

**Clinical trial results:****A Multicenter, Open-Label Study to Evaluate the Safety and Tolerability of Tozadenant as Adjunctive Therapy in Levodopa-Treated Patients with Parkinson's Disease Experiencing End of Dose "Wearing-Off"****Summary**

EudraCT number	2016-003961-25
Trial protocol	DE GB HU ES CZ IT
Global end of trial date	16 January 2018

Results information

Result version number	v1 (current)
This version publication date	30 January 2019
First version publication date	30 January 2019

Trial information**Trial identification**

Sponsor protocol code	10TOZ-CL06
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03051607
WHO universal trial number (UTN)	-
Other trial identifiers	IND Number: 78230

Notes:

Sponsors

Sponsor organisation name	Acorda Therapeutics
Sponsor organisation address	420 Saw Mill River Road, Ardsley, United States, 10502
Public contact	Christopher Kenny, Senior Vice President - Medical Affairs , Acorda Therapeutics , 914 326-5775, ckenney@acorda.com
Scientific contact	Christopher Kenny, 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	16 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 January 2018
Global end of trial reached?	Yes
Global end of trial date	16 January 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of tozadenant in levodopa-treated PD patients experiencing motor fluctuations.

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	25 May 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	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	United States: 51
Worldwide total number of subjects	66
EEA total number of subjects	14

Notes:

Subjects enrolled per age group

In utero	0
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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)	27
From 65 to 84 years	39
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 66 patients were enrolled in 27 study centers across 6 countries and were included in the Safety Set (SS) as well as the Full Analysis Set (FAS).

Pre-assignment

Screening details:

A total of 66 patients were enrolled in 27 study centers across 6 countries.

Period 1

Period 1 title	52 Weeks (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Tozadenant
Arm description: 120 mg BID	
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:

120 mg BID Oral tablet

Number of subjects in period 1	Tozadenant
Started	66
Completed	0
Not completed	66
Consent withdrawn by subject	8
Death	2
Adverser Events	6
Lost to follow-up	1
Sponsor terminated study	49

Baseline characteristics

Reporting groups

Reporting group title	52 Weeks
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Reporting group description: -

Reporting group values	52 Weeks	Total	
Number of subjects	66	66	
Age categorical Units: Subjects			
Adults (18-64 years)	27	27	
From 65-84 years	39	39	
Gender categorical Units: Subjects			
Female	16	16	
Male	50	50	

End points

End points reporting groups

Reporting group title	Tozadenant
Reporting group description:	120 mg BID

Primary: The Safety and tolerability of Tozadenant in Levodopa-treated Parkinson Disease patients experiencing motor fluctuations.

End point title	The Safety and tolerability of Tozadenant in Levodopa-treated Parkinson Disease patients experiencing motor fluctuations. ^[1]
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End point description:

The primary objective of this study was to evaluate the safety and tolerability of tozadenant in levodopa-treated PD patients experiencing motor fluctuations. A total of 66 patients were enrolled in 27 study centers across 6 countries: USA, United Kingdom, Italy, Canada, Spain and Hungary, and were included in the Safety Set (SS). A total of 60 out of 66 enrolled patients completed up to Week 2, 44 completed Week 4, 22 completed Week 12, and 4 completed Week 24.

End point type	Primary
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End point timeframe:

24 Weeks due to early termination of study.

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 were provided for this study.

End point values	Tozadenant			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: Participants				
Subjects with at least one treatment-emergent AE	46			
Subjects with at least one related TEAE	33			
Subjects discontinuing study drug due to an AE	7			
Subjects with at least one SAE	5			
Subjects with at least one life-threatening SAE	5			
Subjects with AE leading to death	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Effects of Tozadenant on the Occurrence of Daytime Drowsiness by Using the Epworth Sleepiness Scale.

End point title	Effects of Tozadenant on the Occurrence of Daytime Drowsiness by Using the Epworth Sleepiness Scale.
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End point description:

The Secondary objectives was to evaluate the effects of tozadenant on the occurrence of daytime

drowsiness by using the Epworth Sleepiness scale. The Epworth Sleepiness Scale (ESS) is a scale intended to measure daytime sleepiness that is measured by use of a short questionnaire. A score within the range 0–9 is considered to be normal while a score within the range of 10–24 would indicate that medical help should be solicited. 60 out of 66 patients completed up to Week 2, 44 completed Week 4, 22 completed Week 12, and 4 completed Week 24.

