Parkinsonism and Related Disorders 60 (2019) 51–56

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

# Naftazone in advanced Parkinson's disease: An acute L-DOPA challenge randomized controlled trial

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ARTICLE INFO

*Keywords:*
Parkinson's disease
Naftazone
Levodopa-induced dyskinesia
Clinical trial

ABSTRACT

*Introduction:* There is an unmet need to better control motor complications in Parkinson's disease (PD). Naftazone, which exhibits glutamate release inhibition properties, has shown antiparkinsonian and anti-dyskinetic activity in preclinical models of PD and in a clinical proof of concept study.

*Methods:* We conducted a double-blind randomized placebo-controlled cross-over trial in PD patients with motor fluctuations and dyskinesia testing naftazone 160 mg/day versus placebo for 14 days. The two co-primary endpoints were the area under curve (AUC) of motor (MDS-UPDRS part III) and dyskinesia (AIMS) scores during an acute levodopa challenge performed at the end of each period. Secondary endpoints were UDysRS and axial symptoms scores during the challenge; AIMS, UDysRS, and time spent with or without dyskinesia the day before the challenge. The primary analysis was performed in the per protocol population.

*Results:* Sixteen patients were included in the analysis. There was no difference between naftazone and placebo for the AUC of MDS-UPDRS III (−89, 95%CI[-1071; 893], p = 0.85), and AIMS (70, 95%CI[-192; 332], p = 0.57). At the end of treatment periods, AIMS score tended to be lower with naftazone than placebo (4.4 ± 3.4 versus 6.7 ± 4.4, p = 0.07), but UDysRS scores and other secondary outcomes were not different. Naftazone was safe and well tolerated.

*Conclusions:* This study did not confirm previous results on the efficacy of naftazone on dyskinesia nor motor fluctuations highlighting the problem of translating results obtained in preclinical models into clinical trials. Further investigation of naftazone may be conducted in PD with longer treatment duration.

## 1. Introduction

Levodopa remains the most effective drug for treating Parkinson's disease (PD), but most patients develop motor fluctuations and dyskinesia which impair their activities of daily living and quality of life [1]. Motor fluctuations are not fully controlled by the adjunction of other

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https://doi.org/10.1016/j.parkreldis.2018.10.005
Received 11 July 2018; Received in revised form 27 September 2018; Accepted 1 October 2018

antiparkinsonian medications in a number of patients, while amantadine, the only approved antidyskinetic drug [2], has a moderate tolerability profile. This leads to the use of second-line device-based approaches, including functional neurosurgery or pump-aided continuous infusion of dopaminergic drugs which are incompletely efficacious, invasive, expensive and indicated for a limited number of patients. There is thus an unmet need to better control motor fluctuations and dyskinesia in PD.

Naftazone (1-2-naphtoquinone-2-semicarbazone) is a molecule registered and marketed for more than 20 years in European countries and South Korea as a 30-mg daily oral treatment for varicose veins and venous insufficiency for its vasoprotectant action [3]. Naftazone exhibits glutamate release inhibition properties [4], which explain its antiparkinsonian and antidyskinetic activity in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned macaque model when associated with an optimal dose of levodopa [5]. In a pilot, randomized, double-blind, placebo-controlled, multiple-cross-over n-of-1 designed trial performed in 7 PD patients with motor complications [6], naftazone has shown potential benefit on motor scores and the duration of "ON-time" without troublesome dyskinesia.

The present study was thus aimed at assessing the efficacy of naftazone on motor symptoms of PD and levodopa-induced dyskinesia during an acute levodopa challenge test in PD patients suffering from levodopa-induced motor complications.

## 2. Methods

### 2.1. Trial design

This was a double-blind, randomized, placebo-controlled, cross-over, multicenter study in patients with advanced PD and levodopa-induced dyskinesia. The study was conducted with the support of the French NS-Park/FCRIN network for clinical research in PD (http://www.parkinson.network/fr). The primary objective was to assess the efficacy of naftazone in combination with levodopa during an acute challenge on (a) motor symptoms of PD, and (b) on levodopa-induced dyskinesia. Secondary objectives were to assess efficacy of naftazone as add-on therapy during 2 weeks on motor and non-motor symptoms, motor fluctuations, time spent with or without dyskinesia, and pharmacokinetic parameters of naftazone in relationship with motor state and dyskinesia during the levodopa challenges.

