BRIEF REPORT

THN 102 for Excessive Daytime Sleepiness Associated with Parkinson's Disease: A Phase 2a Trial

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Members of the THN102-202 Study Investigators are listed in the Appendix.

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ABSTRACT: **Background:** Excessive daytime sleepiness (EDS) is a frequent and disabling symptom of Parkinson's disease (PD) without approved treatment. THN102 is a novel combination drug of modafinil and low-dose flecainide.

Objective: The aim of this study is to evaluate the safety and efficacy of THN102 in PD patients with EDS.

Methods: The method involved a randomized, double-blind, placebo-controlled, crossover trial testing two doses of THN102 (200 mg/d modafinil with 2 mg/d [200/2] or 18 mg/d flecainide [200/18]) versus placebo; 75 patients were exposed to treatment. The primary endpoint was safety. The primary efficacy outcome was the change in Epworth Sleepiness Scale (ESS) score.

Results: Both doses of THN102 were well tolerated. ESS significantly improved with THN102 200/2 (least square means vs. placebo [95% confidence interval, CI]: −1.4 [−2.49; −0.31], $P = 0.012$) but did not change significantly with the 200/18 dosage.

Conclusions: THN102 was well tolerated and showed a signal of efficacy at the 200/2 dose, supporting further development for the treatment of EDS in PD.

Key Words: Parkinson's disease; sleepiness; clinical trial; modafinil; flecainide

Excessive daytime sleepiness (EDS) is a nonmotor symptom present in 20%–60% of patients with Parkinson's disease (PD).[1] It is underreported, significantly impacts quality of life,[2,3] and contributes to serious complications.[4,5] The risk factors of EDS include advanced age, duration of PD, and dopaminergic medication.[6] There is currently no approved treatment for EDS in PD.

Modafinil has shown inconsistent results as a treatment for EDS associated with PD.[7-9] Besides its monoaminergic mechanisms of action, modafinil modulates astrocyte networks by enhancing connexin Cx30 expression and gap junction function.[10] Flecainide, an anti-arrhythmic drug, has been identified as a Cx30 inhibitor.[11,12] THN102 is a combination of modafinil and low-dose flecainide. The mechanism of action of this combination has been related to modulation of astrocyte networks via connexins, which can modulate neuronal activity.[13] In orexin-knockout mice the combination of modafinil and flecainide increased wake periods and working memory when compared to modafinil alone.[11] Similarly, a positron emission tomography study demonstrated a greater increase in regional brain glucose metabolism in the cortex, striatum, and amygdala of rats treated with THN102 as compared to modafinil alone.[14] This enhanced response may be related to the inhibition of the modafinil-induced Cx30 upregulation by flecainide, assuming that the upregulation of Cx30 by modafinil limits its activity on wakefulness. The effect of THN102 (modafinil 300 mg with flecainide 3, 9, and 27 mg/24 hours) on wakefulness and cognitive function was tested in healthy male volunteers versus modafinil alone and placebo in a phase I sleep deprivation study.[15] THN102 at the lowest dose induced significantly higher psychomotor vigilance speed over modafinil and placebo, whereas most doses significantly improved cognitive performance versus modafinil.

The aim of this pilot study was to compare for the first time the safety and efficacy of THN102 versus placebo in EDS associated with PD.

Patients and Methods

Study Design

This was a double-blind, placebo-controlled, complete three-way crossover, phase 2 study performed in 30 sites in 5 countries (ClinicalTrials.gov NCT03624920). The design was chosen to obtain informative results with a relatively small sample size. The washout of at least 1 week was appropriate given the relatively short elimination half-lives of both drugs (modafinil: 15 hours and flecainide 13 hours). The protocol was approved by an institutional review board at each study site and was conducted according to Good Clinical Practice (E6).