End point type	Secondary
End point timeframe:	
24 Weeks due to early termination of study.	

End point values	Tozadenant			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: Score on a scale				
median (standard deviation)				
Baseline	7.9 (± 5.32)			
Week 2	7.4 (± 5.29)			
Week 6	8.5 (± 4.72)			
Week 12	10.0 (± 3.53)			
Week 24	12.0 (± 4.08)			
Early Termination	7.9 (± 5.08)			
Safety Follow-up	7.3 (± 4.95)			

Statistical analyses

No statistical analyses for this end point

Secondary: Effects of Tozadenant on the Occurrence of Suicidality Using the Columbia-Suicide Severity Scale (C-SSRS) Summarized by Visit.

End point title	Effects of Tozadenant on the Occurrence of Suicidality Using the Columbia-Suicide Severity Scale (C-SSRS) Summarized by Visit.
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End point description:

The Columbia Suicide Severity Rating Scale (C-SSRS) is an example of an acceptable instrument that maps to the Columbia Classification Algorithm for Suicide Assessment (C-CASA), directly classifying events of interest into one of 11 categories of suicidal ideation and behavior. Completion of the scale can be based entirely on patient interview, but integration of information from other sources (such as family and friends, significant others, caregivers, health professionals, and medical records) is also allowed. A total of 60 out of 66 enrolled patients completed up to Week 2, 44 completed Week 4, 22 completed Week 12, and 4 completed Week 24.

End point type	Secondary
End point timeframe:	
24 Weeks due to early termination of study.	

End point values	Tozadenant			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: Participants				
Screening - Lifetime: Suicidal Ideation	66			
Screening - Lifetime: Suicidal Behavior	66			
Screening - Past 5 years: Suicidal Behavior	64			
Screening - Past 6 months: Suicidal Ideation	64			
Baseline - Since last visit: Suicidal Ideation	66			
Baseline - Since last visit: Suicidal Behavior	66			
Week 2 - Since last visit: Suicidal Ideation	60			
Week 2 - Since last visit: Suicidal Behavior	60			
Week 6 - Since last visit: Suicidal Ideation	44			
Week 6 - Since last visit: Suicidal Behavior	44			
Week 12 - Since last visit: Suicidal Ideation	22			
Week 12 - Since last visit: Suicidal Behavior	22			
Week 24 - Since last visit: Suicidal Ideation	4			
Week 24 - Since last visit: Suicidal Behavior	4			
Early Termination: Suicidal Ideation	62			
Early Termination: Suicidal Behavior	62			
Safety Follow-up: Suicidal Ideation	57			
Safety Follow-up: Suicidal Behavior	57			

Statistical analyses

No statistical analyses for this end point

Secondary: Effects of Tozadenant on the occurrence of impulsive behavior - Modified Minnesota Impulse Disorder Interview (mMIDI)

End point title	Effects of Tozadenant on the occurrence of impulsive behavior - Modified Minnesota Impulse Disorder Interview (mMIDI)
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End point description:

The Minnesota Impulsive Disorders Interview (MIDI) 8 is a global instrument that includes questions for compulsive gambling, buying, and sexual behavior (as well as other disorders not reported to occur in PD).

The mMIDI consists of 5 modules: compulsive buying, compulsive gambling, compulsive eating, hypersexuality and punning.

Positive Answer: Any answer other than "no" on any question is considered a "yes"/positive answer.

Negative Module: A module is considered negative if the patient's answer to a gateway (initial) question is "no" or if a patient answers "yes" to a gateway question and "no" to all of the remaining answers after the gateway question in that module.

Positive Module: A module is considered positive if a patient gives a positive answer (No = 0, rarely = 1, occasionally = 2, frequently = 3) to any question after the gateway (initial) question in one or more of the 5 modules.