The two co-primary endpoints were the area under curve (AUC) from baseline (t0) to the end of the levodopa challenge of the change (t) in (a) the Movement Disorders Society - Unified PD Rating Scale (MDS-UPDRS) part III, and (b) the Abnormal Involuntary Movement Scale (AIMS) scores. Secondary endpoints during the levodopa challenges were the change of Unified Dyskinesia Rating Scale (UDysRS) part III + IV scores between baseline and 90min post levodopa, evolution of axial symptoms measured on the MDS-UPDRS part III (sum of items 3.9 "arising from a chair", 3.10 "gait", 3.11 "freezing of gait", 3.12 "postural stability", 3.13 "posture"), and ON-time without dyskinesia. Other secondary endpoints were the total ON-time, ON-time without troublesome dyskinesia, "good" ON time (ON-time without dyskinesia + ON-time with non-troublesome dyskinesia), percentage of "good" ON/total ON-time, UDysRS and AIMS scores the day before the challenge test, and safety parameters. Plasma concentrations of levodopa and naftazone were also planned as secondary endpoints.

### 2.2. Participants

Inclusion criteria were male or female patients with PD according to the UK PD Society Brain Bank Clinical Diagnosis criteria [7], aged 40 to 75, Hoehn and Yahr stage between 2 and 4 in OFF state, experiencing motor fluctuations and dyskinesia with at least 2 h of OFF state per day, > 25% of time spent with dyskinesia. Patients had to be under optimal and stable doses/regimens of antiparkinsonian medications for at least one month prior to randomization and intended to remain constant throughout the course of the study. Other inclusion/exclusion criteria are detailed in the Supplementary methods.

### 2.3. Conduct of the study

Patients were recruited from February 2016 to July 2017 at five centers of the NS-Park/F-CRIN network. The visits schedule is presented as supplementary material (Supplementary Fig. S1). After a screening period of 2 weeks, patients were randomized into two cross-over periods of 14 days with naftazone or placebo, separated by a washout period of 1–2 weeks. Three levodopa challenge tests were performed during a 2 days hospitalization: one at screening (V1) with the usual morning levodopa equivalent dose (LED) [8], and one at the end of each treatment period (V3 and V4) with levodopa plus naftazone or placebo (supplementary methods). At each visit, patient assessments included the MDS-UPDRS [9], the AIMS [10], the UDysRS [11], the day before and during the challenge tests. Patients completed the Hauser home diary [12,13] every 30 min for 3 consecutive days before baseline, and before each end of treatment period. Pharmacokinetics of both levodopa and naftazone were performed during the challenge tests (Supplementary methods).

### 2.4. Treatment

Patients were randomized to receive either naftazone then placebo or placebo then naftazone for 14 days, 1 capsule 4 times a day, and 1 capsule on the morning during the levodopa challenge, separated by a washout period of 1–2 weeks (Supplementary methods).

### 2.5. Statistical analysis

Sample size was calculated on the assumption of a 30% increase of the AUC in MDS-UPDRS III scores during the naftazone challenge test versus placebo, and a correlation between periods of 0.6. Thirty patients were needed with a two-sided type-1 error rate of 0.05, a power of 0.9, and a missing data rate of 5%. For this pilot study, the primary analysis was planned to be performed on the per protocol (PP) population. The co-primary criteria were also analyzed in the intent to treat (ITT) population (Supplementary methods).

The comparison of the $AUC_{0\text{-}t}$ between the treatment groups was assessed using a linear mixed model with sequence, period and treatment as fixed effects and patient within sequence as random effect [14]. Statistical tests were two-sided and were carried out at the 5% level of significance. For secondary endpoints, the comparison between the treatment groups was assessed using the same linear model. Considering the small sample size, trends in the direction of improvement reaching a 10% level was also considered as preliminary evidence of efficacy.

