Phase III Dose Selection for PNB01, a Novel Fixed-Dose Combination Antidepressant Inducing a Faster and Sustained Response

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Introduction

- Pipamperone (PIP) is a weak antipsychotic used at doses ranging from 80 to 360 mg/d for the treatment of schizophrenia in a number of European countries. At low doses (5–15 mg/d), PIP is a highly selective 5-HT2a and D4 receptor antagonist.[1]
- The fixed-dose combination of low-dose PIP and CIT (PNB01 or PIPCIT) will be used in this phase III pivotal trial.
- Dose finding based on clinical response is complex, particularly in disorders with risk for a high variability in the quantification of severity, like depression.
- An alternative powerful tool to select a dosing regimen for a phase III study is to use pharmacokinetic/pharmacodynamic (PK/PD) modelling and simulation analysis.[2]

Purpose of the Study

- To identify the potentially optimal dosing combination/regimen of PNB01 through the upcoming phase III pivotal trials using PK/PD modelling and simulation analyses

Methods

- We used the following resources:
  - Results from a POC study[3]
  - Results from a phase I receptor-binding occupancy (RO) study evaluated by means of positron emission tomography (PET) in healthy volunteers
  - Results from a phase I drug-drug interaction (DDI) study in healthy volunteers
  - Historical results (literature) obtained with PIP

POC study

- A proof-of-concept study (POC) in 165 depressed patients showed that addition of 5 mg PIP twice daily (BID) to 40 mg citalopram (CIT) once daily (QD) provided clinically relevant benefit over CIT treatment in terms of a superior rate of early and sustained responders.[3]
- Pipamperone was assayed in plasma at 0.5 and 2 h post-dose at Day 1 and at 0, 1 and 4 h post-dose at Day 28 (preferably at Day 29 or within 7 days after Day 28). Plasma samples were available from 46 patients receiving PIP.

PET study

- 10 healthy subjects received 1 of 4 different treatments with PIP: a single dose of 120 mg (n=2) and of 30 mg (n=2), 10 mg BID for 6.5 days (n=3), and 15 mg QD for 6.5 days (n=3).
- Central nervous RO was assessed by means of PET using a dynamic scanning technique. The specific tracer 11C-MDL100907 was used to assess 5-HT2a RO. D11C-raclopride was used to assess D2 RO. Three scans were made for each subject (including one baseline scan).
- Full PK profiles of PIP were determined in each subject.

PK/PD modelling and simulations combining the POC study and the PET study

- PK/PD modelling was performed to obtain a relationship between PIP plasma concentrations and 5-HT2a and D2 RO (using the software NONMEM). RO was estimated by the sigmoidal model: 100% x C/(C+EC_{50}), C being the estimated PIP plasma concentration at the mid-time of PET assessment and EC_{50} the PIP concentration corresponding to 50% of the maximum binding.
- 5HT2a and D2 RO were plotted against the predicted PIP plasma concentration by the model. These concentration-RO relationships were compared to the effective concentrations obtained in the POC study to obtain a target binding range.

Drug-drug interaction study

- In 3 consecutive sessions 12 healthy subjects randomly received 5 mg PIP BID (days 1–9 with an additional morning dose on day 10), 20 mg CIT BID (days 1–9 with an additional morning dose on day 10), or 5 mg PIP BID co-administered with 20 mg CIT BID (days 1–9 with an additional morning dose of 5 mg PIP and 20 mg CIT on day 10).
- Plasma concentrations of PIP and CIT were determined, and the PK of steady-state CIT and PIP alone were compared with the PK of these compounds when they were co-administered.

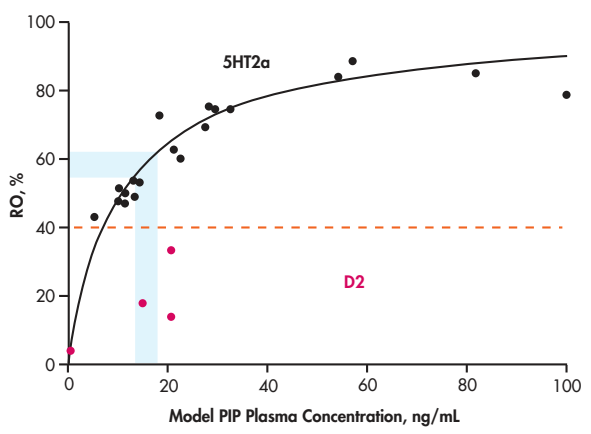
PK/PD modelling and simulations combining the POC study and the DDI study

- PK simulations were performed for 3 different dosing schedules for PIP (10 mg QD, 15 mg QD, and 5 mg BID) assuming 0%, 25%, and 45% increase, respectively, in plasma concentrations due to CIT interaction and compared with the observed mean concentrations in the POC study.

