THE LANCET Neurology

Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Ferreira JJ, Lees A, Rocha J-F, Poewe W, Rascol O, Soares-da-Silva P, for the Bi-Park 1 investigators. Opicapone as an adjunct to levodopa in patients with Parkinson's disease and end-of-dose motor fluctuations: a randomised, double-blind, controlled trial. *Lancet Neurol* 2015; published online Dec 22. http://dx.doi.org/10.1016/S1474-4422(15)00336-1.

Supplementary Appendix:

Full inclusion and exclusion criteria:

Inclusion Criteria
Subjects were to be included in the study if they met all of the following criteria:
Screening visit (up to 14 days before Randomization visit)

1. Able to comprehend and willing to sign an informed consent form.
2. Male and female subjects between 30 and 83 years old, inclusive.
3. Diagnosed with idiopathic PD according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria for at least 3 years.
4. Modified Hoehn and Yahr staging 1 to 3 at ON.
5. Treated with levodopa/DDCI for at least 1 year with clear clinical improvement as per investigator's judgment.
6. Treated with 3 to 8 daily doses of levodopa/DDCI, which could have included a slow release formulation.
7. On a stable regimen of levodopa/DDCI and other anti-PD drugs for at least 4 weeks before Screening.
8. Signs of "wearing-off" phenomenon (end-of-dose deterioration) for a minimum of 4 weeks before Screening, with average total daily OFF-time while awake of at least 1.5 hours, excluding the early morning pre-first dose OFF, despite optimal anti-PD therapy (based on the investigator's judgment).
9. Able to keep reliable diaries of motor fluctuations (alone or with family/caregiver assistance). The diaries were to be sent for central review to SCOPE International AG for an independent verification of the subject's eligibility prior to randomization.
10. Amenorrheic for at least 1 year or surgically sterile for at least 6 months before Screening. Females of childbearing potential were required to be using an effective nonhormonal contraceptive method.
11. Have filled-in self-rating diary charts in accordance with the diary chart instructions and with ≤3 errors per day.
12. At least 1.5 OFF hours per day, excluding the early morning pre-first dose OFF period (i.e. the time between wake-up and response to the first levodopa/DDCI dosage), as recorded in the self-rating diary for at least 2 of the 3 days preceding the Randomization visit.
13. Results of the Screening laboratory tests were considered acceptable by the investigator (i.e. not clinically relevant for the well-being of the subject or for the purpose of the study).

Exclusion Criteria
Subjects were not to be included in the study if they met any of the following criteria:
Screening visit (up to 14 days before Randomization visit)

1. Non-idiopathic PD (atypical parkinsonism, secondary [acquired or symptomatic] parkinsonism, Parkinson-plus syndrome).
2. Dyskinesia disability score >3 in the Unified Parkinson's Disease Rating Scale (UPDRS) Sub-section IV A, Item 33.
3. Severe and/or unpredictable OFF periods.
4. Treatment with prohibited medication: tolcapone, neuroleptics, venlafaxine, monoamine oxidase (MAO) inhibitors (except selegiline up to 10 mg/day in oral formulation or mg/day in buccal absorption formulation or rasagiline up to 1 mg/day), or antiemetics with anti-dopaminergic action (except domperidone) within the month before Screening.
5. Previous use of entacapone.
6. Treatment with apomorphine, alpha-methyldopa, or reserpine within the month before Screening or likely to be needed at any time during the study.
7. Dosage change of concomitant anti-PD medication within 4 weeks of Screening.
8. Previous or planned (during the entire study duration, including the OL period) deep brain stimulation.
9. Previous stereotactic surgery (e.g. pallidotomy, thalamotomy) for PD or with planned stereotactic surgery during the study period.
10. Any IMP within the 3 months (or within 5 half-lives, whichever is longer) before Screening.
11. Any medical condition that might have placed the subject at increased risk or interfere with assessments.
12. Past (within the past year) or present history of suicidal ideation or suicide attempts. Current or

previous (within the past year) diagnosis of major depressive disorder, mania, bipolar disorder, psychosis, dysthymia, generalised anxiety disorder, alcohol or substance abuse excluding caffeine or nicotine, impulse control disorders (e.g. pathological gambling), dementia or eating disorders according to Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), text revision American Psychiatric Association, 2000 criteria, as determined by the investigator.

