THN 102 for excessive daytime sleepiness associated with Parkinson's disease: a phase 2a trial

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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.

Objectives: To evaluate the safety and efficacy of THN102 in PD patients with EDS.

Methods: Randomized, double-blind, placebo-controlled, cross-over trial testing two doses of THN102 (200mg/d modafinil with 2mg/d (200/2) or 18mg/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 versus placebo [95% 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.

Introduction

Excessive daytime sleepiness (EDS) is a non-motor symptom present in 20-60% of patients with Parkinson's disease (PD).[1] It is under-reported, significantly impacts quality of life,[2,3] and contributes to serious complications.[4,5] 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 of EDS associated with PD.[7–9] Besides its monoaminergic mechanisms of action, modafinil also 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 linked to modulation of astrocyte networks via connexins which can modulate neuronal activity.[13] In orexin-knock-out 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 300mg with flecainide 3, 9, and 27mg/24h) 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, while most doses significantly improved cognitive performance versus modafinil.

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

Methods

Study Design

This was a double-blind, placebo-controlled, complete three-way cross-over, 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: 15h and flecainide 13h). 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, Epworth Sleepiness Scale (ESS) score of ≥ 14,[17] Hoehn and Yahr score of ≤ 4,[18] and stable PD medications for at least 4 weeks prior to screening. 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[19] score < 23. Written informed consent was obtained from all participants before study initiation.

Randomization and masking

The treatment conditions were THN102 200mg/d modafinil + 2mg/d flecainide (THN102 200/2), THN102 200mg/d modafinil + 18mg/d flecainide (THN102 200/18) or placebo. Each participant was randomly assigned to one of the six treatment sequences with each of the three treatments during a two-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±1h (assessments were performed after medication intake).

Safety assessments included treatment emergent adverse events (TEAEs), serious adverse events (SAEs), safety laboratory, vital signs, ECG, MDS-UPDRS,[20] the Columbia Suicide Severity Rating Scale (C-SSRS),[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

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 ($\geq$ 25% ESS score improvement),[24] (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 drop-outs, 60 participants were to be randomised.

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

Efficacy variables were analysed 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 two withdrew from 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 (**Figure S1**). Participants had a mean age of 63.5 (SD 9.4), 33% were female, 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 L-dopa equivalent dose of 781mg (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**), 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 treatment emergent adverse events (6 participants, 8%). Three participants each discontinued in the THN102 200/2 and 200/18 groups. All participants recovered spontaneously. One serious adverse event 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), actigraphy results of nocturnal immobility showed similar results (**Table S4**).

The primary efficacy endpoint (ESS) showed a significant improvement vs placebo (LS 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] vs placebo, this difference being non-significant (**Figure 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%, vs 16.2% with placebo (odds ratio (95% CI): 3.08 [0.98; 9.66], p=0.053), and 25.4% with THN102 200/18 (**Figure 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 other secondary efficacy endpoints such as PVT 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 of EDS in PD patients. The two doses chosen correspond to the lowest and highest flecainide dose per 100mg 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 anti-parkinsonian 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 cross-over 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 either be linked to differences in patient characteristics or to problems in scale reliability, as patients are

instructed to “extrapolate” their answer 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 (cross-over) 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 goal 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 200mg and flecainide 2mg 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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Authors roles

JCC, OR, WR, and WO contributed to the conception and design of the study and participated in the writing of the manuscript; BB performed the statistical analysis; JCC, JPA, YD, LD, FK, NK, DM, RP, ST, MV, AV, OR contributed to the acquisition of the data; 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. Upon 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.

Declaration of interests

J.C.C. received personal fees from Air Liquide, personal fees from Biogen, personal fees from Denali, personal fees from Ever Pharma, personal fees from Prevail Therapeutic, personal fees from UCB, grants from Sanofi, grants from Michael J Fox Foundation, outside the submitted work.

