CLINICAL STUDY REPORT SYNOPSIS

SAFETY AND EFFICACY OF THN102 ON SLEEPINESS IN NARCOLEPTIC PATIENTS

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STUDY TITLE:	**SAFETY AND EFFICACY OF THN102 ON SLEEPINESS IN NARCOLEPTIC PATIENTS**
INVESTIGATIONAL PRODUCT NAME:	THN102
INDICATION STUDIED:	Narcolepsy
STUDY DESIGN:	Phase IIa (Proof-of-Concept) study, multi-centre, double-blind, randomized, placebo-controlled, 3-way cross-over trial, involving 2 doses of THN102, a combination of modafinil with flecainide, (Modafinil/Flecainide 300 mg/3 mg, Modafinil/Flecainide 300 mg/27 mg) versus modafinil 300 mg alone. The 3 double blind periods lasted two weeks each and follow an open-label stabilization period with modafinil at 300 mg/day of 2 weeks duration followed by a one-week washout period with the same modafinil dose. The study enrolled Type I and II narcoleptic patients.
SPONSOR NAME:	Theranexus S.A.
PROTOCOL NUMBER:	THN102-201
DEVELOPMENT PHASE:	Phase IIa (Proof-of-concept)
EUDRACT NUMBER	2015-005035-41
STUDY INITIATION DATE	27 Sept 2016 (Fisrt Patient First Visit (FPFV))
STUDY COMPLETION DATE:	17 Dec 2018 (Last Patient Last Visit (LPLV))
COORDINATING INVESTIGATOR NAME:	Pr. Yves Dauvilliers
AFFILIATION-INSTITUTION OF INVESTIGATOR:	Centre Hospitalier Régional Universitaire (CHRU) de Montpellier, Hôpital G. de Chauliac Service de Neurologie F-34195 Montpellier Cedex 5, France
RESPONSIBLE PERSON FOR PV:	Marc Thomson
REPORT DATE:	18 July 2019

This study was performed in accordance with Good Clinical Practice (GCP), including the archiving of essential documents. This report has been prepared in accordance with the International Council for Harmonisation (ICH) Guideline on the Structure and Content of Clinical Study Reports.

SYNOPSIS

Study Title:	Safety and Efficacy of THN102 on Sleepiness in Narcoleptic Patients
Investigational Product Name:	THN102 (as the combination of modafinil 300 mg and flecainide acetate at 3 mg or 27 mg, total daily dose)
Coordinating Investigator:	Pr. Yves Dauvilliers
Number of Investigators:	8 Principal Investigators (PI) in total.
Study Centre(s):	Site 1: CHRU Montpellier - Hôpital Guy de Chauliac - Service de Neurologie – France, PI: Pr. Yves Dauvilliers. Site 2: CHRU Paris - Hôpital de la Pitié-Salpétrière - Service de Neurologie – France, PI: Pr. Isabelle Arnulf. Site 3: CHRU Lille - Hôpital Roger Salengro - Service de Neurologie – France, PI: Pr Christelle Charley Monaca. Site 4: Centre Hospitalier Universitaire (CHU) Bordeaux - Hôpital Pellegrin - Unité de Service et de Recherche SANPSY (Sommeil, Addiction & NeuropPSYchiatrie) – France, PI: Pr Pierre Philip. Site 5: CHU Garches - Hôpital R. Poincaré - Service de Neurologie – France, PI: Pr Maria-Antonia Quera-Salva. Site 6: CHU Grenoble Alpes - Hôpital Michallon - Service de Physiologie Clinique – France, PI: Pr Renaud Tamisier. Site 7: CHU Dijon Bourgogne - Service de Neurophysiologie Clinique - France, PI: Dr Martine Lemesle. Site 8: Pneumocare SPRL - Erpent – Belgium, PI: Dr. Jean-Benoit Martinot.
Publication (reference):	Not applicable
Study Period: **(date of first enrolment):** **(date of last completed):**	FPFV: 27SEP2016 LPLV: 17DEC2018
Phase of Development:	Phase IIa, Proof-of-concept study
OBJECTIVES	**Primary**: To determine the superiority of THN102 (combination modafinil and flecainide acetate) vs modafinil for improving the excessive daytime sleepiness (EDS) assessed by Epworth Sleepiness Scale (ESS) in patients with narcolepsy treated by modafinil.

