

The PNB01 Clinical Development Program: A Novel Boosting Antidepressant Therapy

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Abstract

The development of antidepressants inducing a superior rate of early and sustained responders over standard of care is considered to answer a major medical need.¹ The delay in efficacy seen with current antidepressants is likely to contribute to bad compliance, early treatment discontinuation and poor outcome.² The primary effect of the widely used SSRIs is to block the serotonin transporter responsible for presynaptic reuptake of serotonin. Combining low doses of pipamperone (PIP) (5–15 mg/d) with the SSRI citalopram (CIT) (PNB01/PIPCIT) leads to additional and selective inhibition of the D₂ and 5-HT_{2A} receptors. The clinical relevance of this combination was confirmed in a phase II, double-blind, active-controlled, randomized Proof of Concept study in 165 patients with moderate to severe major depressive disorder (MDD). A significant superior rate of patients with an early and sustained response (ESR, defined as a ≥50% MADRS total score reduction from baseline at week 2 and 4) treated with PNB01 compared with CIT (17% vs 5%, P<0.02) was demonstrated. We will present top-line results of the PNB01 phase II program and the outline of the upcoming phase III clinical development program, during which the ESR will be used as a new primary endpoint in order to confirm superiority of PNB01 over CIT. The PNB01 clinical trial program was born out of initial clinical observations by Dr. Erik Buntinx, psychiatrist, in his search for improved treatment modalities that he could offer to his patients. In the last 10 years, the program has evolved; its rationale has been linked to the mode of action of PIP and SSRIs, such as CIT, and is further substantiated by genetic research showing that patients carrying nonresponse alleles (BDNF and HTR_{2A}) benefit the most from PNB01. This novel treatment showing a clinically relevant ESR over standard of care will be a breakthrough for physicians and patients who are in need of a faster and sustained treatment of MDD.

Introduction

- Selective serotonin reuptake inhibitors and other antidepressants usually require 6–8 weeks to achieve their full antidepressant effect.^{1,2}
- Development of antidepressant treatments with a more rapid and sustained effect is considered a major medical imperative.^{3,4}
- Pipamperone (PIP) is a weak antipsychotic used in the treatment of schizophrenia in a number of European Union countries. At low doses (5–15 mg/d), PIP is a highly selective 5-HT_{2A} and D₂ receptor antagonist.
- PNB01/PIPCIT is a new, fixed-dose combination of low-dose pipamperone 15 mg and citalopram 20/40 mg once daily (QD). The combination has a potential boosting (faster, sustained response) treatment effect.
- Treatment with PNB01 resulted in clinically relevant effects in a phase II, double-blind, active-controlled, randomized Proof of Concept study in 165 patients with moderate to severe MDD.⁵
- We present the results of a phase II PNB01 trial, the post hoc analyses to optimize the phase III trial design, and the innovative approaches that will include, the Early and Sustained Response Rate (ESR) as a new primary endpoint, among others.

The PNB01 Phase II Trial

(EUDRACT 2007-0504-13; ClinicalTrials.gov NCT00672659)

Design

- Multicenter, randomized, double-blind, parallel-group, placebo-controlled; 8-week treatment phase and 4-week safety follow-up (N=165, 18–65 y).
- The clinical study protocol was approved by the relevant ethics committees, and written informed consent was obtained from all patients before enrollment in the study.
- Main inclusion criteria: (1) Moderate to severe MDD (*Diagnostic and Statistical Manual of Mental Disorders [DSM-IV]*); (2) Current nonpsychotic depressed episode lasting 4–26 weeks; Clinical Global Impression–Severity scale rating ≥4 and Hamilton Depression Scale ≥18 at screening and baseline.
- Treatments
 - CIT (n=82): Citalopram 20 mg QD in week 1, 40 mg QD in week 2–8 and placebo twice daily (BID).
 - PNB01 (n=83): Pipamperone 5 mg BID in week 1–8 and citalopram 20 mg QD in week 1, 40 mg QD in week 2–8.
- Outcomes
 - Mean change in MADRS score from baseline to week 8.
 - ESR, defined as the number of patients being early responders (MADRS Total Score [TS] reduction ≥50% from baseline at 2 wk) and sustained responders (at 4 wk).

Results

- The treatment groups were similar in demographic and clinical characteristics (Table 1).