End point type	Secondary
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End point timeframe:

24 Weeks due to early termination of study.

End point values	Tozadenant			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: Participants				
Buying Disorder - Screening - Negative	66			
Buying Disorder - Screening - Positive	0			
Buying Disorder - Week 2 - Negative	59			
Buying Disorder - Week 2 - Positive	1			
Buying Disorder - Week 6 - Negative	43			
Buying Disorder - Week 6 - Positive	1			
Buying Disorder - Week 12 - Negative	22			
Buying Disorder - Week 12 - Positive	0			
Buying Disorder - Week 24 - Negative	4			
Buying Disorder - Week 24 - Positive	0			
Buying Disorder - Early Termination - Neg	60			
Buying Disorder - Early Termination - Pos	2			
Buying Disorder - Safety Follow-up - Negative	56			
Buying Disorder - Safety Follow-up - Positive	1			
Compulsive Gambling - Screening - Negative	65			
Compulsive Gambling - Screening - Positive	1			
Compulsive Gambling - Week 2 - Negative	59			
Compulsive Gambling - Week 2 - Positive	1			
Compulsive Gambling - Week 6 - Negative	44			
Compulsive Gambling - Week 6 - Positive	0			
Compulsive Gambling - Week 12 - Negative	22			
Compulsive Gambling - Week 12 - Positive	0			
Compulsive Gambling - Week 24 - Negative	4			
Compulsive Gambling - Week 24 - Positive	0			
Compulsive Gambling - Early Termination - Negative	61			
Compulsive Gambling - Early Termination - Positive	1			
Compulsive Gambling - Safety Follow-up - Negative	56			
Compulsive Gambling - Safety Follow-up - Positive	1			

Compulsive Sexual Behavior - Screening - Negative	66			
Compulsive Sexual Behavior - Screening - Positive	0			
Compulsive Sexual Behavior - Week 2 - Negative	60			
Compulsive Sexual Behavior - Week 2 - Positive	0			
Compulsive Sexual Behavior - Week 6 - Negative	44			
Compulsive Sexual Behavior - Week 6 - Positive	0			
Compulsive Sexual Behavior - Week 12 - Negative	22			
Compulsive Sexual Behavior - Week 12 - Positive	0			
Compulsive Sexual Behavior - Week 24 - Negative	4			
Compulsive Sexual Behavior - Week 24 - Positive	0			
Compulsive Sexual Behavior - Early Termination-Neg	60			
Compulsive Sexual Behavior - Early Termination-Pos	2			
Compulsive Sexual Behavior - Safety Follow-up -Neg	56			
Compulsive Sexual Behavior - Safety Follow-up-Pos	1			
Compulsive Eating Module - Screening - Negative	66			
Compulsive Eating Module - Screening - Positive	0			
Compulsive Eating Module - Week 2 - Negative	60			
Compulsive Eating Module - Week 2 - Positive	0			
Compulsive Eating Module - Week 6 - Negative	43			
Compulsive Eating Module - Week 6 - Positive	1			
Compulsive Eating Module - Week 12 - Negative	22			
Compulsive Eating Module - Week 12 - Positive	0			
Compulsive Eating Module - Week 24 - Negative	4			
Compulsive Eating Module - Week 24 - Positive	0			
Compulsive Eating Module - Early Termination - Neg	61			
Compulsive Eating Module - Early Termination - Pos	1			
Compulsive Eating Module - Safety Follow-up - Neg	57			
Compulsive Eating Module - Safety Follow-up - Pos	0			
Punding Behavior - Screening - Negative	66			
Punding Behavior - Screening - Positive	0			
Punding Behavior - Week 2 - Negative	60			
Punding Behavior - Week 2 - Positive	0			
Punding Behavior - Week 6 - Negative	44			

Punding Behavior - Week 6 - Positive	0			
Punding Behavior - Week 12 - Negative	22			
Punding Behavior - Week 12 - Positive	0			
Punding Behavior - Week 24 - Negative	4			
Punding Behavior - Week 24 - Positive	0			
Punding Behavior - Early Termination - Negative	62			
Punding Behavior - Early Termination - Positive	0			
Punding Behavior - Safety Follow-up - Negative	57			
Punding Behavior - Safety Follow-up - Positive	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