Participants

Participants had a diagnosis of PD according to MDS criteria[16]; complained of daytime sleepiness affecting their quality of life and/or daytime functioning; and had Epworth Sleepiness Scale (ESS) score of ≥14,[17] Hoehn and Yahr score of ≤4,[18] and stable PD medications for at least 4 weeks before screening. The main exclusion criteria were known or suspected sleep apnea, other neurological and psychiatric disorders, use of stimulants, severe cardiovascular disorders, current impulse control disorder, suicidality, dementia, or MoCA (Montreal Cognitive Assessment)[19] score <23. Written informed consent was obtained from all participants before study initiation.

Randomization and Masking

The treatment conditions were THN102 200 mg/d modafinil + 2 mg/d flecainide (THN102 200/2), THN102 200 mg/d modafinil + 18 mg/d flecainide (THN102 200/18), or placebo. Each participant was randomly assigned to one of six treatment sequences, with each of the three treatments during a 2-week period separated by a 1–2 week washout period.

Participants had assessments at baseline, after each treatment and washout periods, and at a follow-up visit. Participants were instructed to take study medications in the morning at 8.00 ± 1 hours (assessments were performed after medication intake).

Safety assessments included treatment emergent adverse events (TEAEs), serious adverse events (SAEs), safety laboratory, vital signs, ECG (electrocardiogram), MDS-UPDRS (Movement Disorder Society-Unified Parkinson's Disease Rating Scale),[20] the Columbia Suicide Severity Rating Scale,[21] the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS),[22] and a patient diary documenting nightly sleep duration and awakenings and daytime sleepiness, sleep attacks, and naps.

Efficacy assessments included ESS (1 week recall), the Psychomotor Vigilance Test,[23] and MoCA to document vigilance and cognitive function. Participants also reported diurnal and nocturnal sleep-related outcomes (diary). Actigraphy was included as exploratory assessment.

Outcomes

The primary outcome was safety evaluation as this was the first study with THN102 in patients with PD. The key efficacy endpoint was the change from baseline in the ESS score. Other secondary efficacy endpoints were (1) ESS responder rate (≥25% ESS score improvement)[24] and (2) ESS remission rate (ESS < 11).

Statistical Analysis

Sample size estimation was based on ESS results previously reported.[8] A sample size of 54 participants was assumed to have a power of 82% to detect an effect size of 0.40 with a 0.05 two-sided significance level. To account for dropouts, 60 participants were randomly assigned.

The safety set (SS) included all enrolled participants who received at least one dose of study medication. The full analysis set (FAS) included all randomly assigned participants with an evaluable ESS score at the end of at least one treatment period for efficacy analyses.

Efficacy variables were analyzed using a mixed linear regression model with the fixed effects of treatment, period, treatment by period interaction, sequence, and baseline score and subject nested within sequence as a random effect (for details see Appendix S1).

Given the exploratory nature of the efficacy assessments, there was no hierarchical procedure predefined in the statistical analysis plan.

Results

A total of 105 participants were enrolled. Twenty-eight failed screening, and 2 withdrew from the study before taking study medication. A total of 75 participants were exposed to study treatment (SS). The FAS included 72 participants. Eight participants prematurely terminated the study, 4 participants each with THN102 200/2 and THN102 200/18 (Fig. S1). Participants had a mean age of 63.5 (standard deviation 9.4), 33% were women, disease duration was 8.6 (5.3) years, and EDS duration was 3.7 (2.8) years. All participants had PD treatment with a mean daily levodopa equivalent dose of 781 mg (484) which remained stable during the study, 59 (82%) receiving a dopamine agonist. Baseline ESS was 16.4 (2.0), which is in the lower severe range. MoCA mean score was 27.8 points (1.7) (Table S1), and medical history and other concomitant medications were as expected for an elderly population with comorbidities (Tables S2 and S3).

The most common reasons for discontinuation were TEAEs (6 participants, 8%). Three participants each discontinued in the THN102 200/2 and 200/18 groups. All participants recovered spontaneously. One SAE occurred in the THN102 200/18 group: contusions (wrist and back), considered by the investigator as not treatment related. Overall, both doses of the THN102 were well tolerated, with a higher incidence of adverse events in the THN102 200/18 group (Table 1). Laboratory assessments, vital signs, and ECG did not reveal any clinically significant changes. The MDS-UPDRS and QUIP-RS scores did not show any significant differences between treatment periods. Similarly, participants reported only minimal changes in total sleep time from baseline (diary), and actigraphy results of nocturnal immobility showed similar results (Table S4).