	Secondary: - To quantify the efficacy of THN102 (modafinil/flecainide acetate combination) for two daily doses (300/27 mg and 300/3 mg) vs modafinil (300/0 mg) for improving cataplexy (in type 1), sleep paralysis, fatigue, hallucinations, and quality of life - To determine the dose response profile of THN102 vs. modafinil on additional efficacy parameters - To assess the safety profile of THN102 doses vs. modafinil - To determine the plasma levels of modafinil and flecainide at steady state
	Exploratory: Not Applicable
METHODS	This was a prospective, double-blind, randomized, placebo-controlled study using a complete 3-period 3-treatment cross-over design, preceded by an open-label baseline period and followed by a wash-out period, each of 2 weeks. **Number of Subjects/Patients:** A total 51 patients were randomized, and 45 patients completed the study.
Diagnosis and Main Criteria for Inclusion:	Patients with a diagnosis of narcolepsy type 1 (i.e. with cataplexy) or type 2 (without cataplexy) according to the International Classification of Sleep Disorders (ICSD-3) criteria. Males or females aged between 18 and 65-year-old. Body mass index (BMI) >18 kg/m2 and <35 kg/m2. Patients treated with modafinil at stable dosage for at least 2 months and still complaining of EDS despite the treatment. ESS score should be ≥ 14/24 during the baseline period.

Test Product, Dose and Mode of Administration, Lot/batch Number

Study Drugs	**Dose Strength**	**Mode of Administration**	**Drug Product / Lot Numbers:**
THN102: 300mg/3mg THN102: 300mg/27mg	THN102: 300mg/3mg, 300 mg modafinil and 3 mg of flecainide acetate, total daily dose THN102: 300mg/27mg 300 mg modafinil and 27 mg of flecainide acetate, total daily dose	Oral	Flecainide Acetate 1mg: ES057, ES107 (PCA) Flecainide Acetate 9mg: ES059, ES109 (PCA) Modafinil 100 mg tablets (TEVA) - M1061A, M1063 and M1075

Duration of Treatment:	10 weeks in total: baseline (300 mg modafinil, open label, 2 weeks), 3 periods of 2 weeks with THN102 and Reference (14 days ± 1 day), wash-out (300 mg modafinil, open label, 2 weeks). The same formulation and commercial batch of modafinil was used across the periods including baseline and wash-out.

<table>
<tr><td colspan="4">Reference Therapy, Dose, and Mode of Administration, Lot/Batch Number</td></tr>
<tr><td>Study Drug</td><td>Dose Strength</td><td>Mode of Administration</td><td>Drug Product / Lot Numbers:</td></tr>
<tr><td>THN102: 300mg/0mg (Reference)</td><td>300 mg modafinil, total daily dose and placebo of flecainide</td><td>Oral</td><td>Modafinil 100 mg tablets (TEVA) M1061A, M1063 and M1075
Flecainide Acetate 0mg (placebo): ES056, ES106 (PCA)</td></tr>
<tr><td rowspan="4">CRITERIA FOR EVALUATION:</td><td colspan="3">Efficacy:
Primary: Mean ESS total score at the end of each treatment period.
Secondary: Good response on ESS scale: decrease from baseline ΔESS ≥3, Absence of residual somnolence: ESS<11, Daily sleepiness assessment (modified ESS for EDS daily pattern), 14-item Fatigue scale, European Quality of Life (EQ-5D), Patient Global Impression of Severity (PGI-S), PGI for Change (PGI-C), Clinical Global Impression of Severity (CGI-S), CGI for Change (CGI-C), Patient diary data.</td></tr>
<tr><td colspan="3">Pharmacokinetic:
Plasma concentrations of modafinil and flecainide at each study visit.</td></tr>
<tr><td colspan="3">Pharmacodynamic:
Not applicable</td></tr>
<tr><td colspan="3">Safety:
Adverse events (AE), Vital signs, Electrocardiogram (ECG), Physical Examination, Beck Depression Inventory (BDI) evaluation for depressive symptoms (including suicidal thoughts), standard Haematology, Biochemistry, Urinalysis and Pregnancy tests</td></tr>
<tr><td>STATISTICAL METHODS:</td><td colspan="3">Efficacy:
Primary Endpoint: To compare the mean changes in ESS total scores across the THN102 treatment groups, two null hypotheses were constructed:
H01: Effect of THN102 high dose (Modafinil 300mg/27mg) is equal to effect of Reference (Modafinil 300mg/0mg),
H02: Effect of THN102 low dose (Modafinil 300mg/3mg) is equal to effect of Reference (Modafinil 300mg/0mg),
And the accompanying alternative hypotheses as being Not equal (H11 and H12).
The ESS total score was also subjected to Analysis of Variance (ANOVA) using a linear mixed effects model setting, with maximum likelihood estimates and Kenward-Rogers adjustment for degrees of freedom. The</td></tr>
</table>