Table 1. Patient Demographics and Clinical Characteristics, ITT Population

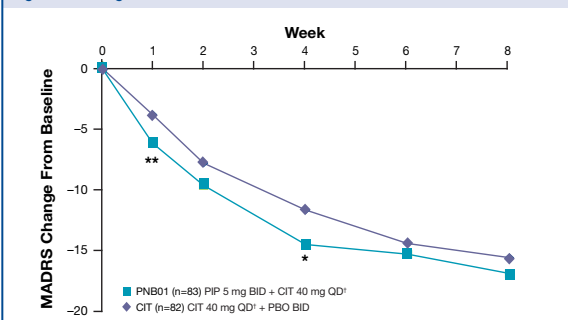
	CIT (n=82)	PNB01 (n=83)
Mean (SD) age, y	39.7 (11.8)	40.1 (11.4)
Sex, n (%)		
Women	63 (77)	70 (84)
Race, n (%)		
White	82 (100)	82 (99)
Mean (SD) weight, kg	79.9 (23.7)	80.0 (22.2)
Mean (SD) duration current MDD episode, d	99.6 (43.1)	94.8 (37.7)
n (%) with duration >12 wk	46 (56)	43 (52)
Mean (SD) MADRS total score	32.4 (5.9)	32.7 (5.1)
n (%) with MADRS ≥30 (severe depression)	58 (71)	57 (69)
Mean (SD) score MADRS item 9: pessimistic thoughts	3.1 (1.0)	2.9 (1.1)
Mean (SD) score MADRS item 10: suicidal thoughts	1.7 (0.9)	1.6 (0.9)
Other psychiatric history not ongoing, n (%)	53 (65)	65 (78)

CIT=citalopram 40 mg once daily; ITT=intent to treat; MADRS=Montgomery-Asberg Depression Rating Scale; MDD=major depressive disorder; PNB01=pipamperone 5 mg twice daily + citalopram 40 mg once daily.

Efficacy of PNB01 compared with CIT

- Better efficacy, with a significant greater improvement on MADRS TS over 4 weeks (intent to treat [ITT], last observation carried forward [LOCF]) (Figure 1).

Figure 1. Change From Baseline in MADRS Total Scores Over Time (ITT, LOCF)



CIT=citalopram; PIP=pipamperone; ITT=intent to treat; LOCF=last observation carried forward; MADRS=Montgomery-Asberg Depression Rating Scale; **P=0.007; *P=0.025; †20 mg QD in week 1, and then titrated up to 40 mg QD. Primary endpoint: change in total MADRS from baseline at week 8 (NS).

- More early and sustained responders (MADRS TS reduction ≥50% from baseline at week 2 and 4):
 - 21% (17/80) in the PNB01 group vs 9% (6/67) in the CIT group (P=0.046; ITT, logistic regression model, [secondary endpoint]).⁶

Global treatment effect of PNB01 compared to CIT

- Superior resolution of reduced sleep evident over 8 weeks of treatment (P=0.001; ITT LOCF).
- Greater improvements on reduced appetite evident over 4 weeks of treatment (P=0.017; ITT LOCF).
- Greater improvement on concentration difficulties over 4 weeks of treatment (P=0.013; ITT LOCF).
- Lesser pessimistic thoughts were evident over 8 weeks of treatment (P=0.019; ITT LOCF).

Treatment adherence

- PNB01 shows a better adherence, with a lower discontinuation compared to CIT, particularly in the first 4 weeks (P=0.003; ITT).

Safety/Tolerability

- Fewer drug-related adverse events with PNB01 than with CIT (35.2% vs 43.6%).
- All adverse events classed as psychiatric disorder were in the CIT group, especially insomnia (3.8% vs 0.0%; P=0.027).

Pharmacogenetic nested study

- Subset of 88 patients of 165 patients from phase II proof of concept study.
- Testing for the influence of genetic variants in 19 genes on antidepressant response.
- Patients carrying the alleles associated with worse antidepressant response overall – the Met allele of the functional BDNF Val66Met polymorphism (rs6265) and the G-allele of rs7997012 in the HTR_{2A} locus – profited most from the PIP augmentation and improved 9 days earlier (T_{50%} P=0.001; general linear model).

Post Hoc Analyses With Phase II Data

Objectives

- Based on the feedback from clinical and regulatory experts regarding the use of the ESR as an endpoint in the phase III clinical trial program of PNB01, we performed post hoc analyses using the results of the PNB01 phase II Proof of Concept study, with the aim to
 - Develop an improved definition of the ESR.
 - Reach consensus regarding the clinical relevance and acceptability of the ESR as a new primary endpoint.
- Calculate sample size and power for the planned pivotal phase III PNB01 study program.

Methods

Study Design

- Data obtained in the phase II multicenter, randomized, double-blind, parallel-group, placebo-controlled, 8-week treatment phase and 4-week safety follow-up (N=165, 18–65 years).