13. A clinically relevant electrocardiogram (ECG) abnormality (relevance was to be assessed by a cardiologist if needed).
14. Evidence of unstable cardiovascular disease at the time of enrolment, including but not limited to uncontrolled hypertension, myocardial infarction with important systolic or diastolic dysfunction, unstable angina, congestive heart failure (New York Heart Association class ≥III), and significant cardiac arrhythmia (Mobitz II 2nd or 3rd degree atrioventricular block or any other arrhythmia causing haemodynamic repercussions as symptomatic bradycardia or syncope).
15. Prior renal transplant or current renal dialysis.
16. Pheochromocytoma, paraganglioma, or other catecholamine secretive neoplasm.
17. Known hypersensitivity to the ingredients of IMPs used.
18. History of neuroleptic malignant syndrome (NMS) or NMS-like syndromes, or non-traumatic rhabdomyolysis.
19. History of or current cancer disease, which in the investigator's opinion would have excluded the subject from the study (e.g. melanoma, prostate cancer).
20. Unstable active narrow-angle or unstable wide-angle glaucoma.
21. History of or evidence at the time of enrolment of any relevant disease in the context of this study, i.e. with respect to the safety of the subject or related to the study conditions, e.g. which might have influenced the absorption or metabolism (such as a relevant liver disease) of the IMP.
22. Pregnant or breastfeeding.
23. Nursing care level II or III, applied to subjects in Germany only
24. Any abnormality in the liver enzymes (aspartate aminotransferase [AST]/serum glutamic-oxaloacetic transaminase [SGOT]) and/or alanine aminotransferase [ALT]/serum glutamic-pyruvic transaminase [SGPT]) >2 x the upper limit of the normal range (ULN), in the Screening laboratory tests results.
25. Plasma sodium <130 mmol/L, white blood cell count <3000 cells/mm3, or any other relevant clinical laboratory abnormality in the Screening laboratory tests results that, in the Investigator's opinion, might have compromised the subject's safety.
26. Inadequate compliance to concomitant levodopa/DDCI and other anti-PD drugs during the Screening period.
27. A subject was not to be enrolled in this study more than once.

Regions included in the primary analysis ANCOVA: Western Europe (Austria, Germany), Southern Europe (France, Italy, Portugal, Spain), North Eastern Europe (Croatia, Czech Republic, Slovakia, Poland, Latvia, Lithuania), Russia and Ukraine, South Eastern Europe (Serbia, Bosnia and Herzegovina, Montenegro, Bulgaria, Hungary, Romania).

Sensitivity analysis of the primary efficacy analysis (Change from Baseline to endpoint in absolute OFF time) using mixed model repeated measures (MMRM) to account for missing data (FAS)

Parameter	Placebo (N=117)	ENT 200mg (N=114)	OPC 5mg (N=113)	OPC 25mg (N=113)	OPC 50mg (N=111)
LS Mean ± SEM change from baseline (minutes)	-57·0 ± 13·3	-99·2 ± 13·4	-95·4 ± 13·5	-90·1 ± 13·6	-118·1 ± 13·8
Difference vs. placebo; LS mean (95%CI)		-42·2 (-78·6, -5·7)	-38·4 (-75·0, -1·8)	-33·1 (-69·9, 3·6)	-61·1 (-97·9, -24·3)
P value		0·0233	0·0399	0·0768	0·0012
Difference vs. entacapone; LS mean (95%CI)			3·8 (-32·9, 40·5)	9·0 (-27·7, 45·8)	-18·9 (-55·9, 18·1)