Pharmacokinetic parameters were calculated for naftazone and levodopa by standard non-compartmental methods for patients with sufficient plasma concentration data (Supplementary methods).

### 2.6. Study sponsoring

The study was sponsored by Clevexel Pharma. Study protocol was reviewed and approved by an ethics committee and the Competent Authorities (CT-CVXL-0107-01, EudraCT Number 2015-004103-23); all participants gave written informed consent. The steering committee (J.C.C., O.R., J.P.A, F.D., W.G.M.) had full access to the data, was responsible for interpretation of the results, and the redaction of the manuscript.

**Table 1**
Patient characteristics.

| | Placebo/naftazone (n = 8) | Naftazone/placebo (n = 8) | Overall (n = 16) |
|---|---|---|---|
| Age, years | 62.5 ± 9.3 | 62.0 ± 7.6 | 62.3 ± 8.2 |
| Male, n (%) | 7 (87.5) | 5 (62.5) | 12 (75.0) |
| PD duration, years | 9.60 ± 2.63 | 11.81 ± 6.88 | 10.71 ± 5.16 |
| MMSE | 28.9 ± 2.0 | 29.1 ± 1.5 | 29.0 ± 1.7 |
| Hoehn and Yahr stage | 1.9 ± 0.4 | 2.4 ± 0.5 | 2.1 ± 0.5 |
| Hauser diary | | | |
| OFF time, h | 4.6 ± 3.0 | 5.1 ± 2.0 | 4.8 ± 2.4 |
| ON time without dyskinesia, h | 5.6 ± 4.2 | 4.5 ± 2.6 | 5.0 ± 3.4 |
| ON time with non-troublesome dyskinesia, h | 4.4 ± 2.6 | 3.1 ± 1.4 | 3.7 ± 2.1 |
| ON time with troublesome dyskinesia, h | 1.7 ± 3.0 | 3.4 ± 4.2 | 2.6 ± 3.6 |
| Levodopa daily dose, mg/day | 831.9 ± 356.9 | 646.9 ± 268.1 | 739.4 ± 319.5 |
| Dopamine agonist daily dose, LEDD, mg/day | 281.6 ± 251.4 | 313.8 ± 94.7 | 297.7 ± 184.3 |
| Total LEDD, mg/day | 1113.5 ± 503.1 | 960.6 ± 304.7 | 1037.1 ± 409.5 |

Values are means ± SD. MMSE, Mini Mental State Examination; LEDD, levodopa equivalent daily dose. Hauser diary: values are mean times (hours) ± SD during the 3 consecutive days before randomization.

## 3. Results

### 3.1. Patient characteristics

A total of 21 patients were screened. Three patients were screen failures: one of them had elevated CPK levels; another one had abnormal ECG at screening; and the third patient had no dyskinesia during the challenge test at screening. The 18 remaining patients were randomized in two groups of 9 patients with reverse treatment sequences. All patients were treated with levodopa, 16/18 (89%) with dopamine agonists, 3 with COMT inhibitor (entacapone), and 9 with monoamine oxidase inhibitors. All 18 patients completed the study, and were included in the ITT analysis. Two patients were excluded from the PP population (one patient in each treatment sequence group) because they presented a major protocol deviation during the study: one patient was not in OFF state at t0 during the challenge tests; the other patient had taken only 40 capsules out of 56 (71% of compliance) at the end of the naftazone period. The PP population was thus composed of 16 patients, 8 patients in each treatment sequence group (Supplementary Fig. S2). Baseline characteristics were similar between sequence period allocation groups (Table 1).