The primary efficacy endpoint (ESS) showed a significant improvement versus placebo (Least Squares means [95% CI] of −1.4[−2.49; −0.31], $P = 0.012$) for THN102/200/2. Treatment with THN102 200/18 improved by −0.74 points [−1.82; 0.34] versus placebo, this difference being nonsignificant (Fig. 1; Tables S5). There was no significant carryover effect.

When response rates were compared, differences between groups were not statistically significant. The remission rate defined as a normal ESS score after treatment was highest after THN102 200/2 with 27.5% versus 16.2% with placebo (odds ratio [95% CI]: 3.08 [0.98; 9.66], $P = 0.053$) and 25.4% with THN102 200/18 (Fig. 1; Table S5).

Diary-reported involuntary sleep attacks and number of diurnal somnolence episodes changed only minimally under the different treatment conditions (Table S5). In accordance with the ESS results, estimated diurnal nap duration significantly decreased with THN102 200/2 compared to placebo in a post hoc analysis ($P = 0.027$). The

TABLE 1 *Incidence of TEAEs by preferred term (≥2 subjects during any treatment period, safety set)*

	Placebo N = 68		THN102 200/2 N = 72		THN102 200/18 N = 73	
Preferred term MedRA	**n (%)**	**E**	**n (%)**	**E**	**n (%)**	**E**
Patients with any TEAE	19 (27.9)	26	23 (31.9)	39	29 (39.7)	48
Headache	–		2 (2.8)	2	4 (5.5)	4
Nausea	–		2 (2.8)	2	3 (4.1)	3
Nasopharingitis	–		1 (1.4)	1	3 (4.1)	3
Dry mouth	–		–		3 (4.1)	3
Fatigue	2 (2.9)	2	–		2 (2.7)	2
Insomnia	–		1 (1.4)	1	2 (2.7)	2
Chest pain	1 (1.5)	1	2 (2.8)	2	1 (1.4)	2
Confusional state	–		–		2 (2.7)	2
Muscle spasms	–		2 (2.8)	2	–	
Nightmare	–		–		2 (2.7)	2

Abbreviations: TEAE, treatment emergent adverse events; MedDRA, Medical Dictionary for Regulatory Activities, version 21.0; N, number of subjects in the safety set with exposure to the corresponding treatment; n, number of subjects with TEAEs; %, percentage based on N; E, number of events.

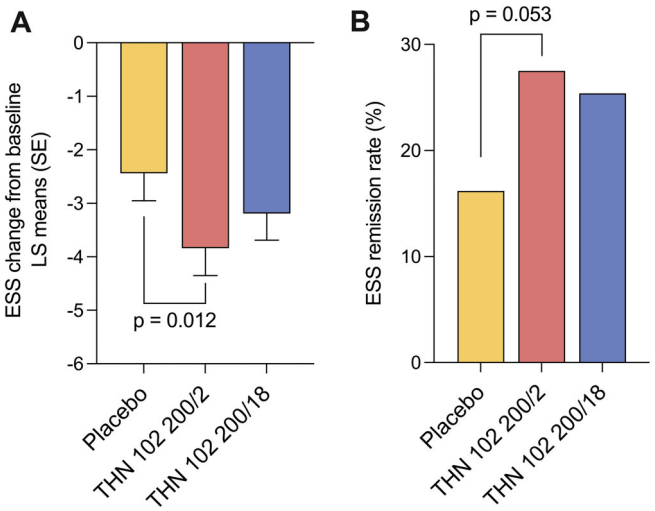

FIG. 1. Epworth Sleepiness Scale (ESS) change and remission rate. ESS change from (**A**) baseline and (**B**) remission rate. [Color figure can be viewed at wileyonlinelibrary.com]

other secondary efficacy endpoints such as psychomotor vigilance test and MoCA showed only minor changes (Table S5) as well as the exploratory daytime actigraphy data (Table S6).