Bi-Park 1 sites and investigators

Investigator	Institution	Number enrolled
Austria		
Regina Katzenschlager	Sociomedical Centre Ost-Donauspital, Wien, Austria	2
Gerhard Ransmayr	General Hospital Linz, , Linz, Austria	3
Bosnia and Herzegovina		
Vlado Djajic	Clinical Centre Banja Luka, Neurological Clinic, Banja Luka,	12
Enra Suljic	Clinical Centre University of Sarajevo, Neurological Clinic, Sarajevo, Bosnia and Herzegovina	7
Bulgaria		
Latchezar Traykov	UMHAT "Alexandrovska" Clinic of Neurology, Sofia, Bulgaria	19
Ivan Petrov	CCB MI Ministry of Interior Clinic of Neurology, Sofia, Bulgaria	5
Dimitar Maslarov	First MHAT-Sofia, Clinic of nerve diseases, Sofia, Bulgaria	8
Ivan Staikov	MHAT "Tokuda Hospital Sofia", Sofia, Bulgaria	6
Dimitar Syankov	MHAT " Stoyan Kirkovich', Stara Zagora, Bulgaria	6
Jacov Mayer	Fourth MHAT Sofia, Second Internal Department, Sofia, Bulgaria	2
Marin Daskalov	UMHAT "Tsaritsa Yoanna – ISUL" Clinic of Neurology, Sofia, Bulgaria	2
Slavi Stanev	Diagnostic & Consultative Center "Sveta Anna" Sofia, Bulgaria	4
Croatia		
Marina Titlić	Clinical hospital Centre Split-Clinic for neurology, Croatia	3
Ivan Bielen	Clinical hospital Sveti Duh-Clinic for neurology, Zagreb, Croatia	1
Silva Butković Soldo	Clinical hospital Osijek-Clinic for neurology, Osijek, Croatia	3
Anamarija Mrđen	General Hospital Zadar- neurology department, Zadar, Croatia	14
Czech Republic		
Martin Vališ	Policlinic Choceň, Neurology out-patient department, Hradec Králové, Czech Republic	9
Radoslav Bembenek	Clintrial, s.r.o., Počernická, Praha, Czech Republic	6
Edvard Ehler	Regional Hospital Pardubice, Pardubice, Czech Republic	20
Danuše Roubcová	Policlinic "Modrý pavilon", Ostrava, Czech Republic	3
Eva Štolcová	Medicentrum Beroun, Beroun, Czech Republic	3
Marek Baláž	St. Anne's University Hospital, Brno, Czech Republic	11
Robert Jech	General Teaching Hospital Department of Neurology of 1st Faculty of Medicine of Charles University, Praha, Czech Republic	3
Petr Kaňovský	University Hospital Olomouc, Olomouc, Czech Republic	2
France		
Olivier Rascol	Clinical Investigational Center University Hospital of Purpan Pierre Paul Riquet Hospital. University Hospital of Toulouse - Purpan Hospital, Building Riser Clinical Investigational Center	3
François Tison	University of Bordeaux (Pellegrin Hospital), Centre Expert Parkinson Bordeaux Cedex, France	4
Jean-Christophe Corvol	Clinical Investigational Center, Paris Cedex, France	3
Jean-Philippe Azulay	University Hospital of la Timone, Marseille Cedex 05, France	2
Pascal Derkinderen	University Hospital of Nantes Laennec, Nantes Cedex 1, France	3
Germany		
Dirk Dressler	Hannover Medical School, Hannover, Germany	1
Bernhard Haslinger	Hospital Rechts der Isar of the TU Munich, München, Germany	1
Daniela Berg	University Hospital Tübingen Centre for Neurology,	1

	Tübingen, Germany	
Andres Ceballos-Baumann	Schön Klinik Munich-Schwabing, München, Germany	15
Siegfried Muhlack	St. Josef Hospital Bochum, Hospital for Neurology, Bochum, Germany	5
Georg Ebersbach	Neurological speciality hospital for movement disorders/Parkinson's disease Hospitals, Beelitz-Heilstätten, Germany	6
Horst Baas	Hospital Hanau GmbH, Hospital for Neurology, Hanau, Germany	3
Reinhard Ehret	Berlin, Germany	12
Imke Galazky	Otto-von-Guericke-University, University Hospital for Neurology and University Hospital for stereotactic neurosurgery University Hospital Magdeburg A.ö.R, Magdeburg, Germany	1
Hungary		
Piroska Imre	Csolnoky Ferenc Hospital, Kórház Hungary.	3
András Folyovich	Metropolitan Municipality St.John Hospital, Budapest, Hungary	3
Judit Semjén	Markhot Ferenc Hospital Health Provider Nonprofit Advanced Public Utility Kft., Eger, Hungary	2
Mária Zsolnai	St. Pantaleon Hospital, Dunaújváros, Hungary	3
Italy		
Angelo Antonini	San Camillo Hospital Foundation, Venezia, Italy	4
Giuseppe Meco	Polyclinic Umberto I of Rome, Parkinson Unit, Roma, Italy	4
Giovanni Abbruzzese	University of Genoa, Largo Paolo Daneo 3, 16132, Genova, Italy	2
Fabrizio Stocchi	San Raffaele Pisana Foundation, Roma, Italy	4
Latvia		
Inara Logina	Pauls Stradins Clinical University Hospital, Riga, Latvia	3
Nora Jurjane	Riga 1st Hospital, Riga, Latvia	1
Ligita Smeltere	Health Centre, Riga, Latvia	5
Lithuania		
Kestutis Juknelis	Alytus County S. Kudirka Hospital, Alytus, Lithuania	3
Ilona Bickuviene	Vilnius University Emergency Hospital, Vilnius, Lithuania	1
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Montenegro		
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Poland		
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Portugal		
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Romania		
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