Results

PK/PD modelling and simulations combining the POC study and the PET study in healthy volunteers (Box 1 and Figure 1)

Figure 1. Observed and Predicted Plasma Concentration of PIP and Observed and Predicted RO of 5-HT2a and D2 Receptors



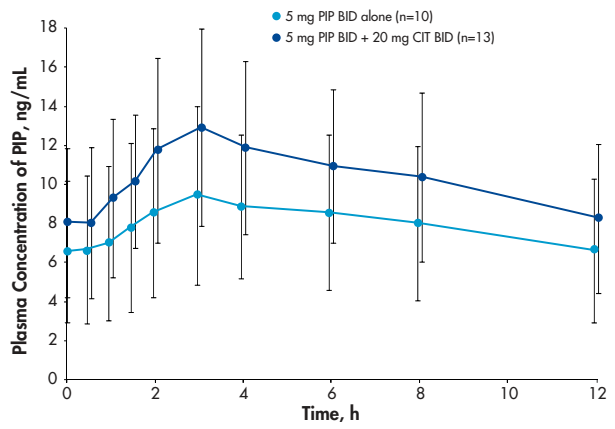
Black dots indicate observed 5HT2a receptor occupancy (RO) and observed plasma pipamperone (PIP) concentrations. Red dots indicate observed D2 RO and observed PIP concentrations. The blue shaded area indicates concentration-RO relationship corresponding to the effective dose of PIP in enhancing antidepressant effect of citalopram (CIT) in the proof-of-concept study (5 mg twice daily).[3] The dashed orange line indicates the % of RO at which effective D2 receptor starts.[4]

- The POC study showed that addition of PIP 5 mg BID to CIT 40 mg QD provided clinically relevant benefit over CIT treatment in terms of a superior rate of early sustained response.[3]
- The fitted dose-response model showed that, at this effective dose, mean binding to 5HT2a receptor at steady state fluctuated between 55% and 62%.
- In the PET study, the PIP 15 mg QD dosing mean steady-state plasma concentration fluctuated between 9.8 and 21 ng/mL, and the 5HT2a RO varied from 43.2%–75.2%. D2 receptor occupancy ranged from 4%–33% for PIP concentrations not exceeding 24.5 ng/mL.
- Based on our previous results and previous data reported in the literature, the low D2 RO is not expected to impact on effectiveness and adverse effects.
  - A PET study in schizophrenic patients treated with antipsychotics showed that effective D2 RO starts at around 40%.[4]
  - In the POC study, we did not observe additional adverse effects of PNB01 when compared with CIT alone.[3]

PK/PD modelling and simulations combining the POC study and the DDI study in healthy volunteers

- From the results that we obtained in the phase I DDI study performed in healthy volunteers, we learned that, after the administration of PIP at 5 mg BID in the presence of CIT at 20 mg BID, CIT increased the maximal PIP plasma concentration by 45% **(Figure 2)** and the area under the plasma concentration-time curve (AUC) with 42%.

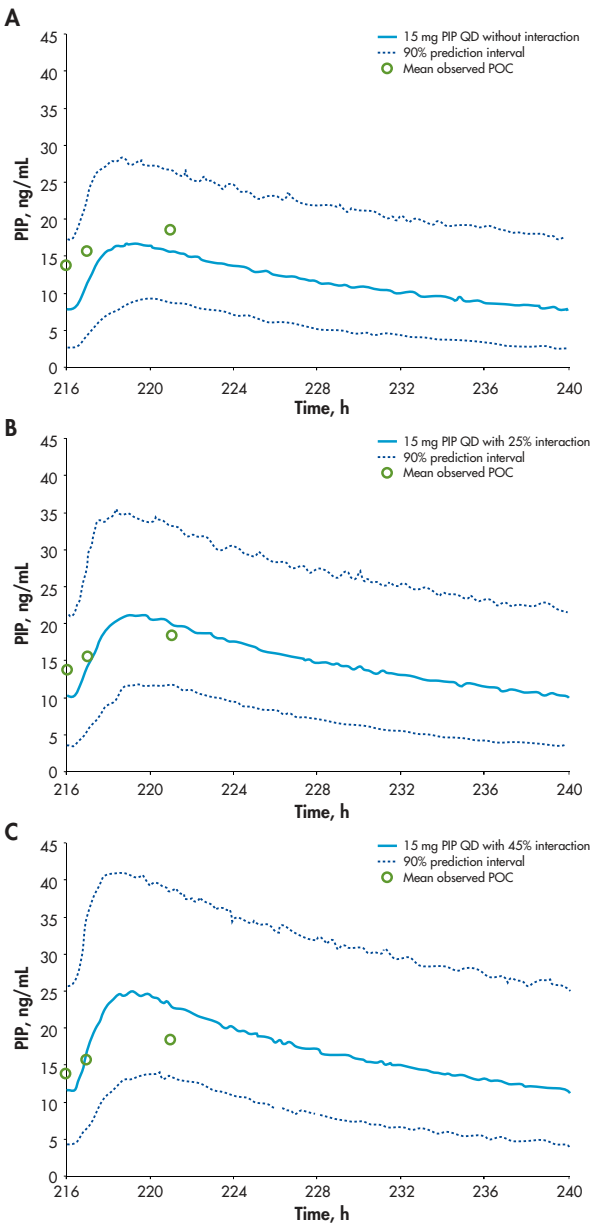
Figure 2. Mean Plasma Concentration-Time Curves of PIP (Including SD Bars) After Administration of PIP Alone at 5 mg BID or in Combination With CIT at 20 mg BID



BID=twice daily; CIT=citalopram; PIP=pipamperone.