52 weeks but due to early termination subjects last visit was at Week 24.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.1
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Reporting groups

Reporting group title	Tozadenant
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Reporting group description: -

Serious adverse events	Tozadenant		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 66 (7.58%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Tibia fracture			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	2 / 66 (3.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis ischaemic			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Gallbladder disorder			

subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atypical pneumonia			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Tozadenant		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 66 (69.70%)		
Investigations			
Blood creatinine increased			

subjects affected / exposed occurrences (all)	2 / 66 (3.03%) 2		
Blood glucose increased subjects affected / exposed occurrences (all)	2 / 66 (3.03%) 2		
Blood pressure increased subjects affected / exposed occurrences (all)	2 / 66 (3.03%) 2		
Injury, poisoning and procedural complications			
Fall subjects affected / exposed occurrences (all)	7 / 66 (10.61%) 7		
Contusion subjects affected / exposed occurrences (all)	2 / 66 (3.03%) 2		
Drug administration error subjects affected / exposed occurrences (all)	2 / 66 (3.03%) 2		
Vascular disorders			
Hypertension subjects affected / exposed occurrences (all)	2 / 66 (3.03%) 2		
Orthostatis hypotension subjects affected / exposed occurrences (all)	2 / 66 (3.03%) 2		
Nervous system disorders			
Dyskinesia subjects affected / exposed occurrences (all)	17 / 66 (25.76%) 17		
Parkinson's disease subjects affected / exposed occurrences (all)	3 / 66 (4.55%) 3		
Headache subjects affected / exposed occurrences (all)	2 / 66 (3.03%) 2		
Tremor			

subjects affected / exposed occurrences (all)	2 / 66 (3.03%) 2		
Blood and lymphatic system disorders Agranulocytosis subjects affected / exposed occurrences (all)	2 / 66 (3.03%) 2		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all)	6 / 66 (9.09%) 6 3 / 66 (4.55%) 3 2 / 66 (3.03%) 2 2 / 66 (3.03%) 2		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	2 / 66 (3.03%) 2		
Psychiatric disorders Hallucination subjects affected / exposed occurrences (all) Anxiety subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all)	3 / 66 (4.55%) 3 2 / 66 (3.03%) 2 2 / 66 (3.03%) 2		
Musculoskeletal and connective tissue disorders Arthralgia			

subjects affected / exposed occurrences (all)	2 / 66 (3.03%) 2		
Joint swelling subjects affected / exposed occurrences (all)	2 / 66 (3.03%) 2		
Infections and infestations			
Upper respiratory tract infection subjects affected / exposed occurrences (all)	4 / 66 (6.06%) 4		
Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 66 (4.55%) 3		
Urinary tract infection subjects affected / exposed occurrences (all)	2 / 66 (3.03%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 February 2017	Protocol Version 2.0 To clarify the exclusion criteria that subjects who have had DBS at least 12-months before screening visit are eligible to participate in the study. To move mMIDI assessment from baseline to the screening visit so that the site has adequate time to rule out ICD prior to subjects performing baseline patient diaries. 120 mg tablet will be blue colored not white to off-white.
09 October 2017	Protocol Version 3.0 New exclusion criteria added: Addition of lower limit of ANC at screening to avoid situation where criteria are met for both study drug withdrawal and continuation. New endpoint added: Fall questionnaire Added discontinuation requirement that needs definition of severe granulocytopenia to avoid risk that continued study drug exposure could worsen neutrophil count further. Added clarification for a scale (Non-motor Symptom Assessment Scale) to be collected in ON state. Added new table to reflect the added hematology testing. Visits added to allow for more frequent hematology monitoring to closely monitor white blood cells and absolute neutrophil counts. Addition of lower limit of ANC at screening to avoid situation where criteria are met for both study drug withdrawal and continuation. Added a statement allowing for additional review of practice PD diaries and contact details. Clarification of scales that should be performed during patient's ON state: PDQ-39 EQ-5D-5L Non-motor Symptom Assessment Scale CG-II PGI-I

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported