Clinical trial results:
A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study with an Open-Label Phase to Determine the Efficacy and Safety of Tozadenant as Adjunctive Therapy in Levodopa-Treated Patients with Parkinson's Disease Experiencing End-of-Dose "Wearing-Off" (TOZ-PD)

Summary

EudraCT number	2014-005630-60
Trial protocol	DE CZ ES AT IT
Global end of trial date	12 January 2018

Results information

Result version number	v1 (current)
This version publication date	23 February 2019
First version publication date	23 February 2019

Trial information

Trial identification

Sponsor protocol code	TOZ-CL05

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02453386
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Acorda Therapeutics
Sponsor organisation address	420 Saw Mill River Road, Ardsley, United States, 10502
Public contact	Christopher Kenney, Senior Vice President - Medical Affairs, Acorda Therapeutics, +914 326-5775, ckenney@acorda.com
Scientific contact	Christopher Kenney, Senior Vice President - Medical Affairs, Acorda Therapeutics, +914 326-5775, ckenney@acorda.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	12 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 January 2018
Global end of trial reached?	Yes
Global end of trial date	12 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary efficacy objective of this study is to demonstrate the efficacy of the A2a receptor antagonist tozadenant in the treatment of levodopa-treated PD patients experiencing end-of-dose "wearing-off", based on the change from Baseline to Week 24 in the number of hours per day spent in the OFF state.

Protection of trial subjects:

Conduct of the study must be approved by an appropriately constituted IRB or IEC. Approval is required for the study protocol, investigational drug brochure, protocol amendments, informed consent forms, patient information sheets, and advertising materials. For each study patient, written informed consent will be obtained prior to any protocol-related activities. As part of this procedure, the principal investigator or one of his/her associates must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the patient is aware of the potential risks, inconveniences, or adverse effects that may occur. The patient should be informed that he/she may withdraw from the study at any time, and the patient will receive all information that is required by local regulations and ICH guidelines. The principal investigator will provide the Sponsor or its representative with a copy of the IRB/IEC-approved informed consent form prior to the start of the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 July 2015
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	Spain: 37
Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	Czech Republic: 66
Country: Number of subjects enrolled	Germany: 57
Country: Number of subjects enrolled	Canada: 15
Country: Number of subjects enrolled	Italy: 59
Country: Number of subjects enrolled	United States: 207
Worldwide total number of subjects	449
EEA total number of subjects	227

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)	200
From 65 to 84 years	249
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 80 sites in 7 countries (United States, Canada, Italy, Austria, Spain, Germany, Czech Republic). Planned patient enrollment numbers were achieved, but the study and the tozadenant development program were terminated prior to study completion by all patients, based on an unexpected emerging safety signal.

Pre-assignment

Screening details:

Of the 616 patients screened in the study, a total of 449 were randomized: 149 to receive placebo, 151 to receive 60 mg BID tozadenant, and 149 to receive 120 mg BID tozadenant.

Period 1

Period 1 title	24 Weeks (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description: -

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

Dosage and administration details:

The patients will take two tablets by mouth BID.

Arm title	60 mg BID Tozadenant

Arm description: -

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

Dosage and administration details:

The patients take 60 mg BID.

Arm title	120 mg BID Tozadenant

Arm description: -

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

Dosage and administration details:
One or two doses of 60 mg or 120 mg BID.

Number of subjects in period 1	Placebo	60 mg BID Tozadenant	120 mg BID Tozadenant
Started	149	151	149
Completed	108	102	100
Not completed	41	49	49
Consent withdrawn by subject	9	10	9
Other	1	1	-
Subject Terminated by Investigator	2	-	1
Sponsor Terminated the Study	11	14	8
Adverse Events	15	22	30
Subject Terminated by Sponsor	1	1	1
Lost to follow-up	1	-	-
Protocol deviation	1	1	-

Baseline characteristics

Reporting groups	
Reporting group title	24 Weeks

Reporting group description: -

Reporting group values	24 Weeks	Total	
Number of subjects	449	449	
Age categorical			
Overall, the majority of patients were male (67.0%) and Caucasian (97.6%), and the average age was 64.7 years (range: 35 to 81 years), characteristic of the general PD population. The treatment groups were well balanced with regard to these demographic variables.			
Units: Subjects			
Adults (18-64 years)	200	200	
From 65-84 years	249	249	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	148	148	
Male	301	301	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	60 mg BID Tozadenant
Reporting group description: -	
Reporting group title	120 mg BID Tozadenant
Reporting group description: -	

Primary: Change from Baseline to Week 24 in the number of hours per day spent in OFF time

End point title	Change from Baseline to Week 24 in the number of hours per day spent in OFF time

End point description:

The primary efficacy endpoint was the change from baseline to Week 24 in OFF time, where OFF time in the Hauser Parkinson's Disease Home Diary (PD) was averaged over 3 days prior to the study visit. During Screening and through Part A of the study, the Hauser Parkinson's Disease Home Diary (PD) was completed on specified days directly preceding the scheduled study visits/assessments. Motor activity was recorded as OFF, ON (mobility improved), or asleep time. Patients were asked to record ON time according to dyskinesia categories "without dyskinesia", "with non troublesome dyskinesia" or "with troublesome dyskinesia". Patients (and/or caregivers) were trained to complete the PD diary to record their status at half hourly intervals as OFF, ON without dyskinesia, ON with non troublesome dyskinesia, ON with troublesome dyskinesia, or asleep.

End point type	Primary

End point timeframe:

Baseline to 24 Weeks

End point values	Placebo	60 mg BID Tozadenant	120 mg BID Tozadenant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	108	104	104	
Units: Hours				
arithmetic mean (standard deviation)	-0.958 (± 2.2725)	-0.835 (± 2.9730)	-1.789 (± 2.4802)	

Statistical analyses

Statistical analysis title	Change from Baseline to Week 24 in OFF time Hours

Statistical analysis description:

The change from baseline OFF hours was analyzed by a mixed model repeated measures ANCOVA that included country/region, treatment group, week, interaction between treatment group and week as fixed terms, baseline number of OFF hours as covariate and subject as random effect.

Comparison groups	Placebo v 120 mg BID Tozadenant

Number of subjects included in analysis	212
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.724
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.362
upper limit	-0.087
Variability estimate	Standard error of the mean
Dispersion value	0.3242

Secondary: Change in Good ON time from baseline to Week 24

End point title	Change in Good ON time from baseline to Week 24

End point description:

The first key secondary efficacy endpoint was the change from baseline to Week 24 in good ON which was defined as ON without dyskinesia or ON with non-troublesome dyskinesia.
Awake Time in Good ON State (hr) is the average of a maximum of 3 days diary. Patients were asked to record ON time according to dyskinesia categories "without dyskinesia", "with non troublesome dyskinesia" or "with troublesome dyskinesia" . Patients (and/or caregivers) were trained to complete the PD diary to record their status at half hourly intervals as OFF, ON without dyskinesia, ON with non troublesome dyskinesia, ON with troublesome dyskinesia, or asleep. For patients with missing baseline or baseline was measured post-dose, screening was used as baseline in the calculation of change from baseline.

End point type	Secondary

End point timeframe:

Baseline to 24 Weeks

End point values	Placebo	60 mg BID Tozadenant	120 mg BID Tozadenant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	108	104	104	
Units: Hours				
arithmetic mean (standard deviation)	1.011 (± 2.5470)	0.705 (± 3.1219)	1.689 (± 2.7335)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Unified Parkinson's Disease Rating Scale (UPDRS) Part II Activities of Daily Living (ADL) subscale + Part III Motor Function

End point title	Change in Unified Parkinson's Disease Rating Scale (UPDRS) Part II Activities of Daily Living (ADL) subscale + Part III Motor

	Function

End point description:

The Unified Parkinson's Disease Rating Scale (UPDRS) is a scale to monitor Parkinson's Disease related disability and impairment. The scale itself has 4 components,(Part I, Mentation, Behavior and Mood; Part II, Activities of Daily Living; Part III, Motor Examination; Part IV, Complications of Therapy). Points are assigned to every item based on the person's response, as well as observation and physical examination. Each part has multiple points that are individually scored, using zero for normal or no problems, 1 for minimal problems, 2 for mild problems, 3 for moderate problems, and 4 for severe problems. These scores are tallied to indicate the severity of the disease, with 199 points being the worst and total disability and 0 meaning no disability. For patients with missing baseline or baseline was measured post-dose, screening was used as baseline in the calculation of change from baseline. Total scores are calculated only when all Part II & III questions.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Placebo	60 mg BID Tozadenant	120 mg BID Tozadenant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	108	103	106	
Units: Score on a scale				
arithmetic mean (standard deviation)	-2.80 (± 8.183)	-2.54 (± 8.584)	-3.68 (± 7.853)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 24 in the ON state in Unified Parkinson's Disease Rating Scale (UPDRS) Part IIl

End point title	Change From Baseline to Week 24 in the ON state in Unified Parkinson's Disease Rating Scale (UPDRS) Part IIl

End point description:

Change from Baseline to Week 24 in the Unified Parkinson's Disease Rating Scale (UPDRS) Parts III Motor Function (motor subscale) total scores. Score Range of 0 - 108. Higher scores indicate greater impact of PD symptoms. Unified Parkinson's Disease Rating Scale (UPDRS) in the ON state was measured at a time representative of the ON state in that patient, not in "best" ON. Unified Parkinson's Disease Rating Scale Part III in OFF was not evaluated. For Patients with missing baseline or baseline was measured post-dose, screening was used as baseline in the calculation of change from baseline. Total scores are calculated only when all Part III questions are answered.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Placebo	60 mg BID Tozadenant	120 mg BID Tozadenant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	108	103	106	
Units: Score on a scale				
arithmetic mean (standard deviation)	-2.15 (± 6.363)	-2.13 (± 6.822)	-2.93 (± 6.048)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Global Assessments of Improvement: Clinical Global Impression of Improvement (CGI-I) Week 24

End point title	Global Assessments of Improvement: Clinical Global Impression of Improvement (CGI-I) Week 24

End point description:

For the Clinical Global Impression of Improvement (CGI-I), the investigator or rater is asked to rate the patient's total improvement, whether or not in his or her judgment it is due entirely to drug treatment, based on a 1-7 point weighted scale ranging from "very much improved" (1) to "very much worse" (7). A zero score is assigned if the score is not assessed. Scale: 1 = Very much improved, 2 = Much improved, 3 = Minimally improved, 4 = No change, 5 = Minimally worse, 6 = Much worse, 7 = Very much worse.

End point type	Other pre-specified

End point timeframe:

At Week 24

End point values	Placebo	60 mg BID Tozadenant	120 mg BID Tozadenant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	111	106	107	
Units: Score on a scale				
arithmetic mean (standard deviation)	3.5 (± 0.92)	3.5 (± 1.07)	3.2 (± 0.98)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Patient Global Impression of Improvement (PGI-I) Week 24

End point title	Patient Global Impression of Improvement (PGI-I) Week 24

End point description:

For the Patient Global Impression of Improvement (PG-I), the patient is asked to rate the total improvement of their Parkinson's Disease, whether or not in the patient's judgment it is due entirely to drug treatment, based on a 1-7 point weighted scale. "very much improved" (1) to "very much worse" (7). A zero score is assigned if the score is not assessed.
Scale: 1 = Normal, not at all ill, 2 = Borderline ill, 3 = Mildly ill, 4 = Moderately ill, 5 = Markedly ill, 6 = Severly ill, 7 = Among the most extremely ill.

End point type	Other pre-specified

End point timeframe:
At Week24

End point values	Placebo	60 mg BID Tozadenant	120 mg BID Tozadenant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	111	106	107	
Units: Score on a scale				
arithmetic mean (standard deviation)	3.6 (± 1.14)	3.6 (± 1.21)	3.4 (± 1.14)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

24 Weeks

Adverse event reporting additional description:

Safety evaluation was based on the Safety Set (SS) population who took at least 1 dose of IMP. In Part A, the SS included 447 of the total of 449 randomized patients.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	60 mg BID Tozadenant
Reporting group description: -	
Reporting group title	120 mg BID Tozadenant