	model included the treatment, period and sequence as fixed effects and the subject nested within sequence as a random effect. The significance of the differences between the THN102 dose levels, or combined dose levels, and reference treatment (Modafinil 300 mg/0 mg Flecainide) were assessed at the two-sided 5% level. Secondary Endpoints: continuous secondary efficacy parameters (modified ESS for daily pattern, EQ-5D score and Visual Analog Scale (VAS), 14-item fatigue score) were analyzed using the same method as for the primary endpoint. Categorical secondary efficacy parameters of Good Response on ESS and the ESS absence of residual somnolence were compared between each THN102 dose group and reference (modafinil alone) using a Mc-Nemar test. Categorical secondary efficacy parameters of EQ-5D category responses, PGI-S and PGI-C score, the CGI-S and CGI-C scores for sleepiness and cataplexy, were compared using the Wilcoxon signed-rank test for paired ordinal data. Sample Size: With 42 subjects to complete the study, this design will have at least 80% power to detect a mean difference of 2.4 points in ESS between either doses of THN102 and the Reference treatment, assuming an intra-subject standard deviation of 3.8 and with two-sided 5% level of significance.
	Bioanalytical: Not applicable.
	Pharmacokinetic: Not applicable.
	Pharmacodynamic: Not applicable.
	Safety Measures: Descriptive statistics only.
SUMMARY OF RESULTS:	**Efficacy:** No statistically significant differences were observed between THN102 (each dose level or combined) and the reference therapy (modafinil only) for any of the parameters analyzed (primary and secondary endpoints) in the modified Intent-to-Treat population (mITT, 48 subjects). The same results were observed in the per-protocol population (PP, 37 subjects)
	Pharmacokinetic: Plasma concentrations of modafinil and flecainide were used for documentation only. Systemic exposures to modafinil and flecainide are compatible with study treatments and dose regimen. No PharmacoKinetics (PK) parameters were estimated.

	Pharmacodynamic: Not applicable
	Safety Results: A total of 51 subjects was randomized and received at least one dose of study drug (safety data set). There was no SAE, including death, and no subject discontinued study treatment or the study due to an AE. All drug related Treatment Emergent Adverse Events (TEAEs) were of mild to moderate intensity. No clinically significant (CS) effects were observed from the recording of ECGs and vital signs measurements including no prolongation of QRS interval of more than 25% (from baseline) in the presence of flecainide (at both dose levels). No clinically significant changes in safety laboratory test were observed that can be attributed to THN102.
CONCLUSIONS:	The administration of THN102, as fixed combination of modafinil 300 mg/day and flecainide 3 mg/day or 27 mg/day, was very well tolerated in subjects with narcolepsy and already pre-treated with modafinil. There was no difference in efficacy between THN102 and modafinil alone in this patient population. It should be noted that the patients included in the study had a high mean ESS score of about 17 at baseline after at least 2 months of pre-treatment with modafinil which remained unchanged after another 2 weeks of open label stabilization under modafinil 300 mg/day before randomization into the tested treatment conditions, indicating treatment resistance.
DATE OF REPORT:	18 JULY 2019