B.B. is an employee of SCOPE International

J.P.A. has nothing to disclose

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L.D. has nothing to disclose.

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D.M. has nothing to disclose.

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R.P. has nothing to disclose.

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M.V. has nothing to disclose.

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Figure legends

Figure 1

Title: Epworth Sleepiness Scale (ESS) change and remission rate

Legend: ESS change from baseline (panel A), and remission rate (panel B)

Tables

Table 1

Incidence of TEAEs by Preferred Term (≥ 2 Subjects during any treatment period, Safety Set)

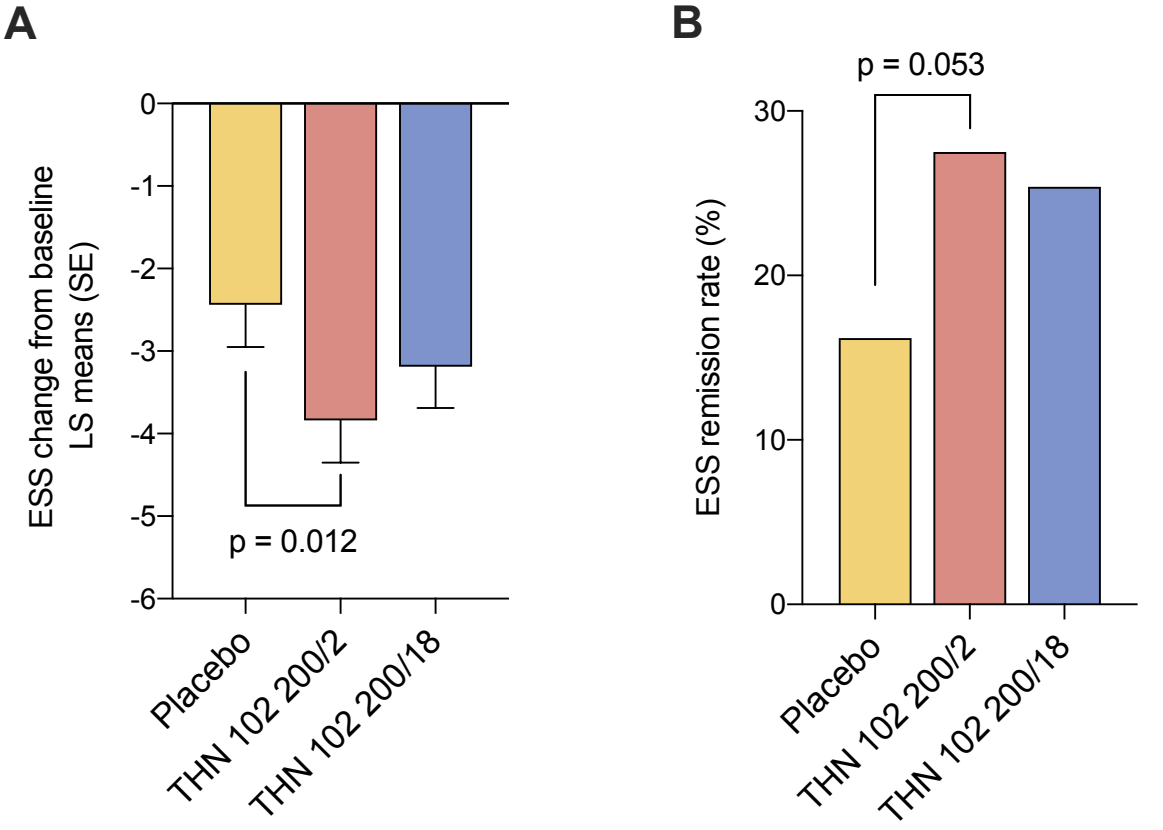
A
ESS change from baseline
LS means (SE)
0
-1
-2
-3
-4
-5
-6
p = 0.012
Placebo
THN 102 200/2
THN 102 200/18
B
p = 0.053
ESS remission rate (%)
30
20
10
0
Placebo
THN 102 200/2
THN 102 200/18

