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Opicapone as an adjunct to levodopa in patients with Parkinson's disease and end-of-dose motor fluctuations: a randomised, double-blind, controlled trial

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See Online for appendix

Summary

Background Opicapone is a novel, once-daily, potent third-generation catechol-*O*-methyltransferase inhibitor. We aimed to assess the safety and efficacy of opicapone as an adjunct to levodopa compared with placebo or entacapone in patients with Parkinson's disease and motor fluctuations.

Methods We did a randomised, double-blind, placebo-controlled and active-controlled trial of opicapone as an adjunct to levodopa in patients with Parkinson's disease with end-of-dose motor fluctuations. Patients aged 30–83 years were enrolled at 106 specialist centres across 19 European countries and Russia and were randomly assigned (1:1:1:1:1) by a proprietary computer-generated sequence to oral treatment with opicapone (5 mg, 25 mg, or 50 mg once daily), placebo, or entacapone (200 mg with every levodopa intake) for 14–15 weeks. Patients and investigators (ie, outcome assessors) were masked to treatment allocation. The primary endpoint was the change from baseline to end of study treatment in absolute time in the off state, as assessed by daily paper patient diaries; the primary analysis followed a hierarchical procedure for each opicapone dose in which superiority compared with placebo in the full analysis set was first tested and then, if positive, non-inferiority to entacapone was tested in the per-protocol set with a margin of 30 min. This trial is registered with EudraCT, 2010-021860-13, and ClinicalTrials.gov, NCT01568073.

Findings Between March 31, 2011, and Nov 30, 2013, of 679 patients screened, 600 were randomly assigned. 590 patients were included in the full analysis set (120 in the placebo group, 120 in the entacapone group, 119 in the opicapone 5 mg group, 116 in the opicapone 25 mg group, and 115 in the opicapone 50 mg group) and 537 in the per-protocol set (112 in the placebo group, 104 in the entacapone group, 110 in the opicapone 5 mg group, 105 in the opicapone 25 mg group, and 106 in the opicapone 50 mg group). The mean change in time in the off state was –56·0 min (SE 13·4; 95% CI –82·3 to –29·7) for placebo, –96·3 min (13·4; –122·6 to –70·0) for entacapone, –91·3 min (13·5; –117·7 to –64·8) for opicapone 5 mg, –85·9 min (13·7; –112·8 to –59·1) for opicapone 25 mg, and –116·8 min (14·0; –144·2 to –89·4) for opicapone 50 mg. Treatment with opicapone 50 mg was superior to placebo (mean difference in change from baseline –60·8 min, 95% CI –97·2 to –24·4; p=0·0015) and non-inferior to entacapone (–26·2 min, –63·8 to 11·4; p=0·0051). Treatment with opicapone 5 mg (p=0·056) or 25 mg (p=0·080) was not significantly different from treatment with placebo. Treatment-emergent adverse events were reported in 60 (50%) of 121 patients in the placebo group, 69 (57%) of 122 in the entacapone group, 63 (52%) of 122 in the opicapone 5 mg group, 65 (55%) of 119 in the opicapone 25 mg group, and 62 (54%) of 115 in the opicapone 50 mg group. The most common adverse events were dyskinesia (in five patients in the placebo group, ten in the entacapone group, 17 in the opicapone 5 mg group, nine in the opicapone 25 mg group, and 18 in the opicapone 50 mg group), insomnia (in one, seven, two, seven, and seven patients, respectively), and constipation (in three, five, four, none, and seven patients, respectively). Serious adverse events were reported in six patients in the placebo group, eight in the entacapone group, four each in the opicapone 5 mg and opicapone 50 mg groups, and one in the opicapone 25 mg group.

Interpretation The addition of opicapone 50 mg to levodopa treatment in patients with Parkinson's disease and end-of-dose motor fluctuations could enable a simplified drug regimen that allows physicians to individually tailor the existing levodopa daily regimen, by potentially reducing the total daily levodopa dose, increasing the dosing interval, and ultimately reducing the number of intakes, thereby maximising its benefit.

Funding BIAL.

Introduction

Levodopa remains the most effective drug for the management of Parkinson's disease,[1,2] but most patients receiving long-term levodopa will develop response fluctuations and dyskinesia.[3] Patients often report spending several hours per day in the off state,[4] and this can have a substantial effect on their quality of life.[5] As such, the control of motor fluctuations eventually becomes a key clinical need for almost all patients.[6]

End-of-dose motor fluctuations are linked to the short half-life of oral levodopa (about 60–90 min).[7] Catechol-*O*-methyltransferase (COMT) inhibitors increase the plasma elimination half-life of levodopa and decrease

Research in context

Evidence before this study

We searched PubMed up to Sept 7, 2015, for English language articles with the terms "catechol-O-methyltransferase inhibitor" (COMT) or "COMT inhibitor" and "Parkinson's disease". Additionally, we did a second search with the terms "Parkinson's disease" and "motor fluctuations". Evidence for the safety and efficacy of the available COMT inhibitors—entacapone and tolcapone—in the management of end-of-dose motor fluctuations is well established, with a mean reduction in time in the off state of 41 min for entacapone and 98 min for tolcapone according to a meta-analytic Cochrane review published in 2004. The moderate efficacy of entacapone and unfavourable safety profile of tolcapone draw attention to the need for novel COMT inhibitors with enhanced safety and efficacy. Opicapone, a third-generation COMT inhibitor, is a hydrophilic 1,2,4-oxadiazole analogue with a pyridine N-oxide residue at position 3 that provides high COMT inhibitory potency and avoids cell toxicity. Opicapone has a high binding affinity (sub-pmol Kd), which translates into a slow complex dissociation rate constant and long duration of action, thereby allowing once-daily dosing. In a phase 2 study, opicapone significantly decreased COMT activity, increased systemic exposure to levodopa, and improved motor response.

Added value of this study

This study is, to our knowledge, the first phase 3 study with opicapone to show that opicapone 50 mg effectively reduced time in the off state, increased time in the on state without troublesome dyskinesia, was non-inferior to entacapone with greater magnitude of reduction in time in the off state, and was generally safe and well tolerated.

Implications of all the available evidence

The results of this study suggest a favourable risk-to-benefit ratio for once-daily opicapone 50 mg in the management of end-of-dose motor fluctuations. The addition of a once-daily, well tolerated, efficacious, and potent COMT inhibitor to the pharmacological armamentarium will provide greater flexibility to tailor treatment to the individual needs of patients with Parkinson's disease.

peak–trough variations.[8] The COMT inhibitor entacapone is a common first-line strategy for the management of end-of-dose motor fluctuations, but reductions in daily time in the off state are moderate (mean 41 min across clinical trials) and it needs to be given concomitantly with each levodopa dose.[9] Tolcapone is generally regarded as more efficacious than entacapone, but its use in clinical practice is limited by the risk of hepatopathy necessitating continuous monitoring of liver function, and it is thus indicated for patients who do not respond to or are intolerant of other COMT inhibitors.[2,10] Thus, a more effective COMT inhibitor that can be easily used in routine clinical practice is needed.[8]

Opicapone (BIA 9-1067) is a hydrophilic 1,2,4-oxadiazole analogue with a pyridine N-oxide residue at position 3 that provides high COMT inhibitory potency and does not cause cell toxicity.[11,12] Opicapone has a high binding affinity (sub-pmol Kd),[13] which translates into a slow complex dissociation rate constant and long duration of action, thereby allowing once-daily dosing. In a phase 2 study, opicapone significantly reduced COMT activity, increased systemic exposure to levodopa, and improved motor response compared with placebo.[14] In healthy volunteers,[15] opicapone had a more pronounced effect than entacapone in increasing levodopa bioavailability, because of its potent, longlasting, and sustained COMT inhibition that lasted throughout the day.

