture				
subjects affected / exposed	2 / 239 (0.84%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Incorrect dose administered				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	3 / 239 (1.26%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Coronary artery disease				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	2 / 239 (0.84%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Atrial fibrillation				
subjects affected / exposed	2 / 239 (0.84%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Atrioventricular block complete				

subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Angina pectoris			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bradycardia			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
On and off phenomenon			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Parkinson's disease			
subjects affected / exposed	3 / 239 (1.26%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Convulsion			

subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	2 / 239 (0.84%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Sciatica			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Multiple sclerosis			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Carotid artery stenosis			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Dyskinesia			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			

Glaucoma			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diplopia			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastritis erosive			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal column stenosis			

subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	2 / 239 (0.84%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 239 (0.84%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	2 / 239 (0.84%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Gas gangrene			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Necrotising fasciitis			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety Evaluation		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	87 / 239 (36.40%)		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	27 / 239 (11.30%)		
occurrences (all)	37		
Nervous system disorders			
Dyskinesia			
subjects affected / exposed	42 / 239 (17.57%)		
occurrences (all)	50		
Parkinson's disease			
subjects affected / exposed	18 / 239 (7.53%)		
occurrences (all)	21		

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