Table 1

Incidence of TEAEs by Preferred Term (≥ 2 Subjects during any treatment period, Safety Set)

Preferred Term MedRA	Placebo N = 68 n (%)	E	THN 102 200/2 N =72 n(%)	E	THN 102 200/18 N = 73 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

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

THN 102 for excessive daytime sleepiness associated with Parkinson's disease: a phase 2a trial

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Supplemental Material

Appendix S1
Statistical analyses

Continuous variables (ESS, PVT, and MoCA change from baseline) were analysed 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. The model was estimated using the restricted maximum likelihood method (REML). Degrees of freedom for the fixed effects were estimated using the Kenward-Roger approximation.

Treatment by period interaction indicating the presence of residual treatment (carryover) effects was checked for significance (p value <0.05), as this may bias the estimates of treatment effects.

The treatment differences for categorical variables (ESS responder and remission rates were assessed using a generalized linear mixed regression model (GLMM) with the fixed effects of treatment, period, treatment by period interaction, sequence, and baseline score, and subject nested within sequence as a random effect. The logit link function was to be used to model the

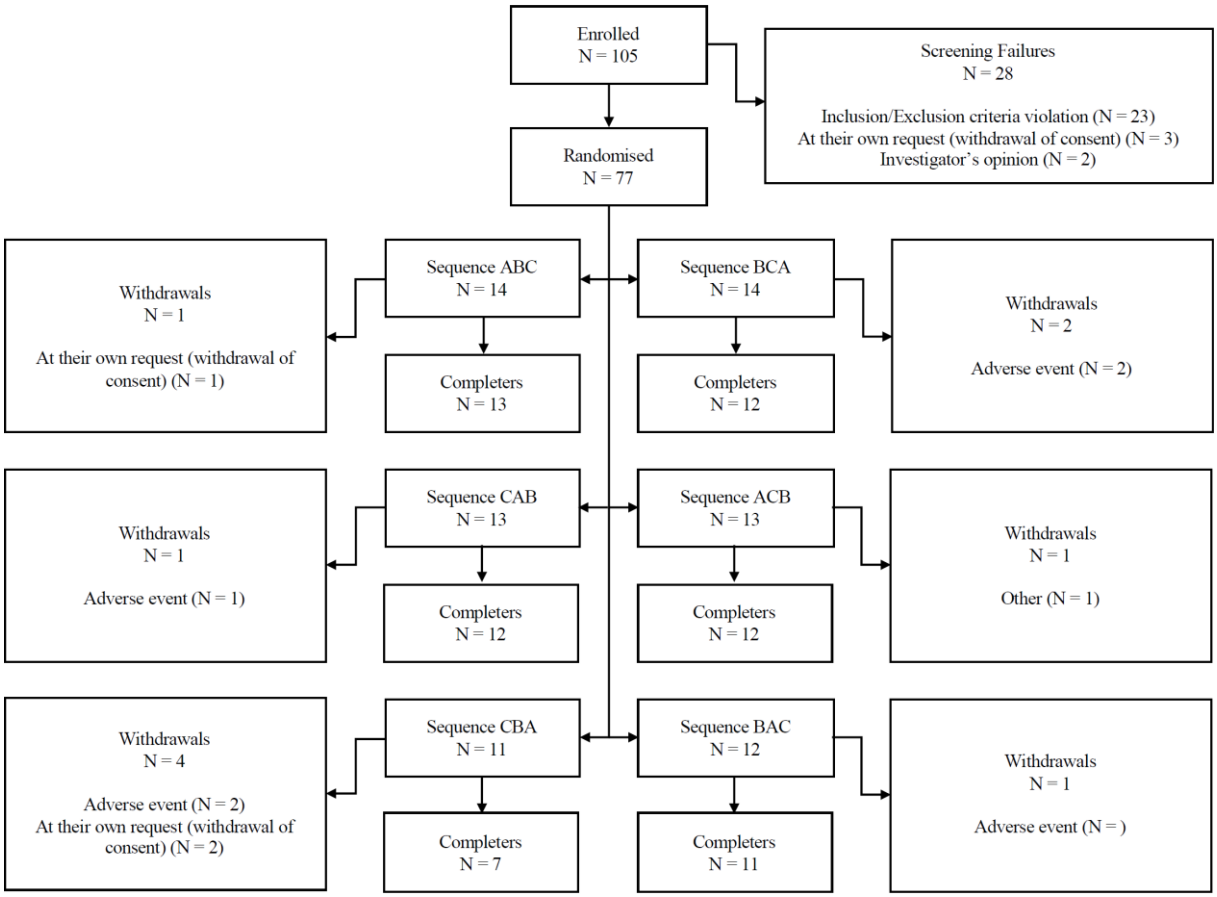
binary response data. The model was to be estimated using the default residual log pseudo-likelihood (RSPL) method. Degrees of freedom for the fixed effects were to be estimated using the Kenward-Roger approximation.