In this study, we aimed to assess the safety and efficacy of opicapone as an adjunct to levodopa compared with placebo or entacapone in patients with Parkinson's disease and motor fluctuations.

Methods

Study design and participants

We did a randomised, double-blind, placebo-controlled and active-controlled trial of three doses of opicapone (5 mg, 25 mg, and 50 mg once daily) as an adjunct to levodopa in patients with Parkinson's disease with end-of-dose motor fluctuations. Entacapone (200 mg with every levodopa intake) was the active control. The study was done at 106 centres across 19 European countries and Russia.

Full details of the inclusion and exclusion criteria are given in the appendix. In brief, participants (aged 30–83 years) were eligible if they had a clinical diagnosis of Parkinson's disease[16] for at least 3 years, a Hoehn and Yahr stage of 1–3 (during the on state), and at least 1 year of clinical improvement with levodopa treatment. Patients had to have been on a stable optimised regimen of three to eight daily doses of levodopa and other drugs for Parkinson's disease for at least 4 weeks before screening. Additionally, patients had to have signs of end-of-dose motor fluctuations for at least 4 weeks before screening, with a mean total awake time in the off state of at least 1·5 h, not including morning akinesia.

Key exclusion criteria included previous use of entacapone; a dyskinesia disability score greater than 3 on item 33 (disability) of the Unified Parkinson's Disease Rating Scale (UPDRS);[17] severe or unpredictable periods in the off state, or both; previous surgery or deep brain stimulation for Parkinson's disease; and a history of neuroleptic malignant syndrome or non-traumatic rhabdomyolysis. Patients with clinically significant and unstable cardiovascular disease or psychiatric illness

(including major depression, dementia, impulse control disorders, and suicide ideation), or any other medical disorder that might have placed the patient at increased risk were also excluded. Concomitant stable treatment for Parkinson's disease was allowed, with the exception of tolcapone, apomorphine (withdrawn ≥1 month before screening), and entacapone (other than that supplied for the study). Treatment with neuroleptics, venlafaxine, monoamine oxidase inhibitors (except selegiline up to 10 mg/day orally or 1·25 mg/day in buccal formulation, and rasagiline up to 1 mg/day), or anti-emetics with antidopaminergic action (except domperidone) were also prohibited during the study (withdrawn ≥1 month before screening).

Institutional review boards at the participating sites provided ethics approval and the trial was done in accordance with the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice Guidelines. All patients provided written informed consent before randomisation.

Randomisation and masking

Eligible patients were randomly assigned (1:1:1:1:1) at baseline using a proprietary computer-generated scheme (Accovion, Eschborn, Germany) to once-daily opicapone 5 mg, 25 mg, or 50 mg, matching placebo, or entacapone (200 mg with every levodopa intake) using blocks of eight to ten depending on regimen, stratified by centre. Patients and investigators (ie, outcome assessors) were masked to treatment allocation throughout the study. Masking of randomisation was maintained by use of identical over-encapsulation of opicapone capsules and entacapone tablets. Placebo capsules were identical and included riboflavin (1 mg per capsule) to mimic the urinary discolouration caused by entacapone.

An independent data safety monitoring board periodically received partly masked safety data—an unmasked biostatistician (SCOPE, Mannheim, Germany) who was independent of the study team was permitted to attend closed meetings in case of a need to unmask patient data; this occurred for one patient in the placebo group.

Procedures

Daytime doses of study drugs were given concomitantly with each levodopa intake (ie, three to eight daily doses). An additional bedtime dose was administered at least 1 h after the last daily dose of levodopa. Patients in the opicapone groups took placebo for the daytime doses and active treatment as their bedtime dose. Patients in the entacapone group took the active treatment during the day and placebo as the bedtime dose. Reductions in the daily dose, but not frequency, of levodopa could be made between baseline and up to 3 weeks according to the clinical response, as judged by the study investigator. The daily dose could then be increased, but was not to exceed the baseline dose. Adjustments were not permitted thereafter.

Patients were assessed at screening (visit 1), baseline (ie, at randomisation; visit 2) and at 1 week after baseline (visit 3). Depending on the need for levodopa adjustment, visit 4 could occur between 2 weeks and 3 weeks after baseline—patients who needed a dose adjustment were permitted a 1-week extension for visit 4. Thereafter, assessments occurred at 4-week intervals (visits 5, 6, and 7); thus, the total duration of the double-blind period was 14–15 weeks (end of study treatment, visit 7).

Outcomes

The primary endpoint was the change from baseline to the end of study treatment in absolute time in the off state, as assessed by daily paper patient diaries.[18]

Key secondary endpoints were the change from baseline to the end of study treatment in the proportion of patients (ie, responders) achieving at least a 1-h reduction in absolute time in the off state and the change from baseline to the end of study treatment in the proportion of patients achieving at least a 1-h increase in absolute total time in the on state.

Other diary-based secondary efficacy variables were changes from baseline in the percentage of time in the off state and in the absolute and percentage of time spent in the on state in total, without troublesome dyskinesia, and with troublesome dyskinesia. Times in the off and on states were calculated as the mean time reported in the 3 preceding diary days, or the mean of available days if fewer than 3 days were recorded. Percentages of time in the off and on states were calculated as the sum in minutes from 30-min periods classified as off or on state divided by the total time awake. Scale-based secondary efficacy variables were the change from baseline in the UPDRS,[17] Parkinson's Disease Sleep Scale (PDSS),[19] 39-item Parkinson's Disease Questionnaire (PDQ-39),[20] Non-Motor Symptoms Scale (NMSS),[21] and the Clinician's and Patient's Global Impression of Change (CGI-C and PGI-C).[22]

Treatment-emergent adverse events and vital signs were recorded throughout the study. Electrocardiogram (ECG) recordings and physical, neurological, and dermatological examinations were done at baseline and at the end of the double-blind period (visit 7). Additionally, standard laboratory safety tests, the Columbia Suicide Severity Rating Scale,[23] and the modified Minnesota Impulsive Disorders Interview (mMIDI)[24] were done at baseline and visits 4–7.

Statistical analysis

Populations sets were defined as the full analysis set, which included all randomly assigned patients who took at least one dose of study drug and had at least one assessment of time in the off state after baseline; the per-protocol set, which included all patients in the full analysis set who did not have any major protocol deviations; and the safety set, which included all patients who received at least one dose of study drug.

The primary efficacy analysis followed a hierarchical procedure for each dose and focused on identification of at least one efficacious dose of opicapone (ie, superiority *vs* placebo) and its subsequent comparison with the active control, entacapone (ie, non-inferiority *vs* entacapone). We used the intention-to-treat approach with the full analysis set because it is the most conservative method to test for superiority versus placebo,

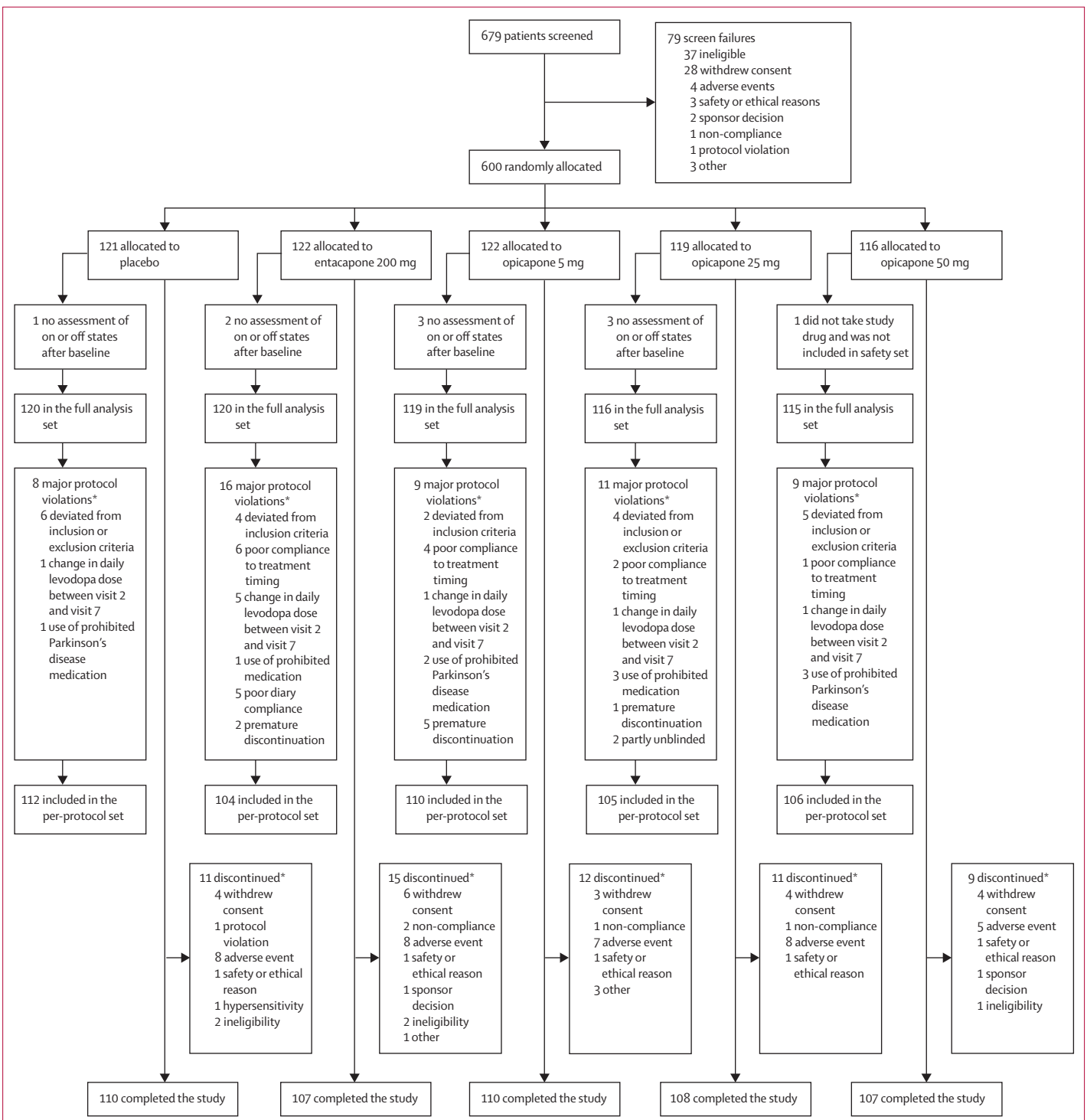

Figure 1: **Trial profile**
*More than one reason for discontinuation and protocol deviation could be specified per patient.

whereas we used a per-protocol analysis as the most conservative approach to test for non-inferiority versus entacapone.[25] We used ANCOVA including treatment group and region (appendix) as fixed effects and time in the off state at baseline as a covariate to test superiority of each opicapone dose versus placebo in the full analysis set and non-inferiority versus entacapone in the per-protocol set (non-inferiority margin of 30 min). To control for multiplicity, we used a sequential gatekeeping procedure.[26,27] We used three one-sided *t* tests to assess the superiority of the opicapone dose group against placebo. For each dose of opicapone, non-inferiority versus entacapone was tested only if the efficacy of opicapone versus placebo had already been established. The family-wise error rate was 0·025 (corresponding to a p value threshold of <0·05 for two-sided tests). We applied a Bonferroni adjustment to ensure that the family-wise error and all comparisons versus placebo were treated equally (Bonferroni-adjusted p value threshold of <0·0083 [ie, 0·025/3]).

	Placebo (n=121)	Entacapone 200 mg (n=122)	Opicapone		
			5 mg (n=122)	25 mg (n=119)	50 mg (n=115)
Sex					
Male	71 (59%)	76 (62%)	71 (58%)	67 (56%)	69 (60%)
Female	50 (41%)	46 (38%)	51 (42%)	52 (44%)	46 (40%)
Age (years)	64·3 (9·3)	63·7 (8·8)	63·6 (9·3)	64·4 (9·0)	63·5 (9·2)
Time since Parkinson's disease diagnosis (years)	7·7 (4·2)	7·1 (4·1)	7·5 (3·6)	7·2 (4·1)	7·0 (3·8)
Time since start of levodopa treatment (years)	5·8 (3·7)	5·6 (4·1)	5·8 (3·5)	5·9 (3·9)	5·3 (3·8)
Time since onset of end-of-dose motor fluctuations (years)	2·2 (1·9)	2·2 (2·1)	2·3 (2·3)	2·3 (2·5)	2·2 (2·3)
Modified Hoehn and Yahr stage during the on state	2·4 (0·5)	2·3 (0·6)	2·4 (0·4)	2·4 (0·5)	2·4 (0·5)
Total UPDRS score	37·6 (16·6)	35·4 (20·0)	38·2 (16·2)	40·1 (18·6)	38·8 (19·0)
UPDRS part III (motor) score during the on state	27·6 (11·7)	25·8 (13·8)	28·5 (11·9)	29·0 (12·9)	28·4 (13·7)
UPDRS part IV (dyskinesia) score	1·0 (1·5)	1·0 (1·5)	1·3 (1·9)	1·1 (1·6)	1·0 (1·5)
Time in the off state					
Absolute time (h)	6·2 (1·8)	6·5 (2·2)	6·7 (2·1)	6·9 (2·0)	6·2 (1·8)
Percentage of total awake time	38·2% (10·8)	40·2% (12·9)	40·9% (12·3)	42·2% (12·9)	38·7% (10·5)
Time in the on state					
Absolute time (h)	10·0 (2·0)	9·6 (2·2)	9·7 (2·3)	9·4 (2·3)	9·9 (2·1)
Percentage of total awake time	61·8% (10·8)	59·8% (12·9)	59·1% (12·3)	57·8% (12·9)	61·3% (10·5)
Time in the on state with non-troublesome dyskinesia					
Absolute time (h)	1·1 (1·8)	1·1 (1·7)	1·1 (2·0)	0·9 (1·8)	1·0 (1·9)
Percentage of total awake time	6·8% (11·1)	6·8% (10·5)	6·8% (11·2)	5·3% (11·9)	6·2% (11·9)
Time in the on state time with troublesome dyskinesia					
Absolute time (h)	0·4 (1·1)	0·3 (0·9)	0·4 (1·2)	0·3 (0·8)	0·3 (1·0)
Percentage of total awake time	2·5% (6·7)	1·9% (6·5)	2·5% (7·0)	1·6% (4·9)	1·9% (5·9)
Presence of dyskinesia	50 (41%)	51 (42%)	57 (47%)	50 (42%)	51 (44%)
Daily levodopa dose (mg/day)	675 (302)	645 (323)	642 (310)	654 (324)	695 (338)
Previous levodopa treatment at baseline*					
Number of levodopa intakes	4·4 (1·1)	4·3 (1·2)	4·5 (1·1)	4·4 (1·1)	4·4 (1·1)
Levodopa and carbidopa	66/120 (55%)	64/120 (53%)	55/119 (46%)	59/116 (51%)	61/115 (53%)
Levodopa and benserazide	66/120 (55%)	61/120 (51%)	73/119 (61%)	62/116 (53%)	59/115 (51%)
Controlled-release levodopa	44/120 (37%)	34/120 (28%)	44/119 (37%)	36/116 (31%)	34/115 (30%)
Combination of controlled-release and immediate-release levodopa	38/120 (32%)	30/120 (25%)	36/119 (30%)	30/116 (26%)	31/115 (27%)
Adjunct treatment at baseline*†					
Dopamine agonists	88/120 (73%)	84/120 (70%)	69/119 (58%)	78/116 (67%)	79/115 (69%)
Monoamine oxidase B inhibitors	23/120 (19%)	28/120 (23%)	20/119 (17%)	24/116 (21%)	25/115 (22%)
Anticholinergics	7/120 (6%)	6/120 (5%)	3/119 (3%)	8/116 (7%)	8/115 (7%)
Amantadine	28/120 (23%)	29/120 (24%)	21/119 (18%)	29/116 (25%)	26/115 (23%)

Data are number (%), mean (SD), or n/N (%). UPDRS=Unified Parkinson's Disease Rating Scale. *Data are for the full analysis set. †Patients could receive more than one adjunct treatment.

Table 1: **Demographics and baseline clinical characteristics of patients in the safety set**

Comparisons of entacapone versus placebo were analysed using the same model as described for opicapone.

We used the last-observation-carried-forward method to adjust for missing diary data. Additionally, we further assessed the sensitivity of the primary last-observation-carried-forward analysis in the full analysis set using a mixed model for repeated measurements to estimate and compare the least-squares means for the reduction in time in the off state from baseline by visit.

Secondary efficacy measures were tested in the full analysis set. For the analysis of the key secondary efficacy variables, we did pairwise Cochran-Mantel-Haenszel tests stratified by region to compare the responder rates in each of the opicapone dose groups versus placebo, and in the entacapone group versus placebo. For the other secondary efficacy measures, we analysed changes from baseline using ANCOVA with treatment group and region included as fixed effect factors and the baseline scale score as a covariate. All safety analyses were descriptive and done using the safety set.

We calculated that 100 patients in each group were needed to provide 97% power to confirm a treatment effect in at least one opicapone dose group, assuming that the mean reductions in time in the off state are 75 min for opicapone 5 mg, 90 min for opicapone 25 mg, 105 min for opicapone 50 mg, and 30 min for placebo (all with SD of 130 min).[28] This sample size would provide 84% power to ensure one significant result in the non-inferiority tests versus entacapone, assuming a mean reduction from baseline of 75 min (SD 130) for entacapone and a non-inferiority margin of 30 min. Because the non-inferiority tests were done in the per-protocol set, a minimum of 110 patients needed to be randomly assigned, assuming protocol violations in 10% of patients.

The study is registered with both EudraCT, 2010-021860-13, and ClinicalTrials.gov, NCT01568073.

Role of the funding source

Two authors (J-FR and PSS) were employed by the funder and participated in the study design, data collection, data management, and data analysis. The funder of the study had no other role in data interpretation or in the decision to submit the manuscript for publication. BIAL also supported reporting of study results by procuring medical writing support. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between March 31, 2011, and Nov 30, 2013, of the 679 patients screened, 600 were enrolled and randomly assigned (figure 1): 121 to placebo, 122 to entacapone 200 mg, 122 to opicapone 5 mg, 119 to opicapone 25 mg, and 116 to opicapone 50 mg. One patient who was randomly assigned to opicapone 50 mg did not start treatment; therefore, the safety population included 599 (>99%) of 600 patients randomly assigned. The full analysis set included 590 (98%) patients and the per-protocol set included 537 (90%) patients; 542 (90%) patients completed the study (figure 1). Patient demographics, baseline Parkinson's disease characteristics, and treatment history did not differ between the treatment groups in the safety set (table 1).

In the first 2–3 weeks of double-blind treatment—when levodopa dose adjustment was permitted—five patients in the placebo group, ten in the entacapone group, 15 in the opicapone 5 mg group, 13 in the opicapone 25 mg group, and 15 in the opicapone 50 mg group had