### 3.2. Efficacy outcomes during the challenge tests

The scores of the MDS-UPDRS III and the AIMS scale over time during the challenge tests are presented in Fig. 1. All patients improved their motor status after levodopa with a relatively small inter-subject variability, with a peak of motor response and dyskinesia around 90 min post-levodopa dosing. Baseline scores (t0) of MDS-UPDRS III and AIMS were not different under naftazone and placebo. No sequence effect or period effect was detected, i.e. there was no carry-over concern in this cross-over trial. The analysis in the PP population (Table 1) showed no significant difference between naftazone and placebo for the two co-primary outcomes, $AUC_{0\text{-}t}$ of the MDS-UPDRS III score (−89, 95%CI[-1071; 893], p = 0.85), and the AIMS score (70, 95%CI[-192; 332], p = 0.57). The analysis in the ITT population showed similar results (data not shown). Secondary outcomes (UDysRS score at 90min, and axial subscore of the MDS-UPDRS III at t0) were not significantly different between groups (Table 2). UDysRS results showed a treatment effect in favor to placebo 180 min post-levodopa dosing (9.3 ± 6.9 versus 11.3 ± 7.1, p = 0.009).

### 3.3. Other secondary outcomes

Other secondary outcomes were assessed at the end of each period, the day before each challenge test during the inpatient hospitalization. AIMS score tended to be lower after 14 days of naftazone than after 14 days of placebo (4.4 ± 3.4 versus 6.7 ± 4.4, p = 0.07). However, results on patient diary and UDysRS did not reveal any significant treatment effect between groups (Table 3). A post-hoc analysis performed on the axial subscore of the MDS-UPDRS III assessed in the same conditions also tended to be lower after 14 days of naftazone than after placebo (2.6 ± 3.5 versus 3.3 ± 3.7, p = 0.08). MDS-UPDRS I score remained stable after 14 days of naftazone and was slightly improved under placebo.

### 3.4. Levodopa and naftazone plasma concentrations

Pharmacokinetic parameters are presented in Supplementary Table 1 and Fig. 1. During the challenge test with naftazone, naftazone pharmacokinetic profiles were heterogeneous between patients with a high inter-variability observed for $C_{max}$ and $AUC_{0\text{-}last}$ (coefficient of variation (%CV) ranging from 96% to 115%). Because the sampling time-points were defined to follow the pharmacokinetic of levodopa and not that of naftazone, the apparent half-life of naftazone could not be estimated. The observed median $t_{max}$ was 1.7 h post naftazone dose (i.e. 2 h post levodopa dose), i.e. later than the both observed levodopa Tmax and the peak dose dyskinesia (90 min). By contrast, under co-administration with placebo or naftazone, levodopa plasma concentrations reached a peak at a similar median $t_{max}$ of 20 min, then declined with a similar mean terminal half-life of nearly 70 min with a low inter-individual variability (%CV 17.0–19.2). $C_{max}$/dose and $AUC_{0\text{-}last}$/dose of levodopa were marginally higher (16% and 18% respectively) in presence of naftazone when compared to the placebo co-administration (ratio naftazone/placebo, 1.163, 95%CI[0.981; 1.379] for $C_{max}$/dose, 1.175, 95%CI[1.031; 1.340] for $AUC_{0\text{-}last}$/dose).

### 3.5. Safety and tolerability outcomes

Three adverse events (vomiting, and two vasovagal episodes) were observed in 2 patients before randomization, due to a too high dose of levodopa used during the first challenge test. The dose for these two patients was then lowered during the next two challenge tests. Study drugs were generally well tolerated. There were no serious adverse events during the study and no study withdrawal due to adverse events. There were 35 treatment emergent adverse events observed in 11 patients (61%) of the safety population (n = 18, Supplementary Table 2). Fourteen adverse events had a possible or probable relationship to treatment; 5 started during the placebo period and 9 during the naftazone period; they were somnolence, PD worsening, abdominal pain upper, dyspepsia, dyskinesia during the placebo period, and gastrointestinal disorder, nausea (x2), dizziness, orthostatic hypotension, fall, balance disorder, muscle spasms, and cognitive disorder during the naftazone period.