ESR endpoint

- Based on expert and regulatory recommendations, the ESR was redefined as the combination of
 - A response, defined as ≥50% reduction in total MADRS score from baseline at week 2, 3, 4, and 6 (all had to be applied).
 - A total MADRS score cut-off from ≤12 to ≤18 at week 2, 3, 4, and 6.

Statistical Analysis

ESR

- Group differences in the proportion of subjects with a ESR (ESR rate) across the treatments was tested using the Fisher exact test (2-sided), with missing ESR values set to 0.

Sample size and statistical power calculation for phase III pivotal trial

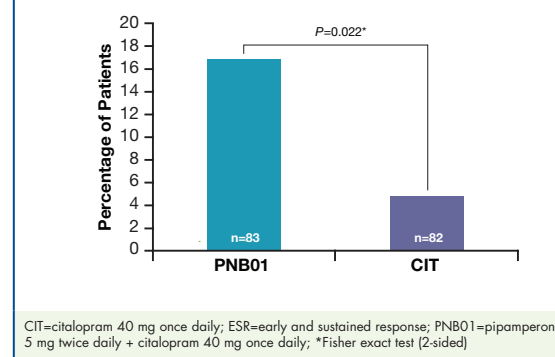
- Based on the recommendations of clinical and regulatory experts, the phase III clinical program will compare PNB01 with both CIT and PIP (3-arm study).
- The sample size was calculated using the new ESR definition as outcome variable.
- As a reference, we used the results of the ESR rates obtained in the phase II study based on this new definition: 3/82 (3.7%) for the CIT alone group and 12/83 (14.5%) for the PNB01 group. As there is no historical data to estimate the ESR rate for PIP alone, ESR rate was assumed to be 3.7% as well.
- Power was calculated to detect a clinically meaningful difference of at least 10% among treatment arms using a Fisher's exact test (2-sided) and a significance level of 0.05.

Results (See Also Poster 39, June 14th)

Early and sustained response

- Overall, the ESR rate — applying the definition without any severity cut-off score, at any visit at week 2, 4, and 6, and setting missing ESR values to 0 (non-ESR) — was 17% (14/83) in the PNB01 group vs and 5% (4/82) in the CIT group vs (P=0.022; Fisher Exact test) (Figure 2).
- After stratifying the ESR rate based on 7 different MADRS score improvement thresholds (from ≤12 to ≤18, at week 2, 4, and 6) we found that compared to CIT
 - The ESR rate was higher for PNB01 at all cut-offs.
 - For all tested cut-offs, the ESR rate was about 2-fold higher for PNB01
- We also found that at a MADRS score cut-off of ≤16 or higher
 - The ESR rate difference between PNB01 and CIT became statistically significant.
 - The number of patients needed to treat with PNB01 was 10 and below for having 1 additional ESR patient in comparison with CIT.

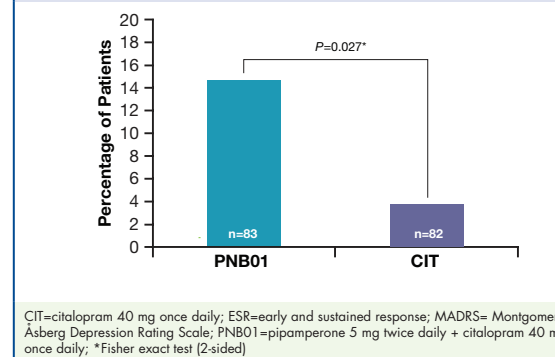
Figure 2. Proportion of Early Responders (Week 2) With Sustained Response at Week 4 and 6 (Combined) Without Any Severity Cut-off Score and Setting Missing ESR Values to 0 (non-ESR)



CIT=citalopram 40 mg once daily; ESR=early and sustained response; PNB01=pipamperone 5 mg twice daily + citalopram 40 mg once daily; *Fisher exact test (2-sided)

- By adding a minimum cut-off of the MADRS score ≤16 to the ESR definition as recommended by expert and regulatory bodies, PNB01 had a significant clinically relevant superior outcome over CIT (14.5% vs 3.7%; P=0.027, Fisher exact test) (Figure 3).
- With an anticipated ESR rate of 14.5% for PNB01 and of 3.7% for both CIT and PIP, the inclusion of 180 patients in each treatment arm in the phase III PNB01 pivotal trial is calculated to result in about 90% power to demonstrate a significantly superior ESR rate of PNB01 over both CIT and PIP alone.
- In the phase III pivotal design, 5 additional patients will be added to each treatment arm to account for treatment nonadherence (total sample size of 555; 185 patients per treatment arm).