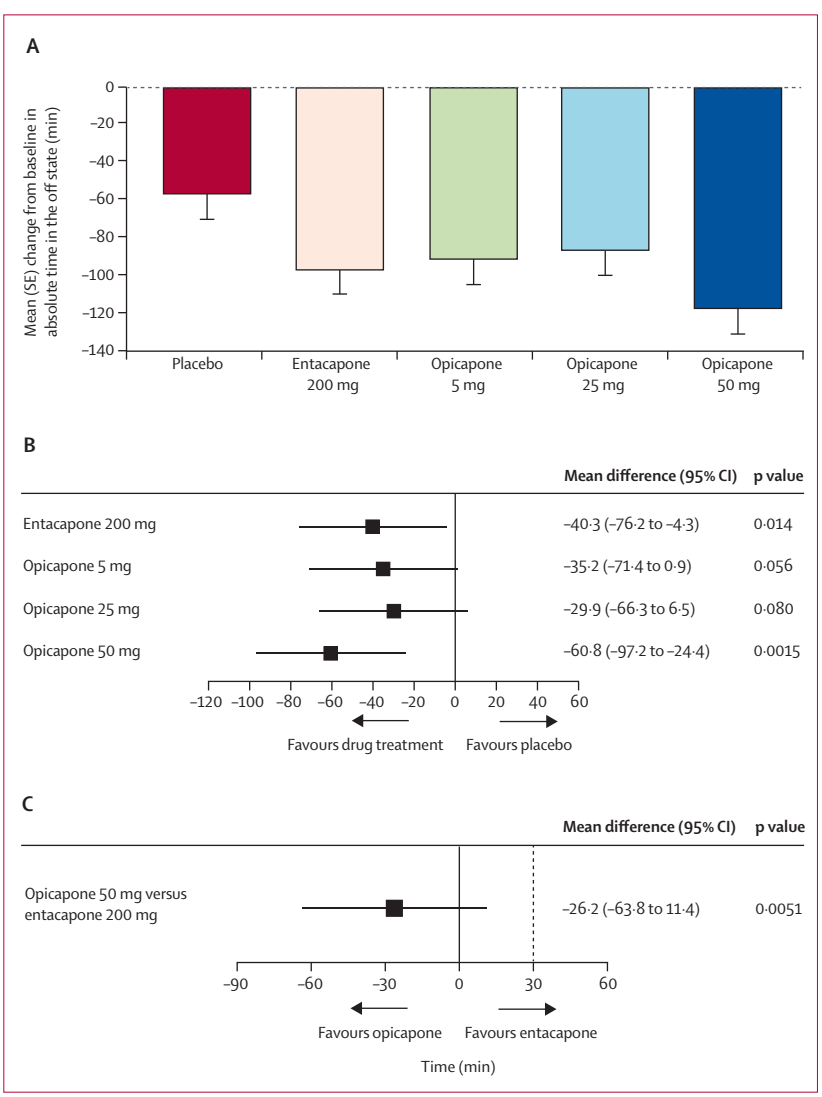

Figure 2: **Change from baseline in time in the off state**
(A) Mean (SE) change in absolute off time in the full analysis set (primary efficacy outcome). (B) Superiority test for the difference in mean change in absolute off time versus placebo in the full analysis set. (C) Non-inferiority test for the difference in mean change in absolute off time versus entacapone in the per-protocol set. The dashed line in (C) shows the non-inferiority margin.

reductions in their total levodopa doses. Mean daily levodopa doses were decreased by 6·1 mg (SD 49·6) in the placebo group compared with 14·5 mg (87·0) in the entacapone group, 20·3 mg (74·5) in the opicapone 5 mg group, 20·2 mg (92·5) in the opicapone 25 mg group, and 31·6 mg (104·8) in the opicapone 50 mg group.

	Placebo (n=120)	Entacapone 200 mg (n=120)	Opicapone		
			5 mg (n=119)	25 mg (n=116)	50 mg (n=115)
Number (%) of patients with a reduction of ≥1 h in time in the off state	57 (48%)	70 (58%)	71 (60%)	70 (60%)	80 (70%)
Comparison with placebo					
OR (95% CI)	..	1·6 (0·9–2·6)	1·6 (1·0–2·7)	1·7 (1·0–2·8)	2·5 (1·5–4·3)
p value	..	0·094	0·065	0·046	0·001
Comparison with entacapone					
OR (95% CI)	..	..	1·1 (0·6–1·8)	1·1 (0·7–1·8)	1·6 (1·0–2·8)
p value	..	..	0·82	0·74	0·063
Number (%) of patients with an increase of ≥1 h in time in the on state	55 (46%)	69 (58%)	65 (55%)	66 (57%)	75 (65%)
Comparison with placebo					
OR (95% CI)	..	1·6 (1·0–2·7)	1·4 (0·9–2·4)	1·6 (0·9–2·6)	2·2 (1·3–3·8)
p value	..	0·067	0·17	0·095	0·003
Comparison with entacapone					
OR (95% CI)	..	..	0·9 (0·5–1·5)	1·0 (0·6–1·6)	1·4 (0·8–2·4)
p value	..	..	0·66	0·93	0·15
Total time in the on state at end of study treatment (min)					
Least-squares mean change (SE)	47·1 (13·6)	99·7 (13·6)	90·3 (13·6)	86·1 (13·9)	119·0 (14·1)
Comparison with placebo					
Least-squares mean difference (95% CI)	..	52·6 (16·1 to 89·1)	43·2 (6·7 to 79·8)	39·0 (2·1 to 75·9)	71·9 (35·0 to 108·8)
p value	..	0·005	0·02	0·04	0·0001
Comparison with entacapone					
Least-squares mean difference (95%CI)	..	..	–9·4 (–45·9 to 27·1)	–13·6 (–50·4 to 23·1)	19·3 (–17·6 to 56·2)
p value	..	..	0·61	0·47	0·30
Time in the on state without troublesome dyskinesia (min)					
Least-squares mean change (SE)	46·5 (14·2)	94·1 (14·3)	85·9 (14·3)	84·7 (14·6)	109·1 (14·9)
Comparison with placebo					
Least-squares mean difference (95% CI)	..	47·6 (9·3 to 86·0)	39·4 (1·0 to 77·8)	38·2 (–0·6 to 77·0)	62·6 (23·8 to 101·4)
p value	..	0·02	0·04	0·053	0·002
Comparison with entacapone					
Least-squares mean difference (95%CI)	..	..	–8·2 (–46·6 to 30·1)	–9·4 (–48·0 to 29·1)	15·0 (–23·8 to 53·7)
p value	..	..	0·67	0·63	0·45
Time in the on state with troublesome dyskinesia (min)					
Least-squares mean change (SE)	0·6 (6·0)	5·6 (6·0)	4·4 (6·0)	1·4 (6·2)	9·9 (6·3)
Comparison with placebo					
Least-squares mean difference (95% CI)	..	5·0 (–11·2 to 21·2)	3·8 (–12·4 to 20·0)	0·8 (–15·5 to 17·2)	9·3 (–7·0 to 25·7)
p value	..	0·54	0·64	0·92	0·26
Comparison with entacapone					
Least-squares mean difference (95%CI)	..	..	–1·2 (–17·4 to 15·0)	–4·2 (–20·5 to 12·1)	4·3 (–12·0 to 20·7)
p value	..	..	0·89	0·61	0·60
Percent of time in the off state					
Least-squares mean change (SE)	–5·6 (1·4)	–10·3 (1·4)	–9·1 (1·4)	–8·8 (1·4)	–12·1 (1·4)
Comparison with placebo					
Least-squares mean difference (95% CI)	..	–4·7 (–8·3 to –1·0)	–3·4 (–7·1 to 0·2)	–3·2 (–6·9 to 0·5)	–6·5 (–10·2 to –2·7)
p value	..	0·01	0·07	0·09	0·0007
Comparison with entacapone					
Least-squares mean difference (95%CI)	..	..	1·2 (–2·5 to 4·9)	1·5 (–2·2 to 5·2)	–1·8 (–8·3 to –1·0)
p value	..	..	0·52	0·43	0·34