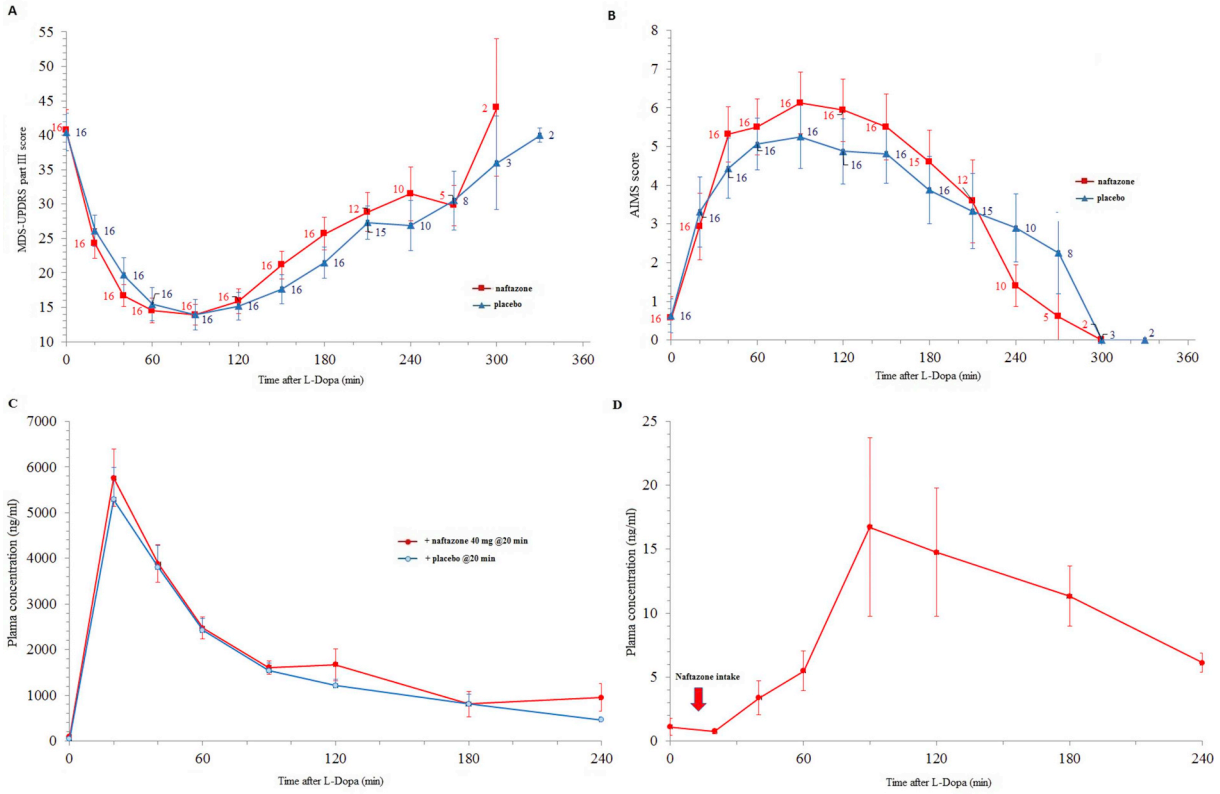


**Fig. 1.** Values are quoted as the mean of individual scores ± SEM and have not been adjusted for the levodopa dose. n are reported as labels on graphs A and B. A: Time-course of motor score (MDS-UPDRS part III) in treatment population. B: Time-course of dyskinesia score (7 first items of AIMS) in treatment population. C: Time-course of levodopa plasma level in PK population/levodopa (n = 15, 1 patient with missing values). C: Time-course of naftazone plasma level in PK population/naftazone (n = 14, 2 patients with missing values).

