Accelerated antidepressant effect of pipamperone characterized by non-linear mixed effect model

(using a mixture model to differentiate between responders and non-responders)

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Background

Selective serotonin reuptake inhibitors (SSRIs) and other antidepressants are reported to require several weeks to achieve their full antidepressant effect. Accelerating this effect is considered to be a major medical need [i]. However, no consensus exists on how to best assess speed of antidepressant effect[ii] Pipamperone (PIP) is a mild neuroleptic that is under development by PharmaNeuroBoost as a fixed, low-dose combination with citalopram (CIT). The highly selective 5HT2A and D4 receptor blockade of low dose PIP is thought to accelerate the antidepressant effect of CIT. In the PIPCIT Clinical Trial Program the speed of effect of PIPCIT is assessed using newly developed endpoints.

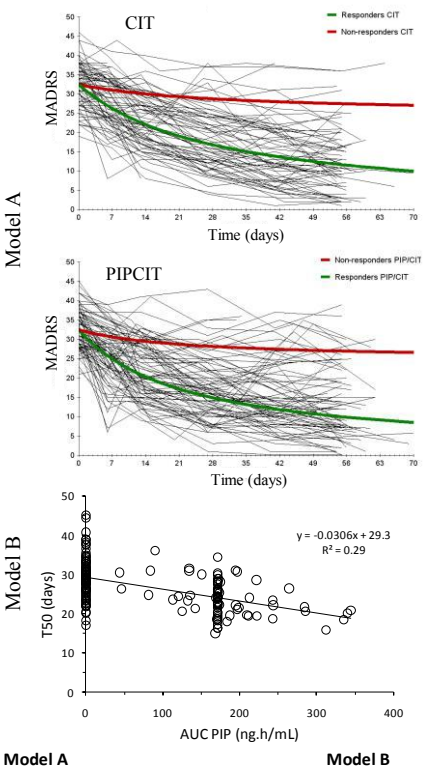
[i] Machado-Vieira et al. Rapid Onset of Antidepressant Action: A New Paradigm in the Research and Treatment of Major Depression. J Clin Psychiatry 2008: 69(6):946-958
[ii] Laska et al. Assessing Onset of Treatment Benefit in Depression and Anxiety: Conceptual Considerations. J Clin Psychiatry 2009: 70(8):1138-45

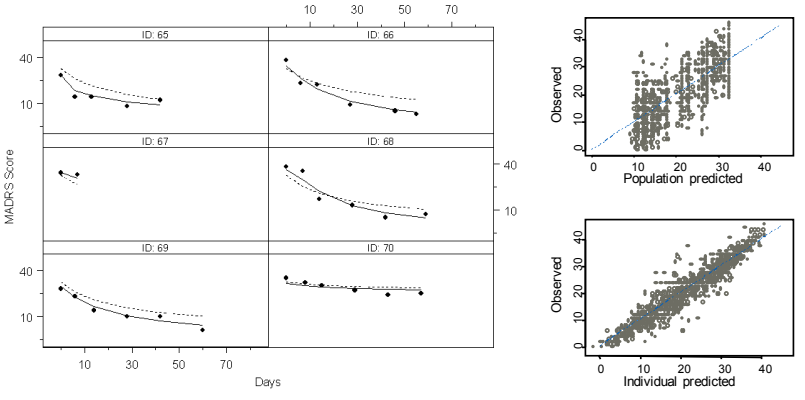
Methods

In an 8-week, randomized, double - blind Proof-of-Concept (POC) study CIT 40 mg daily plus PIP 5 mg twice daily (PIPCIT) was compared to CIT 40 mg daily in terms of magnitude and onset of therapeutic effect. It was conducted in 165 patients (CIT, n=82; PIPCIT, n=83) with major depressive disorder who had a mean MADRS score (Montgomery - Asberg Depression Rating Scale) of 32.6 (SD 5.5) at baseline. MADRS was assessed at baseline, week 1, 2, 4, 6 and 8 of treatment. Sparse plasma samples were taken in a PK subset of patients (n=45) to assay for concentrations of PIP and CIT. These data were combined with data from healthy subjects (n=12) receiving a single dose of 40 mg PIP. Nonlinear -mixed effects models were used to characterize the PK of PIP and the change in MADRS score (using NONMEM VI). A sigmoid E_{max} model was used to describe the change in MADRS with time as independent variable [iii]. T50 defined the time to reach 50% of the maximum decrease in total MADRS score (E_{max}). E_{max} was estimated as a fraction (α) of baseline (E_0). N described the steepness of the sigmoid. A mixture model for E_{max} was included in the final model to differentiate between responders and non-responders. The steady state AUC of PIP estimated for each patient in the PK subset was used as covariate. For patients without PK sampling AUC was set at the geometric mean (=171 ng.h/mL).

[iii] Gex-Fabry et al. Time course of response to paroxetine: Influence of plasma level. Progress in Neuro-Psych & Biol Psych 2007: 31: 892-900

Results





Plots. (Upper left) Population mean fits vs observed individual MADRS - time profiles; (Upper middle) Examples of individual data fits. Note population fit is represented by dashed line. ID 70 is non-responder; (Upper right) Observed vs population and individual predicted; (Lower left) T50 vs AUC PIP plasma.

Model A

	Parameter	Value	%CV
TH1	E0	32.4	1.35
TH2	α (resp.)	0.959	7.27
TH3	α (non-resp.)	0.174	44.4
TH4	T50 CIT	29.5	15.4
TH5	delta T50	-6.07	54
TH6	N	1 (FIX)	NA
TH7	fraction resp.	0.863	5.5
OM1	IIV E0	19.3	17.2
OM2	IIV α	0.0465	49.2
OM3	IIV T50	0.145	63.8
OM4	IIV N	0.239	28.5
SIGMA1	add. error	17.2	9.77

Model B

	Parameter	Value	%CV
TH1	E0	32.4	1.35
TH2	α (resp.)	0.959	7.26
TH3	α (non-resp.)	0.164	46.9
TH4	T50 CIT	29.3	15.3
TH5	slope AUC PIP	-0.0306	45.4
TH6	N	1 (FIX)	NA
TH7	fraction resp.	0.867	5.41
OM1	IIV E0	19.2	17.2
OM2	IIV α	0.0472	49.8
OM3	IIV T50	0.14	65.3
OM4	IIV N	0.237	28.9
SIGMA1	add. error	17.3	9.65

Discussion

Initially the data were fitted assuming the same T50 for patients treated with CIT or PIPCIT (=base model). Two alternative models were explored. Model A estimated the treatment effect of PIP by assessing the change in T50 of CIT. Model B assumed that T50 of CIT (=intercept) decreased linearly with increasing steady state exposure (AUC) of PIP . Both models described the data equally well. Model A estimated a reduction of 6 days in the T50 of CIT by the addition of PIP (drop in Minimum Value of the Objective Function (MVOF) of 3.53 points; p=0.06). Model B estimated a reduction of about 3 days in the T50 of CIT for every 100 units increase in AUC of PIP (drop in MVOF of 3.84 points; p=0.05). Although both improvements were borderline statistically significant (probably due to the small sample size of the POC), it suggests that the parameter T50 was able to demonstrate the accelerated antidepressant effect of PIPCIT compared to CIT alone. Furthermore, the results suggest that it is worthwhile to explore higher dose levels of PIP in subsequent trials to provide a further accelerated anti-depressant effect.

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The authors like to thank Eugene Cox (Quantitative Solutions) for his valuable suggestions and Martijn Ruppert (Kinesis-Pharma) for his contribution to this work.

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