Participants with major deviations concerning their planned treatments or doses or missing outcome measurements were not excluded from the primary analysis in the full analysis set (FAS). Under the assumption that outcomes are missing at random, missing data were not imputed or replaced prior to the analysis.

SAS system version 9.4 for Windows was used for all statistical analyses.

Figure S1

Participant flow-chart



Tables

Table S1

Baseline characteristics

	Safety population (n = 75)
Age (years), mean (SD) range	63.5 (9.35) 38-80
Gender: n (%) Male Female	 50 (66.7%) 25 (33.3%)
Duration of PD (years) mean (SD)	 8.55 (5.3)
Duration of EDS (years) mean (SD)	 3.66 (2.86)
Hoehn-Yahr stage* n (%) 1 1.5 2 2.5 3 4	 5 (6.7%) 3 (4.0%) 34 (45.3%) 16 (21.3%) 15 (20.0%) 2 (2.7%)
UPDRS-MDS mean (SD) Total score Part I Part II Part III* Part IV	 51.9 (19.9) 10.6 (4.3) 11.9 (6.1) 26.5 (13.7) 2.9 (3.3)
QUIP-RS mean (SD)	6.3 (10.4)
Total daily LED (mg) mean (SD)	 781 (484)
	Efficacy population n = 72
ESS mean (SD)	16.4 (2.0)
PVT RT msec mean (SD) Lapses mean (SD) Total errors mean (SD)	 368.2 (109.0) 3.1 (4.2) 3.5 (4.2)
MoCA total score mean (SD)	 27.8 (1.7)

PD = Parkinson's disease, EDS = excessive daytime sleepiness, * Modified Hoehn-Yahr scale, UPDRS-MDS = Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale, Part I = Non-Motor Aspects of Experiences of Daily Living, Part II = Motor Aspects of Experiences of Daily Living, Part III = Motor Examination, Part IV = Motor Complications, QUIP-RS = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale, LED = Levodopa Equivalent Dose, ESS = Epworth Sleepiness Scale, PVT = Psychomotor Vigilance Test, RT = Reaction Time, MoCA = Montreal Cognitive Assessment. * All but one patient in on-state

Table S2

Ongoing Medical Conditions (Safety Set)