(Table 2 continues on next page)

	Placebo (n=120)	Entacapone 200 mg (n=120)	Opicapone		
			5 mg (n=119)	25 mg (n=116)	50 mg (n=115)
(Continued from previous page)					
Percent of time in the on state					
Least-squares mean change (SE)	5·5 (1·4)	9·9 (1·4)	9·6 (1·4)	9·0 (1·4)	11·7 (1·4)
Comparison with placebo					
Least-squares mean difference (95% CI)	..	4·4 (0·7 to 8·1)	4·1 (0·4 to 7·8)	3·4 (–0·3 to 7·2)	6·2 (2·4 to 9·9)
p value	..	0·02	0·03	0·07	0·001
Comparison with entacapone					
Least-squares mean difference (95%CI)	..	..	–0·3 (–4·0 to 3·4)	–1·0 (–4·7 to 2·8)	1·8 (–1·9 to 5·5)
p value	..	..	0·87	0·61	0·35
Percent of time in the on state without troublesome dyskinesia					
Least-squares mean change (SE)	5·4 (1·4)	9·6 (1·4)	9·1 (1·4)	8·8 (1·5)	10·8 (1·5)
Comparison with placebo					
Least-squares mean difference (95% CI)	..	4·2 (0·4 to 8·1)	3·7 (–0·1 to 7·6)	3·5 (–0·4 to 7·4)	5·4 (1·5 to 9·3)
p value	..	0·03	0·06	0·08	0·007
Comparison with entacapone					
Least-squares mean difference (95%CI)	..	..	–0·5 (–4·3 to 3·4)	–0·7 (–4·6 to 3·2)	1·2 (–2·7 to 5·1)
p value	..	..	0·80	0·71	0·54
Percent of time in the on state with troublesome dyskinesia					
Least-squares mean change (SE)	0·2 (0·6)	0·4 (0·6)	0·5 (0·6)	0·1 (0·6)	0·9 (0·7)
Comparison with placebo					
Least-squares mean difference (95% CI)	..	0·2 (–1·5 to 1·9)	0·4 (–1·3 to 2·1)	–0·1 (–1·8 to 1·6)	0·8 (–0·9 to 2·5)
p value	..	0·83	0·67	0·94	0·38
Comparison with entacapone					
Least-squares mean difference (95%CI)	..	..	0·2 (–1·5 to 1·9)	–0·2 (–1·9 to 1·5)	0·6 (–1·1 to 2·3)
p value	..	..	0·83	0·78	0·50
UPDRS total score*					
Least-squares mean change (SE)	–5·4 (0·9)	–6·1 (0·9)	–7·3 (0·9)	–7·0 (0·9)	–6·1 (0·9)
p value *vs* placebo	..	0·56	0·13	0·19	0·56
PDSS score†	(n=117)	(n=118)	(n=118)	(n=115)	(n=112)
Least-squares mean change (SE)	1·0 (1·8)	2·9 (1·8)	5·2 (1·8)	5·5 (1·8)	2·9 (1·9)
p value *vs* placebo	..	0·45	0·09	0·07	0·45
PDQ-39 score‡					
Least-squares mean change (SE)	–2·6 (0·9)	–4·0 (0·9)	–4·1 (0·9)	–2·5 (0·9)	–2·8 (0·9)
p value *vs* placebo	..	0·28	0·24	0·90	0·90
NMSS score§					
Least-squares mean change (SE)	–5·7 (1·4)	–4·7 (1·5)	–5·6 (1·5)	–4·2 (1·5)	–2·0 (1·5)
p value *vs* placebo	..	0·63	0·98	0·45	0·06

NMSS=Non-motor Symptoms Scale. OR=odds ratio. PDQ-39=39-item Parkinson's Disease Questionnaire. PDSS=Parkinson's Disease Sleep Scale. UPDRS=Unified Parkinson's Disease Rating Scale. *Analysed in 114 patients in the placebo group, 111 in the entacapone group, 113 in the opicapone 5 mg group, 111 in the opicapone 25 mg group, and 109 in the opicapone 50 mg group. †Analysed in 117 patients in the placebo group, 118 in the entacapone group, 118 in the opicapone 5 mg group, 115 in the opicapone 25 mg group, and 112 in the opicapone 50 mg group. ‡Analysed in 120 patients in the placebo group, 117 in the entacapone group, 118 in the opicapone 5 mg group, 115 in the opicapone 25 mg group, and 113 in the opicapone 50 mg group. §Analysed in 118 patients in the placebo group, 116 in the entacapone group, 116 in the opicapone 5 mg group, 114 in the opicapone 25 mg group, and 112 in the opicapone 50 mg group.

Table 2: **Change from baseline to end of study treatment in secondary efficacy outcomes in the full analysis set**

The adjusted least-squares mean change from baseline in absolute time in the off state (primary endpoint) in the full analysis set was largest in the opicapone 50 mg group at –116·8 min (SE 14·0; 95% CI –144·2 to –89·4), compared with –96·3 min (13·4; –122·6 to –70·0) in the entacapone group, –91·3 min (13·5; –117·7 to –64·8) in the opicapone 5 mg group, –85·9 min (13·7; –112·8 to –59·1) in the opicapone 25 mg group, and –56·0 min (13·4; –82·3 to –29·7) in the placebo group (figure 2A). Similar results were noted in the per-protocol set (data not shown) and, since few data were missing (compliance with diary entries was 90–100% at all visits for all groups [data not shown]), results were similar in the mixed model for repeated measurements sensitivity analysis (appendix).

Only opicapone 50 mg was tested for non-inferiority of absolute time in the off state in the stepwise gate-keeping procedure, and was both superior to placebo (p=0·0015) and non-inferior to entacapone (p=0·0051; figure 2B and C). No significant differences were noted between placebo and opicapone 5 mg (p=0·056) or opicapone 25 mg (p=0·080; figure 2). Entacapone was superior to placebo (p=0·014; figure 2).

Table 2 summarises the results of the secondary outcomes. Compared with placebo, the proportion of patients with a reduction in time in the off state of at least 1 h was significantly higher in both the opicapone 25 mg (p=0·046) and 50 mg (p=0·001) groups, and the proportion of patients with an increase in time in the on state of at least 1 h was significantly higher in the opicapone 50 mg group (p=0·003; table 2). No significant differences were noted in off and on state rates for entacapone versus placebo (table 2).