- PK simulations assuming 0%, 25%, and 45% increase in plasma concentrations due to CIT interaction showed that the predicted plasma concentrations of PIP when given at a 15 mg QD dose were very close to the 5 mg BID effective dose in enhancing antidepressant effects of CIT in the POC study **(Figure 3)**.
- **Box 1** summarises the steps used to find the optimal PIP dose for the phase III pivotal trial of PNB01.

Figure 3. Plots of the PIP Predicted Concentration Profile vs Time Profiles in the Absence (A) or Presence of a 25% (B) or 45% (C) CIT Interaction

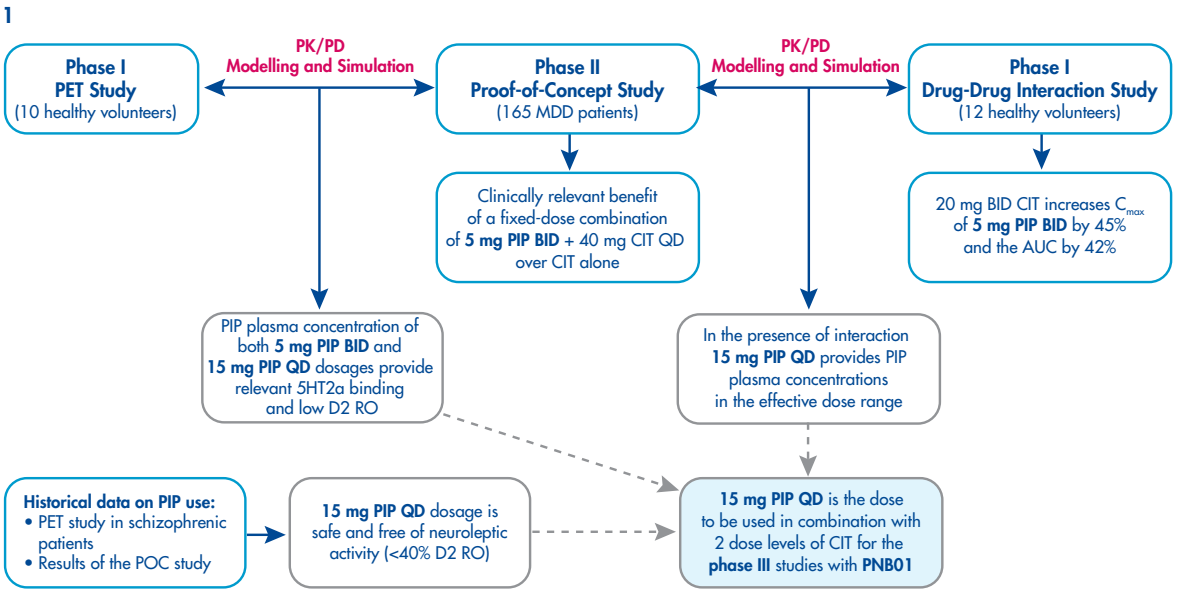


PIP=pipamperone; POC=proof-of-concept; QD=once daily.

Conclusions

- **We demonstrated that, through PK/PD modelling and simulation, the complex dosage schemes usually used for the development of a combination of drugs can be reduced to a few relevant dosages, accelerating the drug development process and reducing trial costs.**
- **To estimate the preferred dose of PIP to be used in the phase III PNB01 pivotal trial, we used PK/PD modelling and simulation combining the data obtained in a few well-designed independent phase I and phase II studies.**
- **15 mg QD PIP will be the preferred dose to be used in further phase III studies. This dose, that is slightly higher than the 5 mg BID dose used in the POC study, showed —over a period of 24 h— a relevant 5HT2a binding, a lack of clinically relevant D2 binding, and delivered PIP plasma levels in the effective dose range.**

Box 1



AUC= area under the plasma concentration-time curve; BID=twice daily; Cmax=maximal plasma concentration; CIT=citalopram; MDD=major depressive disorder; PET=positron emission tomography; PIP=pipamperone; POC=proof-of-concept; QD=once daily

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Author's Disclosures

Erik Buntinx is Chief Executive Officer and Managing Director of PharmaNeuroBoost and is also a shareholder in PharmaNeuroBoost. Kees Bol and Paul van den Berg are consultants to PharmaNeuroBoost. Ludo Haazen is consultant to and Chief Medical Officer in PharmaNeuroBoost. Remi van den Broeck is consultant to and Chief Development Officer in PharmaNeuroBoost. Didier de Chaffoy is consultant and Chief Scientific Officer in PharmaNeuroBoost.

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