Figure 3. Patients with ESR Applying Expert and Regulatory Recommended Definition: MADRS TS Reduction ≥50% From Baseline and MADRS TS Threshold ≤16 at week 2, 4, and 6 (Combined)



CIT=citalopram 40 mg once daily; ESR=early and sustained response; MADRS= Montgomery-Asberg Depression Rating Scale; PNB01=pipamperone 5 mg twice daily + citalopram 40 mg once daily; *Fisher exact test (2-sided)

Planned Phase III Acute Efficacy Trial

(EUDRACT 2011-001190-11; ClinicalTrials.gov NCT01312922)

Design

- Multicenter, centrally randomized, double-blind, 3-arm, fixed-dose study with a 10-week treatment phase and 1-week safety follow-up (N=555, aged ≥18 years) (Figure 4).

Figure 4. Schematic Representation of the Phase III Pivotal Trial of PNB01

	Pre-Treatment Phase	Double-Blind 10-Week Treatment Phase		Double-Blind 1-Week Safety Follow-up
		Week 1	Week 2–10	
Screening	Central Randomization (N=555)	PNB01: fixed combination PIP 15 mg QD CIT 20 mg QD (N=185)	PNB01: fixed combination PIP 15 mg QD CIT 40 mg QD (N=185)	After Study Treatment Discontinuation
		CIT 20 mg QD (N=185)	CIT 40 mg QD	
		PIP 15 mg QD (N=185)	PIP 15 mg QD	
Premature Study Treatment Discontinuation Follow-up With Phone Call Assessments				

- Main inclusion criteria: 1) Moderate to severe MDD according to the DSM-IV; 2) Patient Score of MADRS ≥26; 3) Current nonpsychotic depressed episode lasting 4–76 weeks; 4) Clinical Global Impression–Severity of Illness scale rating ≥4.
- Treatments
 - PNB01 group: PIP 15 mg QD + CIT 20 mg QD (week 1), 40 mg QD (week 2–8) (N=185).
 - CIT group: CIT 20 mg QD (week 1), 40 mg QD (week 2–8) (N=185) + Placebo.
 - PIP group: PIP 15 mg QD (N=185) + Placebo.

Innovations in the Trial Design

- Patient-reported primary and secondary outcomes will be collected electronically (ePRO) using an Interactive Voice Response System (IVRS) via telephone. This will
 - Eliminate inter-rater variability and the clinician rating as a source of bias in multicenter studies^{8,7}.
 - Limit the number of missing data, including after premature study treatment discontinuation.
 - Permit the follow-up of drop-outs without violation of the patient's right to discontinue participation at any time of the study treatment.
- A 3 active treatment arm study, because
 - PNB01 is a fixed combination of 2 drugs, and benefit must be demonstrated over its constituents separately⁴.
 - Low-dose Pipamperone is considered as an active-placebo.
 - Increasing the number of active treatment arms in excess of 1 reduces the chances to detect any differences^{8,9}.
- ESR rate (MADRS TS reduction ≥50% from baseline and MADRS TS threshold ≤16 at week 2, 3, 4, and 6 [combined]), used as primary endpoint, is justified because
 - A 50% decrease — combined with a cut-off score of ≤16 — in total MADRS score after 2 weeks is considered as a clinically relevant measure of an early antidepressant effect¹, but such a response needs to be sustained over time¹⁰.
 - From the PNB01 phase II results, ESR is a clinically relevant measure which captures antidepressant response over time.

Summary of the PNB01 pipeline

- In the phase II study, PNB01 was associated with
 - Significant clinical advantage in ESR
 - Improvements in sleep and appetite
 - Improved adherence
 - Possibly less drug-related adverse events
- Over active treatment with citalopram 40 mg QD
- Positive phase II data justify Phase III development of PNB01, in which
 - The design will include a 3 active treatment arm: PNB01, CIT, and PIP
 - ESR (Primary End Point) will be used as clinically relevant measure, which captures superior sustained response over time
 - Variables to be assessed will be obtained using IVRS ePRO

Authors' Disclosures

Dr. Erik Buntinx is Chief Executive Officer and Managing Director of PharmaNeuroBoost and is also a shareholder in PharmaNeuroBoost. Dr. Ludo Haazen is consultant to PharmaNeuroBoost and Chief Medical Officer in PharmaNeuroBoost. Dr. Remi van den Broeck is consultant to PharmaNeuroBoost and Chief Development Officer. Dr. Didier de Chaffoy is consultant to PharmaNeuroBoost and Chief Scientific Officer in PharmaNeuroBoost. Prof. Dr. Michael Thase received grants from PharmaNeuroBoost in relation to scientific and regulatory advice.

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