System Organ Class Preferred Term	**Total** **(N=75)** **n (%)**
Number of subjects with at least one prior medical condition	66 (88.0)
Vascular disorders	**30 (40.0)**
Hypertension	25 (33.3)
Psychiatric disorders	**27 (36.0)**
Depression	16 (21.3)
Insomnia	6 (8.0)
Metabolism and nutrition disorders	**21 (28.0)**
Hypercholesterolaemia	8 (10.7)
Hyperlipidaemia	6 (8.0)
Nervous system disorders	**18 (24.0)**
Musculoskeletal and connective tissue disorders	**17 (22.7)**
Back pain	6 (8.0)
Gastrointestinal disorders	**16 (21.3)**
Constipation	8 (10.7)
Social circumstances	**10 (13.3)**
Postmenopause	8 (10.7)
Endocrine disorders	**9 (12.0)**
Renal and urinary disorders	**8 (10.7)**
Skin and subcutaneous tissue disorders	**8 (10.7)**
Eye disorders	**7 (9.3)**
Reproductive system and breast disorders	**7 (9.3)**
Surgical and medical procedures	**6 (8.0)**
Deep brain stimulation	6 (8.0)

Table S3

Other Concomitant Medication by Substance Name, Frequency > 5% of Subjects by Treatment (Safety Set)

ATC 2nd level subgroup	Total (N=75) n (%)
Agents acting on the renin-angiotensin system	20 (26.7)
Psychoanaleptics	19 (25.3)
Antithrombotic agents	17 (22.7)
Drugs for acid related disorders	17 (22.7)
Lipid modifying agents	15 (20.0)
Beta blocking agents	14 (18.7)
Urologicals	14 (18.7)
Analgesics	13 (17.3)
Antiinflammatory and antirheumatic products	13 (17.3)
Psycholeptics	9 (12.0)
Drugs for constipation	8 (10.7)
Drugs for functional gastrointestinal disorders	8 (10.7)
Drugs used in diabetes	8 (10.7)
Thyroid therapy	8 (10.7)
Vitamins	8 (10.7)
Vasoprotectives	5 (6.7)
Corticosteroids for systemic use	4 (5.3)
Diuretics	4 (5.3)
Mineral supplements	4 (5.3)

Table S4

Actigraphy Night-time

Analysis of Objective Activity Measures (Full Analysis Set)

Variable	LS-Mean	Estimate	95% CI	p-value
Night time immobility duration (min)	Placebo	20.8742	(1.3202;40.4282)	0.0366
	Test 200/2	15.8535	(-3.5809;35.2879)	0.1088
	Test 200/18	24.1822	(4.9772;43.3871)	0.0141
	Contrast			
	Test 200/2 – Placebo	-5.0207	(-25.0222;14.9808)	0.6191
	Test 200/18 – Placebo	3.3080	(-16.6617;23.2776)	0.7428
	Test 200/18 – Test 200/2	8.3287	(-11.6435;28.3008)	0.4095
Night time mobility periods	Placebo	0.6001	(-0.1863;1.3865)	0.1334
	Test 200/2	0.1007	(-0.6798;0.8812)	0.7987
	Test 200/18	0.6971	(-0.0747;1.4690)	0.0762
	Contrast			
	Test 200/2 – Placebo	-0.4994	(-1.3901;0.3913)	0.2682
	Test 200/18 – Placebo	0.09702	(-0.7917;0.9857)	0.8288
	Test 200/18 – Test 200/2	0.5964	(-0.2934;1.4862)	0.1863
Night time mobility duration (min)	Placebo	-0.8206	(-14.5650;12.9238)	0.9060
	Test 200/2	-11.3969	(-25.0904;2.2966)	0.1019
	Test 200/18	-4.1441	(-17.6279;9.3397)	0.5437
	Contrast			
	Test 200/2 – Placebo	-10.5763	(-24.8799;3.7272)	0.1453
	Test 200/18 – Placebo	-3.3235	(-17.5834;10.9364)	0.6445
	Test 200/18 – Test 200/2	7.2528	(-7.0707;21.5762)	0.3171