Discussion

This was the first study comparing THN102 to placebo as treatment for EDS in PD patients. The two doses chosen correspond to the lowest and highest flecainide dose per 100 mg of modafinil tested in phase I. Both doses of THN102 were well tolerated in this population of relatively aged patients with comorbidities and a high level of antiparkinsonian medication. The adverse event profile is close to the known profile of modafinil. The results show that THN102 200/2 significantly improved EDS. This result was also supported by a higher remission rate as compared to placebo ($P = 0.053$). THN102 200/18 showed a smaller treatment effect that did not reach significance.

In healthy volunteers, the modafinil–flecainide combination showed improved vigilance and executive function as compared to modafinil alone, with no dose effect of flecainide.[15] In our study, similar to the phase I study, the higher dose of flecainide did not increase effects in PD patients. The absence of flecainide dose–response may be explained by a ceiling effect already obtained at a very low dose of flecainide or a bell-shaped dose–response curve. Because our study was performed versus placebo, the dose–response of added flecainide needs to be further explored in a comparison with modafinil alone in PD patients.

These results are of interest considering the lack of approved treatment for EDS in PD, the negative results with the norepinephrine–dopamine reuptake inhibitor solriamfetol (NCT03037203) and the histamine H3 antagonist bavisant (NCT03194217), and the inconsistent results with modafinil alone. Modafinil (200 mg/d) improved ESS significantly in two small crossover trials (12 and 20 patients),[7,8] without changes in objective measures (Maintenance of Wakefulness Test) in one of them.[7] Conversely, a parallel-group study failed to show efficacy of modafinil in subjective (ESS) and objective measures (Multiple Sleep Latency Test) at 400 mg/d.[9] Such discrepancies may be related to the high variability of ESS scores in the PD population in which EDS is multifactorial. ESS variability could be related either to differences in patient characteristics or to problems in scale reliability, as patients are instructed to "extrapolate" their answers to items assessing events that did not actually occur during the observation period. The treatment effect of 1.4 points between THN102 200/2 and placebo was modest and possibly not clinically important, but it should be emphasized that the design (crossover) and the short duration of exposure (2 weeks) of this pilot trial were not expected to provide an estimate of the full therapeutic potential of THN102.

There are several limitations to this study. As the primary aim of our study was to demonstrate for the first time the safety and efficacy of THN102 in PD patients, a direct comparison with modafinil alone was not performed. This should be addressed in a subsequent study. For feasibility reasons, no objective measurement of EDS was included in the trial. ESS and objective data have been notably discrepant in previous modafinil studies, and this should be further explored. Finally, safety and impact on quality of life of THN102 need to be documented in larger and longer-term studies.

Conclusion

The combination of modafinil 200 mg and flecainide 2 mg was well-tolerated and improved EDS in PD patients. Our results support further development of THN102 for the treatment of EDS in PD.

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Appendix

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Data Availability Statement

Access to participant-level data from this study will not be made available while THN 102 is in clinical development for excessive daytime sleepiness associated with Parkinson Disease. Thereafter, qualified academic researchers may request further details regarding trial data availability through the Theranexus website.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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J.-C.C., O.R., W.R., and W.G.O. contributed to the conception and design of the study and wrote the manuscript; B.B. performed statistical analysis; J.-C.C., J.-P.A., Y.D., L.D., F.K., N.K., D.M., R.P., S.T., M.V., A.V., and O.R. contributed to data acquisition; all authors contributed to the interpretation of the data, revised the manuscript for important intellectual content, approved the final version, and are accountable for all aspects of the work. The authors and the sponsor were responsible for the study design, statistical plan, interpretation of data, writing the manuscript, and decision to publish. On request, all authors had full access to the database, could do independent statistical analyses, and could verify the completeness and accuracy of the data and analyses. The corresponding author had final responsibility for the decision to submit for publication.

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