

Creating a New, Clinically Relevant Endpoint in the PIPICIT Trial Program: The ESR (Early and Sustained Antidepressant Response)

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Abstract

Background: Development of antidepressant treatments with a rapid effect is considered a major medical imperative but is limited by the lack of consensus regarding how to best measure this rapid effect. The PIPICIT clinical trial program is designed to assess the boosting effect of low-dose pipamperone (PIP, 15 mg) when used in a fixed-dose, once-daily (QD) combination with citalopram (CIT, 40 mg). Based on the results of a phase II trial (n=165, mean baseline [MADRS]=32), PIPICIT will move into phase III development. The ESR is one of the key endpoints, and here we present a rationale for its use.

Methods: Data from the PIPICIT phase II trial were used to assess the clinical relevance of the ESR, defined as a $\geq 50\%$ MADRS total score reduction from baseline at week 2, 4, and 6. ESR scores were compared between patients treated with PIPICIT and CIT. A 50% MADRS score improvement may not result in a significant clinical improvement. Therefore, we included a maximum severity threshold in the ESR definition and applied different total MADRS cut-off scores to the ESR calculation (MADRS from ≤ 12 to ≤ 18 , at week 2, 4, 6).

Results: Overall, the ESR rate was 21% in the PIPICIT group vs 9% in the CIT group ($P=0.046$), without applying any severity cut-off score, at week 2 and 4 (secondary endpoint). The ESR rate in PIPICIT was higher than in CIT when using all 7 MADRS cut-offs: 7.2% vs 2.4%, 7.2% vs 3.7%, 12% vs 3.7%, 12% vs 3.7%, 14.5% vs 3.7%, 16.9% vs 3.7%, and 16.9% vs 4.9% (MADRS cut-off from 12–18, respectively) at week 2, 4, and 6. This difference was statistically significant at a cut-off of 16 and higher. The ESR rate was approximately a factor 2 higher for PIPICIT compared with CIT, at all cut-offs.

Conclusions: A 50% decrease in total MADRS score after 2 weeks is considered a clinically relevant measure of an early antidepressant effect, but such a response needs to be sustained over time. The ESR is a clinically relevant measure which captures this response over time, and should be advocated as a key endpoint in pivotal trials. A doubling of the ESR rate compared with a reference antidepressant can be considered clinically relevant.

Introduction

- Selective serotonin reuptake inhibitors (SSRIs) 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.^{3,5}
- 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 D₄ receptor antagonist.
- PIPICIT (PNB01) is a fixed-dose combination of low-dose pipamperone (PIP), 15 mg once daily (QD) and citalopram (CIT) 20/40 mg QD. The combination has a potential boosting (fast and sustained response) treatment effect.
- In a phase II, double-blind, active-controlled, randomized Proof of Concept study in 165 patients with moderate to severe major depressive disorder (MDD)⁶ (see also Poster 31, 15th June), it was shown that PIPICIT (5 mg PIP BID + 40 mg CIT QD) provided
 - A better total change from baseline than CIT in Montgomery-Åsberg Depression Rating Scale (MADRS) total scores (TS) at week 1 and 4 of treatment ($P=0.007$ and $P=0.03$, respectively [last observation carried forward]).
 - Overall, the ESR rate was 21% in the PIPICIT group vs 9% in the CIT group ($P=0.046$; intent to treat [ITT], logistic regression model, [secondary endpoint])⁶, without applying any severity cut-off score, at week 2 and 4.

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 PIPICIT (PNB01), we performed post hoc analyses using the results of the PIPICIT 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):
 - Main inclusion criteria: (1) Moderate to severe MDD (*Diagnostic and Statistical Manual, Fourth Edition*); (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 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.

ESR Endpoint

- Based on expert and regulatory recommendations, the ESR was redefined as the combination of
 - A response, defined as $\geq 50\%$ reduction in total MADRS TS 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 Fisher exact test (2-sided), with missing ESR values set to 0 (non-ESR).

Sample size and statistical power calculation for phase III pivotal trial

- Based on the recommendations of clinical and regulatory experts, phase III clinical program will compare PNB01 to 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 are 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 2-sided Fisher's exact test and a significance level of 0.05.

Results

Patient Characteristics

- 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-Åsberg Depression Rating Scale; MDD=major depressive disorder; PNB01=pipamperone 5 mg twice daily + citalopram 40 mg once daily.

Early and Sustained Response

- Overall, the ESR rate applying the definition without any severity cut-off score at any visit was
 - Between end of week 2 and 4: 21% (17/80) in the PNB01 group vs 9% (6/67) in the CIT group ($P=0.046$; logistic regression model, ITT analysis [secondary endpoint])⁶
 - At week 2, 4, and 6 and with setting missing ESR values to 0 (non-ESR), 17% (14/83) in the PNB01 group vs 5% (4/82) in the CIT group ($P=0.022$; Fisher Exact test)
- 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 (Table 2).
 - For all tested cut-offs, the ESR rate was about 2-fold higher for PNB01.

