

Introduction

Pipamperone (PIP) is a weak antipsychotic used at doses ranging from 80 to 360 mg/d for the treatment of schizoaffective disorder in a number of European countries. At low doses (15–45 mg/d), PIP is highly selective for D2 and D4 receptor antagonism.

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.

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.
- Results from a phase I DDI study in healthy volunteers.

PK/PD 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.

- Pipamperone was included in plasma at 0.3 and 2 h post-dose at Day 1 and at 1, 2, 4 h and post-dose at Day 2 (predominantly Day 29 or within 7 days after Day 28). Plasma samples were available from 66 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=1), 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 tracer 11C-dihydroxy-2-DOPA was used to assess SRT2A receptor. D111 raclopride was used to dose 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 SRT2A and D2 RO by using the software NONMEM-R. RO was estimated by the sigmoid-rectangular model: \( \frac{C_{\text{max}}}{C_{\text{EC50}}} \pm \text{(C+EC50)} \), C being the estimated PIP plasma concentration at the mid-time of PET assessment and EC50 the PIP concentration corresponding to 50% of the maximum binding.

- SRT2A 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, 5 mg PIP BID) 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 plasma 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.

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

Results

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

- The POC study showed that addition of 5 mg PIP to CIT 40 mg QD provided clinically relevant benefit over CIT treatment in terms of a superior rate of early sustained responders.

- The final dosing regimen model showed that, at this effective dose, mean binding to SRT2A receptor at steady state fluctuated between 55% and 62%.

- In the POC study, the PIP 15 mg QD dosing mean steady-state plasma concentrations fluctuated between 9.8 and 21 ng/mL and the SRT2A RO varied from 43%–73% QD. D2 receptor occupancy corresponding to 43%–53% 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 was not expected to impact on effectiveness and adverse effects.

- A PET study in schizophrenia patients treated with antipsychotics showed that effective D2 RO states at around 40%.

- In the POC study, we did not observe additional adverse effects of PNB01 when compared with CIT alone.

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 RO 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%.

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.

- 1.5 mg QD PIP will be 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 SRT2A binding, a lack of clinically relevant D2 binding, and delivered PIP plasma levels in the effective dose range.

References

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Author’s Disclosures

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