**Table 2**
Efficacy outcomes during the challenge tests.

| | Placebo N = 16 | Naftazone N = 16 | p-value |
|---|---|---|---|
| Co-primary outcomes | | | |
| $AUC_{0\text{-}t}$ of MDS-UPDRS Part III | 5102 ± 1984 | 5013 ± 1746 | 0.85 |
| $AUC_{0\text{-}t}$ of AIMS | 997 ± 637 | 1067 ± 542 | 0.57 |
| Secondary outcome | | | |
| UDysRS at 90 min | 13.6 ± 5.8 | 14.0 ± 5.6 | 0.53 |
| Axial subscore of MDS-UPDRS Part III at t0 | 5.8 ± 3.7 | 5.6 ± 3.4 | 0.65 |

Outcomes results are given as means ± SD.

## 4. Discussion

Our results did not show significant evidence of clinical efficacy of naftazone compared to placebo on motor symptoms or dyskinesia, as assessed during an acute challenge of levodopa. It should be considered that such negative results might represent "false negatives" caused by methodological biases. We used a cross-over design with acute levodopa challenges at the end of each treatment period because this strategy has been previously successful for detecting efficacy of drugs either prolonging the response to levodopa, like entacapone [15], or improving dyskinesia, like amantadine [16], both effects being expected for naftazone. We did not use intravenous levodopa infusions for practical and regulatory issues, and this might have induced greater variability due to levodopa absorption, leading to greater variance in pharmacokinetic and pharmacodynamics responses, thus reducing the power and sensitivity of the trial [17]. However, to limit inter- and intra-individual variability and to optimize individual dose of levodopa, we performed an oral levodopa challenge prior to the two cross-over periods. Levodopa was administered in fasting conditions, using a dispersible formulation, rapidly followed by a light breakfast to facilitate gastric emptying and absorption. We used a supra-optimal dose of levodopa (50 mg supplement over the morning dose) to maximize the chance to observe peak-dose dyskinesia. As a result, all patients experienced "ON" condition after each of the two challenges, with peak-dose dyskinesia around 90 min post-dose as expected, and with relatively limited variability of levodopa plasma concentrations. Consequently, despite a lower number of patients than targeted according to our initial hypotheses, the study turned-out to be sufficiently powered to detect an effect of 33% of naftazone on the AUC of MDS-UPDRS part III. This suggests that using such a cross-over design, 20 patients provide a sufficient power to detect a potentially clinically significant effect.

If study under-power is unlikely to explain our negative findings, other potential explanations could be related to dosing, timing and/or pharmacokinetic issues. The schedule of administration of levodopa and naftazone was designed to standardize as much as possible the response to levodopa between the 2 treatment periods. Naftazone/placebo was administered 20 min *after* levodopa and previous pharmacokinetic data (median Tmax of about 1 h) suggested a maximum exposure to naftazone at the time of the peak-dose effect of levodopa on motor symptoms and dyskinesia. However, it turned-out that the Tmax of naftazone occurred later than anticipated, with a median delayed Tmax of 2.1 h, consequently after the maximal effect of levodopa (90 min) and maybe too late to observe potential interactions. Another possibility might be that the tested dose of levodopa or naftazone was inappropriate. We added 50 mg to the usual morning dose of equivalent levodopa to maximize the chance to induce peak dose dyskinesia in patients, but this supra-optimal dose may have masked a potential