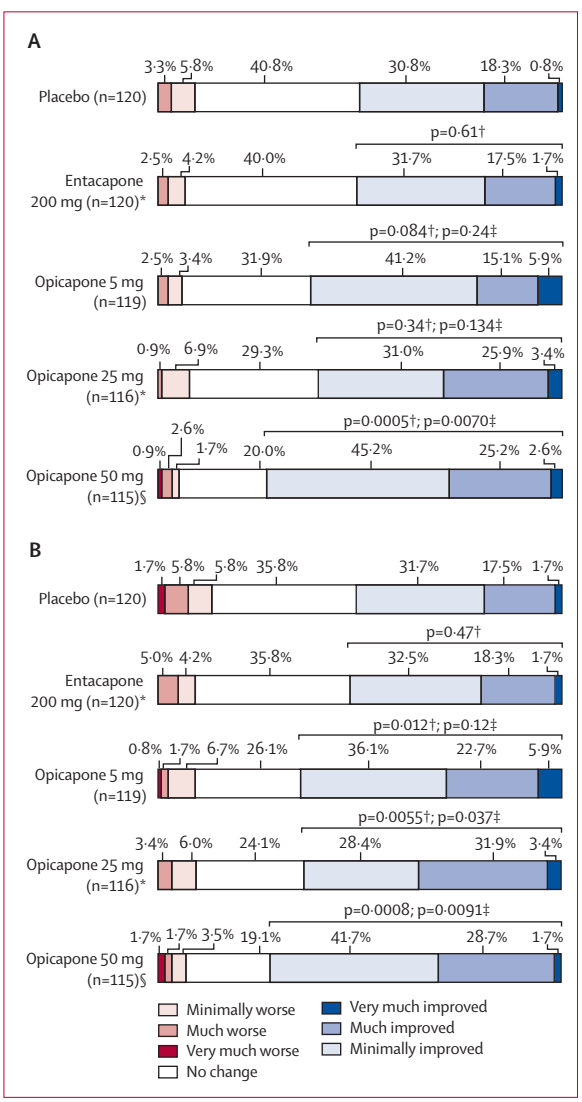

Figure 3: **Global assessment of change from baseline to end of study treatment**

(A) Clinician's Global Impression of Change and (B) Patient's Global Impression of Change in the full analysis set. p values are for the comparison between improved scores and worse scores only (excluding no change scores). *For three patients, data were missing or they were not assessed. †Versus placebo. ‡Versus entacapone. §For two patients, data were missing or they were not assessed.

Results from the other diary-reported secondary efficacy endpoints supported those of the primary analysis and confirmed that treatment with opicapone 50 mg resulted in significantly larger reductions in percentage of time in the off state (p=0·0007) and increases in absolute (p=0·0001) and percentage of time in the on state versus placebo (p=0·001; table 2). Similar results were reported for the percentage of time in the on state without troublesome dyskinesia (opicapone 50 mg *vs* placebo p=0·007; table 2). Only a small percentage of overall awake time took place in the on state with troublesome dyskinesia (≤3% at any visit [data not shown]; mean ≤2·5% for each group at baseline visit; table 1) and the changes compared with baseline were small (<1% in all groups), with no significant differences between treatment groups (table 2).

A higher proportion of opicapone-treated patients than those in the placebo group showed improvements from baseline (minimally, much, or very much) as assessed by CGI-C and PGI-C (figure 3); this difference was significant for all doses except for opicapone 5 mg (p=0·084), with differences in CGI-C scores ranging from 10% to 23% of patients. By contrast, no differences were noted for entacapone compared with placebo in either of these assessments. Additionally, a higher proportion of patients in the opicapone 50 mg group than in the entacapone group had improved on both the CGI-C (p=0·0070) and PGI-C (p=0·0091). Generally, all groups showed numerical improvements from baseline in UPDRS, PDSS, NMSS, and PDQ-39 scores, but the differences between active treatment and placebo groups were not significant (table 2).

The percentage of patients who discontinued because of treatment-emergent adverse events was low and similar across the treatment groups (table 3). The most common treatment-emergent adverse events leading to discontinuation were diarrhoea (two in the entacapone group and one in the placebo group), visual hallucinations (one in the opicapone 5 mg group, two in the opicapone 25 mg group, and two in the opicapone 50 mg group), and dyskinesia (two in the opicapone 5 mg group).

Dyskinesia was the most frequently reported treatment-emergent adverse events possibly related to the study drug, with the highest incidence in the opicapone groups; 47 (80%) of 59 treatment-emergent dyskinesias occurred in patients (in all groups) who were already experiencing dyskinesia at baseline. The incidence of serious treatment-emergent adverse events was low across all groups (all ≤7%; table 3) and 12 (35%) of 34 were judged to be unrelated to study drug. Two cases of increased liver enzymes were recorded as

	Placebo (n=121)	Entacapone 200 mg (n=122)	Opicapone		
			5 mg (n=122)	25 mg (n=119)	50 mg (n=115)
At least one treatment-emergent adverse event	60 (50%)	69 (57%)	63 (52%)	65 (55%)	62 (54%)
Treatment-emergent adverse events affecting ≥5% of patients in any group					
Dyskinesia	5 (4%)	10 (8%)	17 (14%)	9 (8%)	18 (16%)
Insomnia	1 (1%)	7 (6%)	2 (2%)	7 (6%)	7 (6%)
Constipation	3 (2%)	5 (4%)	4 (3%)	0	7 (6%)
Dizziness	1 (1%)	5 (4%)	2 (2%)	6 (5%)	3 (3%)
Hallucinations (any type)	2 (2%)	1 (1%)	2 (2%)	9 (8%)	5 (4%)
Nausea	2 (2%)	8 (7%)	2 (2%)	3 (3%)	3 (3%)
Back pain	6 (5%)	1 (1%)	4 (3%)	3 (3%)	0
Treatment-emergent adverse events leading to study drug discontinuation	8 (7%)	8 (7%)	7 (6%)	8 (7%)	5 (4%)
Serious treatment-emergent adverse events	6 (5%)	8 (7%)	4 (3%)	1 (1%)	4 (3%)
Number of serious treatment-emergent adverse events	11	14	4	1	4
Number of serious treatment-emergent adverse events possibly related to treatment	5	4	2	0	1
Dyskinesia	0	0	0	0	1
Syncope	0	1	0	0	0
Increased hepatic enzymes	1	0	1	0	0
Angina	0	1	0	0	0
Acute pulmonary heart disease	0	1	0	0	0
Pulmonary embolism	0	1	0	0	0
Visual impairment	1	0	0	0	0
Pancreatitis	1	0	0	0	0
Hepatitis	1	0	0	0	0
Basal cell carcinoma	0	0	1	0	0
Melanoma	1	0	0	0	0

Data are number of patients (%), unless otherwise specified.

Table 3: **Treatment-emergent adverse events reported in at least 5% of patients in any group in the safety set**

serious treatment-emergent adverse events: one in the placebo group and one in the opicapone 5 mg group (elevation of γ-glutamyl transferase >6·6×the upper limit of normal [ULN], aspartate aminotransferase >2·0×ULN, and alanine aminotransferase >1·6×ULN, with no hyperbilirubinaemia and no clinical symptoms). No deaths occurred during the study.

Changes in laboratory tests, vital signs, ECG parameters, or physical or neurological tests differed by less than 2% across visits for any treatment group (data not shown). We did not identify any increased suicidality in the opicapone or entacapone groups compared with placebo (data not shown). Treatment-emergent impulse control disorders (based on mMIDI scores) were reported in ten patients or fewer per group (nine in the opicapone 5 mg group, five in the opicapone 25 mg group, eight in the opicapone 50 mg group, ten in the entacapone 200 mg group, and five in the placebo group); the most commonly reported disorder in all groups was so-called buying disorder (four each in the placebo and opicapone 25 mg groups, nine in the entacapone group, seven in the opicapone 5 mg group, and eight in the opcapone 50 mg group).