Table S5

Efficacy results

	Placebo N= 68	THN 102 200/2 N = 70	THN 102 200/18 N = 72	Difference/OddsRatio vs placebo (95% CI)	p-value
Primary efficacy endpoint					
ESS change from baseline Total score	-2.44 (0.51)	-3.84 (0.51)	-3.19 (0.50)	200/2: -1.4 (-2.49; -0.31) 200/18: -0.74 (-1.82; 0.34)	0.012 0.177
Secondary efficacy endpoints					
ESS response rate (%)	27.9	40.6	35.2	OR 200/2: 1.98 (0.83 ; 4.68) OR 200/18: 1.5 (0.64 ; 3.53)	0.121 0.353
ESS remission rate (%)	16.2	27.5	25.4	OR 200/2: 3.08 (0.98; 9.66) OR 200/18: 2.62 (0.82; 8.32)	0.053 0.102
PVT change from baseline					
RT (msec)	-21.22 (10.06)	-24.11 (9.94)	-19.64 (9.88)	200/2: -2.89 200/18: 1.57	ns ns
Lapses	- 0.67 (0.38)	-0.66 (0.37)	-0.26 (0.37)	200/2: 0.01 200/18: 0.41	ns ns
Total errors	-0.78 (0.40)	-0.69 (0.39)	-0.28 (0.39)	200/2: 0.09 200/18: 0.50	ns ns
MoCA change from baseline Total score	0.22 (0.19)	0.03 (0.19)	0.42 (0.19)	200/2: -0.19 200/18: 0.20	ns ns
Sleep attacks* Change from baseline	-0.38 (1.18)	-0.40 (1.33)	-0.49 (1.16)		
Diurnal somnolence* Change from baseline	-0.55 (1.13)	-0.56 (1.45)	-0.53 (1.09)		
Nap duration (min) Change from baseline	-6.52 (3.77)	-15.57 (3.72)	12.34 (3.72)	200/2: -9.06 (-17.07; -1.04) 200/18: -5.83 (-13.87; 2.22)	0.027 0.154

Changes from baseline are LS-Means (SE), 95% CI = Confidence Intervals (CI), ESS = Epworth Sleepiness Scale, PVT = Psychomotor Vigilance Test, RT = Reaction Time, MoCA = Montreal Cognitive Assessment, * data summarized as means (SD)

Table S6

Actigraphy Day-time

Analysis of Objective Activity Measures (Full Analysis Set)

	LS-Mean	Estimate	95% CI	p-value
Diurnal immobility periods	Placebo	0.4555	(-0.5907;1.5017)	0.3901
	Test 200/2	0.4352	(-0.6031;1.4735)	0.4079
	Test 200/18	1.0355	(0.0120;2.0589)	0.0474
	Contrast			
	Test 200/2 – Placebo	-0.02028	(-1.1375;1.0970)	0.9713
	Test 200/18 – Placebo	0.5800	(-0.5367;1.6967)	0.3047
	Test 200/18 – Test 200/2	0.6003	(-0.5150;1.7156)	0.2877
Diurnal immobility duration (min)	Placebo	23.3816	(-5.3116;52.0747)	0.1091
	Test 200/2	21.1971	(-7.3147;49.7089)	0.1434
	Test 200/18	30.9885	(2.8893;59.0878)	0.0310
	Contrast			
	Test 200/2 – Placebo	-2.1844	(-32.2449;27.8760)	0.8854
	Test 200/18 – Placebo	7.6070	(-22.4179;37.6318)	0.6156
	Test 200/18 – Test 200/2	9.7914	(-20.2329;39.8158)	0.5184
Daily physical activity (g*)	Placebo	-0.00139	(-0.00305;0.00027)	0.1010
	Test 200/2	-0.00067	(-0.00234;0.00101)	0.4328
	Test 200/18	-0.00052	(-0.00217;0.00113)	0.5330
	Contrast			
	Test 200/2 – Placebo	0.000724	(-0.00142;0.00286)	0.5039
	Test 200/18 – Placebo	0.000869	(-0.00127;0.00301)	0.4213
	Test 200/18 – Test 200/2	0.000146	(-0.00201;0.00230)	0.8935

*mean acceleration magnitude per day