**Table 3**
Other secondary outcomes measured at the end of each treatment period.

| | Placebo N = 16 | | | Naftazone N = 16 | | | p-value |
|---|---|---|---|---|---|---|---|
| AIMS | 6.7 ± 4.4 | | | 4.4 ± 3.4 | | | 0.07 |
| UDysRS Part III + IV | 12.0 ± 5.9 | | | 10.8 ± 7.0 | | | – |
| MDS-UPDRS | | | | | | | |
| Part I | 10.1 ± 4.3 | | | 11.8 ± 3.8 | | | 0.04 |
| Part II | 14.6 ± 5.0 | | | 15.4 ± 5.2 | | | 0.47 |
| Part IV | 10.0 ± 2.6 | | | 10.6 ± 2.7 | | | 0.27 |
| Diaries | Baseline | End of period | Change | Baseline | End of period | Change | |
| OFF time | 5.0 ± 2.6 | 4.8 ± 1.7 | −0.2 ± 2.4 | 4.8 ± 1.7 | 5.5 ± 2.9 | 0.7 ± 2.4 | – |
| ON without dyskinesia | 5.7 ± 3.4 | 6.1 ± 3.3 | 0.4 ± 1.5 | 5.6 ± 3.0 | 5.4 ± 3.1 | −0.1 ± 2.7 | 0.26 |
| ON with non-troublesome dyskinesia | 3.4 ± 2.2 | 3.3 ± 2.3 | −0.2 ± 2.5 | 3.3 ± 1.7 | 2.9 ± 1.9 | −0.4 ± 1.9 | – |
| ON with troublesome dyskinesia | 2.0 ± 2.7 | 1.8 ± 2.3 | −0.2 ± 2.6 | 2.5 ± 3.5 | 2.3 ± 2.9 | −0.3 ± 2.9 | 0.76 |
| ON time | 11.2 ± 2.5 | 11.2 ± 2.0 | 0.04 ± 2.7 | 11.4 ± 2.3 | 10.6 ± 3.3 | −0.8 ± 2.3 | 0.54 |
| “Good” ON time | 9.2 ± 3.3 | 9.4 ± 2.6 | 0.2 ± 2.8 | 8.9 ± 3.7 | 8.3 ± 3.8 | −0.6 ± 2.9 | 0.32 |
| Ratio Good/total | 0.8 ± 0.2 | 0.9 ± 0.2 | 0.02 ± 0.2 | 0.8 ± 0.29 | 0.8 ± 0.3 | 0.01 ± 0.2 | 0.46 |

Outcomes results are given as means ± SD. AIMS, UDysRS, and MDS-UPDRS scores are at the end of each periods. For diaries, values (hours) are given at baseline, end of period, and change. p-values are naftazone versus placebo for values at the end of each period for pre-specified secondary endpoints.

effect of naftazone in enhancing levodopa efficacy or reducing milder dyskinesia. Pharmacokinetic relationships analyses suggested that naftazone marginally increased levodopa AUC and $C_{max}$ which may explain the increase of the UDysRS score observed at 180min under naftazone. The AIMS scale used in our trial to assess dyskinesia may be less sensitive than the UDysRS scale [18], but it was easier to perform in the context of an acute challenge with repeated measures. Finally, we cannot exclude that the dose of naftazone by itself was not appropriate to demonstrate efficacy even though we used a higher dose (160 mg/day) than reported in a previously published n-of-one trial (120 mg/day) [6]. Longer naftazone exposure may also be necessary to detect an effect on motor complications in PD.

The present results are in contrast with the positive effects found in a primate model of LID [5] and with prior pilot clinical results from a n-of-one clinical trial [6]. In the model of MPTP-lesioned non-human primates, naftazone prolonged the effect of levodopa on motor symptoms and decreased dyskinesia during an acute challenge as compared to placebo This effect could be linked to the anti-glutamatergic properties of naftazone [4], as overactive glutamatergic transmission in the striatum has been found to be associated with levodopa-induced dyskinesias [19]. Such a design is rather comparable to that of the cross-over acute levodopa challenge we used in the present study. However, cross-over designs may not be adequate because improvement of dyskinesia may be sustained for a long-period of time, and the rate of disappearance of dyskinesia may not be similar to the re-emergence of motor fluctuations following withdrawal of the drug [20,21]. The reliability of animal models' acute levodopa challenge test to predict clinical responses in PD patients is thus a challenging issue. In some instances, animal and clinical findings have been consistent [16,22,23]. However, in many cases, clinical findings failed to confirm positive animal experiments [24–27]. Reasons for these discrepancies remain poorly understood and quite controversial. In the previous n-of-one clinical trial comparing naftazone with placebo, patients were treated for longer periods (four consecutive 28-days cross-over periods instead of 14 days), and with a lower dose (120 rather than 160 mg/day). It is possible that naftazone requires more than a 2-weeks exposure to develop its full effects in humans, and/or that some “inverted U-shape” dose-response relationship exists. Such hypotheses should be considered if further studies are planned to assess the antiparkinsonian effects of the drug in PD patients. In the present study, AIMS and UDysRS scores assessed the day before levodopa challenges tended to be lower under naftazone than placebo. Such a trend must be interpreted cautiously as the study was not powered to detect such effects. On the other hand, they are consistent with results in the previous n-of-one trial in which 5/7 patients “responded” positively to naftazone regarding “ON-time with troublesome dyskinesia”, and 6/7 regarding “ON-time without troublesome dyskinesia” [6]. Similarly, some improvement was reported in the same trial regarding levodopa non-responsive UPDRS items with 7/7 patients “responding” to naftazone for falling, freezing when walking, posture, gait, postural stability. Interestingly, a post-hoc analysis of the present data found a trend in favor of naftazone over placebo for “axial” motor functions (MDS UPDRS items 3.9 to 3.13) the day before the levodopa challenge. Such exploratory findings would need to be confirmed in specific clinical trials specifically designed to assess axial motor functions.