Discussion

In this phase 3 study, the opicapone 50 mg group met the primary efficacy outcome of superiority compared with placebo and non-inferiority compared with entacapone in the change from baseline in absolute time in the off state. Of the three opicapone doses tested, the 50 mg dose had the most consistent effects versus placebo and entacapone.[14] Opicapone 50 mg resulted in a mean reduction in time in the off state of 60·8 min versus placebo and is, therefore, the only once-daily COMT inhibitor to provide a mean reduction in time in the off state that is clinically relevant.[29,30] The beneficial effects of opicapone 50 mg at reducing the time in the off state were accompanied by a corresponding increase in time in the on state without troublesome dyskinesia, whereas the duration of time in the on state with troublesome dyskinesia did not change. Global assessments using CGI-C and PGI-C also showed clinically significant improvements for opicapone 50 mg versus placebo and entacapone.

The study included an active control group of entacapone 200 mg with each levodopa dose, and the

confirmed superiority of entacapone versus placebo validates the findings of this trial.[31,32] For the entacapone group, the mean difference in time in the off state compared with placebo was in line with what has been reported (40·3 min in this study *vs* 41 min in previous reports[9]). Although not well studied in advanced-stage disease, placebo and so-called lessebo effects are strong in Parkinson's disease trials[33,34] and the placebo response was also high in this study. Indeed, all groups showed numerical improvements in UPDRS, PDSS, NMSS, and PDQ-39 scores, with no significant differences between active treatment and placebo. We did not expect large treatment differences versus placebo in UPDRS scores because we recruited patients who were best suited for symptomatic control with levodopa. Likewise, improvements in quality of life are notoriously hard to show in studies of advanced-stage disease,[35] when aspects such as cognitive status, depression, and other non-motor symptoms heavily affect patients' sense of wellbeing.[36] Nevertheless, responder rates (both time in off and on states) and the proportions of patients rated as improved by both investigators and patients themselves were significantly higher for the opicapone 50 mg dose than for placebo, which was not the case for entacapone.

Opicapone was safe and well tolerated and there was no apparent dose relation for most treatment-emergent adverse events. As might be expected, dyskinesia was generally more common with opicapone than entacapone, although the incidence of dyskinesia was similar for the opicapone 25 mg group and the entacapone group. This finding is in line with opicapone's more potent inhibition of COMT resulting in greater levodopa bioavailability. For reasons of data interpretation,[37] levodopa dose reductions were not permitted during the last 12 weeks of the study, but this would not be an issue in clinical practice. As noted earlier, most dyskinesias were deemed non-troublesome by the patients. The incidence of serious treatment-emergent adverse events with opicapone did not differ from that in the placebo or entacapone groups. There were no issues regarding liver safety events with opicapone.

In comparison with many previous studies of adjunct therapy in Parkinson's disease, this study has several important strengths: the proportion of patients remaining in the study and completing treatment was high and the study incorporated both a placebo group and entacapone, which is commonly used in the management of end-of-dose motor fluctuations, as an active comparator arm. Since opicapone is not excreted in the urine and as such does not produce urine discolouration, masking was carefully maintained by use of riboflavin to mimic the urinary discolouration caused by entacapone.

Limitations of the study include the exclusion of a broad population of patients. We excluded patients with severe or unpredictable off episodes and patients with severe dyskinesia because this study was explicitly designed to assess the effect of opicapone in patients with end-of-dose wearing off, which is characterised by predictability of off episodes. We report here the results of the short (14–15 weeks) double-blind phase of the study; results of the open-label extension study will be reported separately and will provide further detail on the long-term safety and efficacy of opicapone. We also used different study populations to test for superiority versus placebo (analysed in the full analysis set) and non-inferiority versus entacapone (analysed in the per-protocol set). In both cases, the most conservative statistical approach was chosen—the per-protocol method is generally preferred for tests of non-inferiority because of concerns that protocol violations can dilute the treatment effect (in either group).[25] Thus, results suggest that opicapone 50 mg is non-inferior to entacapone, with a greater magnitude of effect for opicapone.

Opicapone once daily could enable a simplified drug regimen that allows the physician to individually tailor the existing levodopa daily regimen by potentially decreasing the total daily levodopa dose, increasing the dosing interval, and ultimately reducing the number of intakes, thereby maximising its benefit. When combined with the favourable safety and tolerability profile, these characteristics suggest an overall positive risk-to-benefit ratio for the use of opicapone in patients with Parkinson's disease with end-of-dose motor fluctuations.

Contributors

All authors participated in the design of the study. J-FR and PS-d-S participated in study implementation and data analysis. All authors were involved in data interpretation and together discussed the initial ideas presented in the introduction and discussion of this Article. JJF wrote the first draft of the manuscript; AL, WP, and OR made substantial contributions to the revision of the manuscript, and J-FR and PS-d-S provided critical review. All authors approved the final submitted manuscript.

Declaration of interests

JJF has held consultancy functions with GlaxoSmithKline, Novartis, Teva, Lundbeck, Solvay, Abbott, BIAL, Merck-Serono, Merz, Ipsen, and Biogen; has received lecture fees from Biogen and BIAL; has received grants from GlaxoSmithKline, Grünenthal, MSD, Allergan, Novartis, Fundação MSD (Portugal), and Teva; and has been employed by Centro Hospitalar Lisboa Norte, Faculdade de Medicina de Lisboa. AL is funded by the Reta Lila Weston Institute of Neurological Studies, University College London, Institute of Neurology, and reports consultancies for Britannia Pharmaceuticals and BIAL Portela; grants or research support, or both, from the PSP Association, Weston Trust, and the Reta Lila Howard Foundation; and honoraria from Britannia, UCB, Roche, Novartis, Boehringer Ingelheim, Lundbeck, GE Healthcare, Teva, GlaxoSmithKline, Ipsen, Allergan, Orion, BIAL, AbbVie Lucid, and Nordicinfu Care. WP reports receiving consulting fees from AbbVie, Allergan, AstraZeneca, BIA, Boehringer Ingelheim, Boston Scientific, GlaxoSmithKline, Ipsen, Lundbeck, Medtronic, MSD, Merck-Serono, Merz Pharmaceuticals, Novartis, Orion Pharma, Teva, UCB, and Zambon. OR reports receiving consulting fees from AbbVie, BIAL, Britannia, Lundbeck, Merck, Mundipharma, Sanofi, Servier, Teva, UCB, XénoPort, and Zambon; and grant support from Agence Nationale de la Recherche, Boehringer Ingelheim, CHU de Toulouse, French Parkinson, GlaxoSmithKline, INSERM-DHOS, the Michael J Fox Foundation, Programme Hospitalier de Recherche Clinique, Recherche Clinique Translationnelle, UCB, Teva, and Lundbeck. J-FR and PS-d-S are employed by BIAL.

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