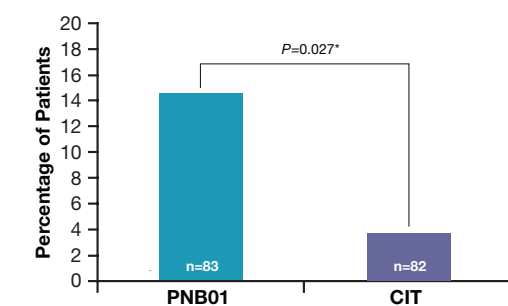
Table 2. Comparison of ESR Rates in Each Treatment Arm Stratified by 7 Different Total MADRS Score Severity Thresholds at Week 2, 4, and 6

MADRS score	ESR rate (n, %)		P value	Number needed to treat *
	CIT (N=82)	PNB01 (N=83)		
No cut-off	4 (4.9%)	14 (16.9%)	0.022	9
≤ 12	2 (2.4%)	6 (7.2%)	0.277	21
≤ 13	3 (3.7%)	6 (7.2%)	0.496	29
≤ 14	3 (3.7%)	10 (12%)	0.08	12
≤ 15	3 (3.7%)	10 (12%)	0.08	12
≤ 16	3 (3.7%)	12 (14.5%)	0.027	10
≤ 17	3 (3.7%)	14 (16.9%)	0.009	8
≤ 18	4 (4.9%)	14 (16.9%)	0.022	9

CIT=citalopram 40 mg once daily; ESR=early and sustained response; MADRS=Montgomery-Åsberg Depression Rating Scale.
*Number of patients needed to treat with PNB01 to have 1 additional patient with ESR in comparison with CIT treatment

- We found that at a MADRS score cut-off of ≤ 16 or higher
 - The ESR rate difference between PNB01 and CIT became statistically significant (Table 2).
 - The number of patients needed to treat with PNB01 was 10 and below for having 1 additional ESR patient in comparison with CIT (Table 2).
- By adding a minimum cut-off of the MADRS score ≤ 16 to the ESR definition, as recommended by expert feedback, PNB01 had a significant clinically relevant superior outcome over CIT (14.5% vs 3.7%; $P<0.027$; Fisher Exact test) (Figure 1).

Figure 1. Number of ESR Applying a Minimum MADRS Cut-off Score of 16

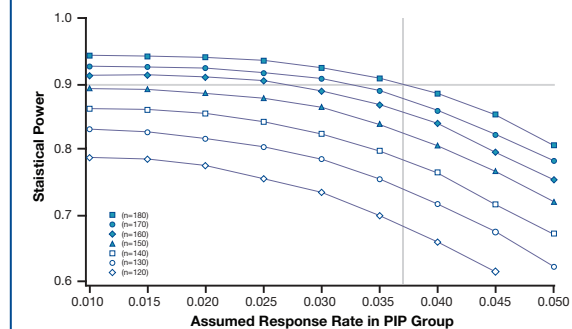


CIT=citalopram 40 mg once daily; ESR=early and sustained response; MADRS=Montgomery-Åsberg Depression Rating Scale; PNB01=pipamperone 5 mg twice daily + citalopram 40 mg once daily; * Fisher exact test (2-sided)

Power Analysis and Sample Size Estimation for Phase III Trial

- With an anticipated ESR rate of 14.5% for PNB01, the inclusion of 180 patients in each treatment arm is calculated to result in about 90% power to demonstrate a significantly superior ESR rate of PNB01 over both CIT and PIP alone (Figure 2).

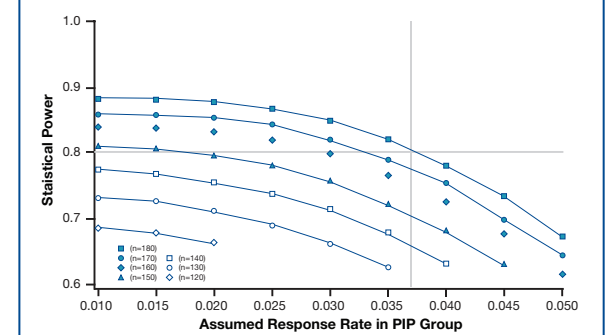
Figure 2. Sample Power Curve Considering a Fixed ESR Rate of 14.5% and 3.7% for PNB01 and CIT, Respectively



CIT=citalopram 40 mg once daily; ESR=early and sustained response; PIP=pipamperone; PNB01=pipamperone 5 mg twice daily + citalopram 40 mg once daily.

- With a somewhat lower expected ESR rate of 13.1%, still 80% power is available with 180 patients in each treatment arm (Figure 3).
- 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. Sample Power Curve Considering a Fixed ESR rate of 13.5% and 3.7% for PNB01 and CIT, Respectively



CIT=citalopram 40 mg once daily; ESR=early and sustained response; PIP=pipamperone; PNB01=pipamperone 5 mg twice daily + citalopram 40 mg once daily.

Conclusions

- The proposed definition of the ESR ($\geq 50\%$ decrease in MADRS TS and a total MADRS score of ≤ 16 at all visits between week 2 and week 6) has proven to potentially capture the speed of antidepressant response and also its maintenance over time.
- An increase of 50% in the ESR rate compared with a reference antidepressant can be considered as clinically relevant. From post hoc analyses with the phase II PNB01 data, the ESR rate of PNB01 doubled the one of CIT.
- Our findings indicate that the new ESR agreed definition is clinically relevant and thus can be advocated as a key primary endpoint in the phase III PNB01 pivotal trials, to be conducted with 185 patients per treatment arm.

Authors' Disclosures

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

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