Reporting group description: -

Serious adverse events	Placebo	60 mg BID Tozadenant	120 mg BID Tozadenant
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 148 (10.14%)	13 / 150 (8.67%)	12 / 149 (8.05%)
number of deaths (all causes)	1	1	1
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Thyroid adenoma			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	0 / 149 (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
Vascular disorders			
Accelerated hypertension			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	0 / 149 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 148 (0.00%)	0 / 150 (0.00%)	1 / 149 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	0 / 149 (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
Gait disturbance			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	0 / 149 (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
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	0 / 149 (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
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 148 (0.00%)	0 / 150 (0.00%)	1 / 149 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	0 / 148 (0.00%)	0 / 150 (0.00%)	1 / 149 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination, visual			
subjects affected / exposed	0 / 148 (0.00%)	0 / 150 (0.00%)	2 / 149 (1.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Burns third degree			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	0 / 149 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Face injury			

subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	0 / 149 (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
Fall			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	0 / 149 (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
Femur fracture			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	0 / 149 (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
Fractured sacrum			
subjects affected / exposed	0 / 148 (0.00%)	0 / 150 (0.00%)	1 / 149 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	0 / 149 (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
Pubis fracture			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	1 / 149 (0.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory fume inhalation disorder			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	0 / 149 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 148 (0.00%)	0 / 150 (0.00%)	1 / 149 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			

subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	0 / 149 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 148 (0.00%)	0 / 150 (0.00%)	1 / 149 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	0 / 149 (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
Torsade de pointes			
subjects affected / exposed	0 / 148 (0.00%)	0 / 150 (0.00%)	1 / 149 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 148 (0.00%)	0 / 150 (0.00%)	1 / 149 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery occlusion			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	0 / 149 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carpal tunnel syndrome			
subjects affected / exposed	0 / 148 (0.00%)	0 / 150 (0.00%)	1 / 149 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 148 (0.00%)	0 / 150 (0.00%)	1 / 149 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyskinesia			

subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	0 / 149 (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
Intracranial aneurysm			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	0 / 149 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parkinson's disease			
subjects affected / exposed	1 / 148 (0.68%)	2 / 150 (1.33%)	0 / 149 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	0 / 149 (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
Gastrointestinal disorders			
Colitis ischaemic			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	0 / 149 (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
Inguinal hernia			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	0 / 149 (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
Pancreatitis			
subjects affected / exposed	0 / 148 (0.00%)	0 / 150 (0.00%)	1 / 149 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Anuria			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	0 / 149 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Calculus ureteric			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	0 / 149 (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
Musculoskeletal and connective tissue disorders			
Cervical spinal stenosis			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	0 / 149 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	0 / 149 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	2 / 148 (1.35%)	0 / 150 (0.00%)	0 / 149 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle spasms			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	0 / 149 (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
Muscular weakness			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	0 / 149 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	0 / 149 (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
Spinal column stenosis			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	0 / 149 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	0 / 149 (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
Bronchitis			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	0 / 149 (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
Pneumonia			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	0 / 149 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 148 (0.00%)	0 / 150 (0.00%)	1 / 149 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	0 / 149 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Placebo	60 mg BID Tozadenant	120 mg BID Tozadenant
Total subjects affected by non-serious adverse events			
subjects affected / exposed	111 / 148 (75.00%)	115 / 150 (76.67%)	111 / 149 (74.50%)
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	3 / 148 (2.03%)	4 / 150 (2.67%)	6 / 149 (4.03%)
occurrences (all)	3	4	6
Weight decreased			
subjects affected / exposed	0 / 148 (0.00%)	4 / 150 (2.67%)	2 / 149 (1.34%)
occurrences (all)	0	4	2