Overall, naftazone, at 160 mg/day for 2 weeks proved to be safe and well tolerated. Although the levodopa challenge test was well designed and permitted a low variability in motor symptom and dyskinesia ratings, it did not confirm previous results on the efficacy of naftazone on dyskinesia nor motor fluctuations. Further investigation of pharmaco-clinical dose-response of naftazone may be conducted in PD, with a special emphasis on postural/gait disturbances and possibly with longer treatment duration.

## Declaration of interest

J.C.C. has served in scientific advisory board for Clevexel, Biogen, Air Liquide, BrainEver, Theranexus, BMS, Zambon, Pfizer, Ipsen, Abbvie, Amarantus; received research grant from Actelion, Michael J Fox Foundation; received travel grant from Novartis, Clevexel.

F.D. declares no conflict of interest.

W.G.M. has received fees for editorial activities with Nature Springer, for serving as advisory board member for Astra Zeneca, for consultancy activities from Sanofi, teaching honoraria from UCB, Aguettant and MDS, as well as research support from the Michael J Fox Foundation, the University Hospital Bordeaux, the French Health Ministry, the European Community, ANR, MSA Coalition, LABEX Excellence Initiative.

J.P.A. has served in advisory board for clevexel, tharanexus, Zambon, BMS, Abbvie, Orkyn, Allergan, and received travel grant from Abbvie.

R.H. is an employee of Clevexel Pharma.

R.G.C declares no conflict of interest.

L.L.M. has received research support grants from INSERM, JNLF, The L'Oreal Foundation; speech honoraria from CSL, Sanofi-Genzyme, Lundbeck, Teva; and received travel funding from the Movement

Disorders Society, ANAINF, Merz, Medtronic, Teva and AbbVie, outside the submitted work.

F.C.D. declares no conflict of interest.

C.T. declares no conflict of interest.

M.G. declares no conflict of interest.

T.B. declares no conflict of interest.

B.D. declares no conflict of interest.

A.E. has served in scientific advisory board for Air Liquide, Aguettant, received honoraria form Teva and received travel grants from Aguettant, Everpharma.

M.H. declares no conflict of interest.

E.D. declares no conflict of interest.

V.C. declares no conflict of interest.

A.S. declares no conflict of interest.

L.L. declares no conflict of interest.

L.B. is a co-founder, shareholder and employee of Clevexel Pharma.

O.R. reports fees for scientific advising from AbbVie, Adamas, Acorda, Addex, Apopharma, Bial, Biogen, Britannia, Clevexel, Cynapsus, INC Reasearch, Lundbeck, Merck, MundiPharma, Neuroderm, Novartis, Oxford Biomedica, Parexel, Pfizer, Prexton.

## Acknowledgements

Funding agencies: This study was supported by Clevexel Pharma SA. We thank Antoine Faurie Grepon (clinical research assistant, Toulouse), Valérie Vaquié (research nurse, Toulouse), Nathalie Jarry (research nurse, Paris) for their involvement in this study. We thank the patients for participating to this study.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2018.10.005.

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