White blood cell count decreased			
subjects affected / exposed	4 / 148 (2.70%)	2 / 150 (1.33%)	0 / 149 (0.00%)
occurrences (all)	4	2	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	5 / 149 (3.36%)
occurrences (all)	1	0	5
Fall			
subjects affected / exposed	9 / 148 (6.08%)	22 / 150 (14.67%)	13 / 149 (8.72%)
occurrences (all)	9	22	13
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 148 (0.68%)	1 / 150 (0.67%)	4 / 149 (2.68%)
occurrences (all)	1	1	4
Hypertension			
subjects affected / exposed	3 / 148 (2.03%)	5 / 150 (3.33%)	3 / 149 (2.01%)
occurrences (all)	111	115	111
Nervous system disorders			
Dizziness			
subjects affected / exposed	9 / 148 (6.08%)	7 / 150 (4.67%)	7 / 149 (4.70%)
occurrences (all)	9	7	7
Dyskinesia			
subjects affected / exposed	13 / 148 (8.78%)	22 / 150 (14.67%)	22 / 149 (14.77%)
occurrences (all)	13	22	22
Parkinson's disease			
subjects affected / exposed	7 / 148 (4.73%)	11 / 150 (7.33%)	3 / 149 (2.01%)
occurrences (all)	7	11	3
Somnolence			
subjects affected / exposed	5 / 148 (3.38%)	5 / 150 (3.33%)	8 / 149 (5.37%)
occurrences (all)	5	5	8
Sudden onset of sleep			
subjects affected / exposed	4 / 148 (2.70%)	7 / 150 (4.67%)	7 / 149 (4.70%)
occurrences (all)	4	7	7
Headache			
subjects affected / exposed	5 / 148 (3.38%)	3 / 150 (2.00%)	2 / 149 (1.34%)
occurrences (all)	5	3	2

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 148 (1.35%)	7 / 150 (4.67%)	4 / 149 (2.68%)
occurrences (all)	2	7	4
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 148 (1.35%)	15 / 150 (10.00%)	8 / 149 (5.37%)
occurrences (all)	2	15	8
Dry mouth			
subjects affected / exposed	0 / 148 (0.00%)	2 / 150 (1.33%)	4 / 149 (2.68%)
occurrences (all)	0	2	4
Nausea			
subjects affected / exposed	6 / 148 (4.05%)	8 / 150 (5.33%)	13 / 149 (8.72%)
occurrences (all)	6	8	13
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 148 (1.35%)	1 / 150 (0.67%)	4 / 149 (2.68%)
occurrences (all)	2	1	4
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 148 (2.03%)	5 / 150 (3.33%)	2 / 149 (1.34%)
occurrences (all)	3	5	2
Confusional state			
subjects affected / exposed	1 / 148 (0.68%)	2 / 150 (1.33%)	4 / 149 (2.68%)
occurrences (all)	1	2	4
Hallucination, visual			
subjects affected / exposed	2 / 148 (1.35%)	8 / 150 (5.33%)	8 / 149 (5.37%)
occurrences (all)	2	8	8
Insomnia			
subjects affected / exposed	9 / 148 (6.08%)	9 / 150 (6.00%)	9 / 149 (6.04%)
occurrences (all)	9	9	9
Disorientation			
subjects affected / exposed	0 / 148 (0.00%)	4 / 150 (2.67%)	0 / 149 (0.00%)
occurrences (all)	0	4	0
Renal and urinary disorders			

Micturition urgency			
subjects affected / exposed	0 / 148 (0.00%)	3 / 150 (2.00%)	4 / 149 (2.68%)
occurrences (all)	0	3	4
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	8 / 148 (5.41%)	4 / 150 (2.67%)	7 / 149 (4.70%)
occurrences (all)	8	4	7
Myalgia			
subjects affected / exposed	0 / 148 (0.00%)	4 / 150 (2.67%)	2 / 149 (1.34%)
occurrences (all)	0	4	2
Pain in extremity			
subjects affected / exposed	6 / 148 (4.05%)	5 / 150 (3.33%)	3 / 149 (2.01%)
occurrences (all)	6	5	3
Arthralgia			
subjects affected / exposed	6 / 148 (4.05%)	3 / 150 (2.00%)	2 / 149 (1.34%)
occurrences (all)	6	3	2
Musculoskeletal pain			
subjects affected / exposed	1 / 148 (0.68%)	4 / 150 (2.67%)	0 / 149 (0.00%)
occurrences (all)	1	4	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	10 / 148 (6.76%)	7 / 150 (4.67%)	5 / 149 (3.36%)
occurrences (all)	10	7	5
Upper respiratory tract infection			
subjects affected / exposed	7 / 148 (4.73%)	6 / 150 (4.00%)	1 / 149 (0.67%)
occurrences (all)	7	6	1
Urinary tract infection			
subjects affected / exposed	4 / 148 (2.70%)	4 / 150 (2.67%)	9 / 149 (6.04%)
occurrences (all)	4	4	9

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 May 2015	Amendment 1 Revisions: 1. Updated List of Abbreviations (p. 8-9). 2. Corrected typographical errors in Table 1: Part A - Schedule of Events/Evaluations (p. 30). 3. Revised Section 11.6, Unblinding Upon Completion of Part A (p. 131) to clarify that primary and secondary efficacy analyses will be conducted after the Part A data base is locked and will not be modified; and to clarify that exploratory analyses that do not involve the primary or secondary efficacy analyses are subject to modification. 4. Added the following exploratory endpoints to Parts A and B: Part A 15. EuroQol 5D-5L Health Questionnaire (EQ-5D-5L). 16. Treatment Satisfaction Questionnaire for Medication (TSQM 9) (evaluated at Weeks 6 and 24). Part B 11. EQ-5D-5L. 12. TSQM 9 (evaluated at Week 76).
10 June 2015	Amendment 2 Revisions: 1. Revised Exclusion Criteria (EC) #24 to delete "including any history of hepatic or renal failure" (p. 22; p. 55). 2. Added EC #27: "Patients with moderate to severe hepatic or renal impairment." (p. 22; p. 55). 3. Added EC #28: "Patients who have taken strong CYP3A4 inhibitors or inducers within 4 weeks prior to Baseline (Visit 2) or who anticipate requiring the use of strong CYP3A4 inhibitors or inducers during the duration of the trial (see Section 5.9.2 and Appendix 15.15)" (p. 22; p. 55). 4. Added EC #29: "Patients with pacemakers or implantable cardioverter defibrillators" (p. 22; p. 55). 5. Added to Section 4.3.2, Definite Criteria for Withdrawal from Study: "9. Patients noted to have an elevated BP post-baseline, with a systolic BP ≥ 160 mmHg and/or a diastolic BP≥ 100 mmHg that is present at 2 consecutive post-baseline study visits" (p. 57). 6. Added to Section 5.9.2, Prohibited Concomitant Medications/ Treatments, regarding medications prohibited throughout the study (Parts A and B): "Strong CYP3A4 inhibitors or inducers. Refer to Appendix 15.15" (p. 61). 7. Added paragraph at end of Section 9.5.1, Blood Pressure and Pulse Measurements: "Patients noted to have an elevated BP post-baseline, with a systolic BP ≥ 160 mmHg and/or a diastolic BP ≥ 100 mmHg that is present at 2 consecutive post-baseline study visits, will be discontinued from study (see Section 4.3.2)" (p. 118). 8. Added Appendix 15.15, Prohibited CYP3A4 Inhibitors and Inducers (p. 183).

13 October 2017	Amendment 3 Revisions 1. Updated company name, email addresses and telephone numbers of Study Director, and Chief Medical Officer in multiple places. 2. Updated Study Contact Information 3. Updated safety reporting fax number 4. Added to Abbreviations ANC (absolute neutrophil count), WBC (white blood cells) 5. Inserted into Parts A and B procedures additional blood draws for hematology. 6. Added Tables 1.1 (Part A – Schedule of Events/ Evaluations for Hematology Monitoring) and 2.1 Part B – Schedule of Events/ Evaluations for Hematology Monitoring. 7. Inserted into Criteria for Patient Discontinuation a lower limit for absolute neutrophils. 8. Added the following as section 6.2.6 a Visit 3.5 (Week 4). 9. Inserted section 6.2.9 a Visit 4.3 (Week 8). 10. Inserted section 6.2.10 a Visit 4.8 (Week 10) 11. Section 6.2.12: Clarified the next visit by number and differentiates next blood draw (visit 16) and telephone call (visit 18). 12. Insert section 6.2.13 a Visit 5.5 (Week 16) 13. Insert section 6.2.16 a Visit 6.5 (Week 22)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported