How to Assess the Speed of Antidepressant Effect: Insights From the PIPCIT Clinical Trial Program

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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 effect is considered a major medical imperative,[3,4] but progress toward this objective is limited by the lack of consensus regarding how to best assess the speed of antidepressant effect.[3]
- Pipamperone (PIP) is a novel second-generation neuroleptic and high-affinity antagonist at 5-HT_{2A} and D_4 receptors[5]; PIP is under development with citalopram (CIT) as a fixed-dose combination (PIPCIT) for treatment of major depressive disorder (MDD).
- Low-dose PIP (5–15 mg/d) is predicted to accelerate the antidepressant effect of CIT via selective blockade of 5-HT_{2A} and D_4 receptors.
- In the PIPCIT clinical trial program, speed of effect is being assessed with newly developed endpoints.

Objective

- To assess the speed of antidepressant effect of PIPCIT using multiple new endpoints

Methods

Study Design

- Phase II multicenter clinical trial with randomized assignment to double-blind treatment with PIPCIT (CIT 40 mg once daily [QD] plus PIP 5 mg twice daily [BID]) or CIT 40 mg QD and placebo BID for 8 weeks
- The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice; all patients provided written informed consent.
- This report presents results from an analysis of select secondary endpoints and exploratory post hoc analyses assessing the speed of effect.

Main Inclusion Criteria

- Men and women aged 18–65 years with moderate to severe MDD as defined by the *Diagnostic and Statistical Manual, Fourth Edition,* and a current episode lasting 4–26 weeks
- Patients were required to have a Clinical Global Impression–Severity scale rating ≥4 and Hamilton Depression Scale ≥18 at screening and baseline.

Main Exclusion Criteria

- Significant risk of suicide as determined by the investigator, significant physical or other psychiatric illness that could undermine trial assessments, resistant depression, use of antidepressants or other psychotropic substances in past week, formal psychotherapy or alternative treatments in past week or during study, or electroconvulsive therapy during current episode

Treatment

- All patients initiated CIT at 20 mg QD for 1 week and were then force-titrated to CIT 40 mg QD with PIP 5 mg BID or placebo BID for 8 weeks; patients intolerant of CIT 40 mg were discontinued from the study.

Endpoints

- Change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total scores at weeks 1–8 (secondary trial endpoint)
- Early and sustained response (ESR), defined as ≥50% reduction in total MADRS score from baseline at weeks 2 and 4 (secondary trial endpoint), at weeks 2 and 6 (post hoc endpoint), and at weeks 2 and 8 (post hoc endpoint)
- T_{50}, defined as the time to reach 50% of the maximum decrease in total MADRS score, was identified by a nonlinear mixed-effect model that described the MADRS scores from the phase II study (post hoc endpoint). The treatment effect of PIP was assessed by a difference in T_{50} from the CIT group.
- Onset of action according to a cure-rate model[3] (ie, the proportion of patients who are permanently cured by a given treatment; post hoc endpoint)
  - For the cure-rate model, response was defined as a 50% decrease in MADRS total score and a Clinical Global Impression–severity score ≤2.

Statistical Analysis

- Analyses included
  - The intent-to-treat (ITT) population, which comprised all randomized patients
  - The per-protocol (PP) population, which comprised members of the ITT population who attended all study visits and exhibited ≥80% (PIP and placebo) or ≥70% (CIT) of expected dosing compliance
  - The population of severely depressed patients, defined as those with baseline MADRS total score ≥30
- Patients with missing data were assumed not to have ESR; all other data were imputed using last observation carried forward.
- Group differences in the changes in MADRS scores from baseline were compared using 2-sample *t* tests; differences in ESR were compared using the Fisher exact test (2-sided).
- For T_{50}, significance was set as a difference of 3.841 in the minimum value of the objective function (MVOF) with 1 degree of freedom ($P<0.05$).

Results

Patient Disposition

- 165 patients (CIT, n=82; PIPCIT, n=83) were randomized to treatment (ITT), 126 patients (CIT, n=62; PIPCIT, n=64) were included in the PP population, and 115 patients (CIT, n=58; PIPCIT, n=57) were considered severely depressed.
- 21 patients (26%) in the CIT group and 14 patients (17%) in the PIPCIT group discontinued the study, primarily because of loss to follow-up (CIT, n=8; PIPCIT, n=6) and unwillingness to continue (CIT, n=5; PIPCIT, n=2).
- 4 patients (5%) in the CIT group and 2 patients (2%) in the PIPCIT group discontinued because of an adverse event; 1 patient in the PIPCIT group discontinued because of lack of efficacy.

Patient Characteristics

- The treatment groups were similar in demographic and clinical characteristics **(Table 1)**.
- ≥77% of patients in each group were women, ≥99% were white, and mean age was 40 years.
- Mean duration of the current MDD episode was ≥94.8 days, and ≥69% had severe depression.

Table 1. Patient Demographics and Clinical Characteristics, ITT Population

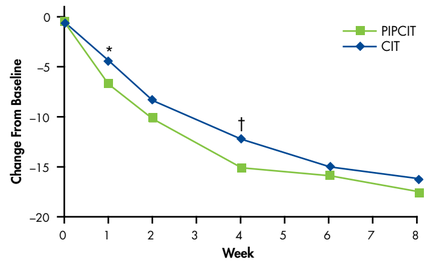
	CIT (n=82)	PIPCIT (n=83)
Mean (SD) age, y	39.7 (11.8)	40.1 (11.4)
Sex, n (%) Women	63 (77)	70 (84)
Race, n (%) White	82 (100)	82 (99)
Mean (SD) weight, kg	79.9 (23.7)	80.0 (22.2)
Mean (SD) duration current MDD episode, d n (%) with duration >12 wk	99.6 (43.1) 46 (56)	94.8 (37.7) 43 (52)
Mean (SD) MADRS total score n (%) with MADRS ≥30 (severe depression)	32.4 (5.9) 58 (71)	32.7 (5.1) 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; PIPCIT=pipamperone 5 mg twice daily + citalopram 40 mg once daily.

Montgomery-Asberg Depression Rating Scale Improvement

- Mean (SD) MADRS scores decreased during the 8 weeks of treatment from 32.4 (5.9) to 16.2 (11.1) for the CIT group and from 32.7 (5.1) to 15.2 (10.3) for the PIPCIT group **(Figure 1)**.
- There was significantly greater improvement in the PIPCIT group vs the CIT group at week 1 ($P=0.03$) and week 4 ($P=0.01$).

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

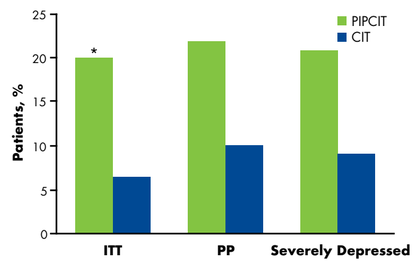


CIT=citalopram 40 mg once daily; ITT=intent to treat; LOCF=last observation carried forward; MADRS=Montgomery-Asberg Depression Rating Scale; PIPCIT=pipamperone 5 mg twice daily + citalopram 40 mg once daily.
*$P=0.03$ between groups.
†$P=0.01$ between groups.

Early and Sustained Response

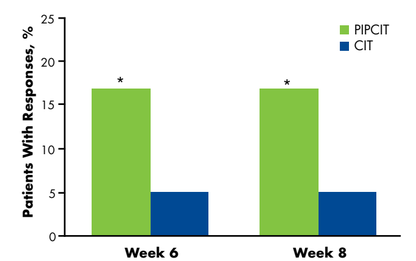
- In the ITT population, 7% (n=6/82) of the CIT group and 20% (n=17/83) of the PIPCIT group demonstrated ESR (≥50% reduction in MADRS total score at weeks 2 and 4; $P=0.02$; **Figure 2**).
- There were similar group differences in ESR rates (weeks 2 and 4) in the PP population (CIT, 10% [n=6/62]; PIPCIT, 22% [n=14/64]; $P=0.09$; **Figure 2**) and in the population of severely depressed patients (CIT, 9% [n=5/58]; PIPCIT, 21% [n=12/57]; $P=0.07$; **Figure 2**).
- PIPCIT was also associated with significantly higher percentages of early responders (week 2) with sustained response at week 6 (17% [n=14/83]) or 8 (17% [n=14/83]) compared with CIT (5% [n=4/82] and 5% [n=4/82], respectively; each $P=0.02$; **Figure 3**).

Figure 2. ESR Rates in the ITT, PP, and Severely Depressed Populations



CIT=citalopram 40 mg once daily; ESR=early and sustained response; ITT=intent to treat; PIPCIT=pipamperone 5 mg twice daily + citalopram 40 mg once daily; PP=per protocol.
*$P=0.02$ vs CIT.

Figure 3. Proportion Early Responders (Week 2) With Sustained Response at Week 6 or Week 8, ITT Population

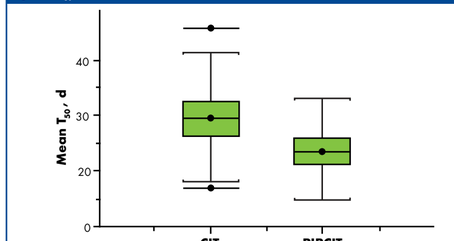


CIT=citalopram 40 mg once daily; ITT=intent to treat; PIPCIT=pipamperone 5 mg twice daily + citalopram 40 mg once daily.
*$P=0.02$ vs CIT.

Time to 50% of the Maximum Decrease in Total MADRS Score

- The model estimated that responders in the CIT group achieved T_{50} 6 days after responders in the PIPCIT group (reduction in MVOF of 3.53 points with PIPCIT; $P=0.06$; **Figure 4**).

Figure 4. T_{50} Values for PIPCIT and CIT



CIT=citalopram 40 mg once daily; PIPCIT=pipamperone 5 mg twice daily + citalopram 40 mg once daily; T_{50}=time to reach 50% of maximum decrease in Montgomery-Asberg Depression Rating Scale.
*Shown are the 95% CI (error bars) and 25%–75% CI (boxes); single dots represent outliers.

Cure-Rate Model

- Analysis of discrete observation times (based on visit number) indicated the presence of nonresponders in both the CIT and PIPCIT groups, and analysis of continuous observation times (based on actual date of assessment) indicated the presence of nonresponders in the PIPCIT group.
- However, because a considerable proportion of observations (CIT, 16% [n=13/82]; PIPCIT, 7% [n=6/83]) were censored before week 6 for lack of response during the study period, there were an inadequate number of observations at later time points for valid application of the cure-rate model.

Conclusions

- **Both T_{50} and ESR appear to be valid and informative approaches in assessing the speed of antidepressant response.**
- **The approaches are complementary, T_{50} being more sensitive and ESR being more clinically relevant.**
- **Although improvements with the nonlinear mixed-effects models were borderline statistically significant, use of T_{50} appeared to demonstrate an exposure-dependent accelerated antidepressant effect of PIPCIT compared with CIT alone.**
- **Our findings indicate that a cure model cannot be reliably applied to data with a limited follow-up time of 8 weeks.**
- **To assess the speed of antidepressant effect, ESR may be a clinically valuable primary or secondary endpoint in future clinical trials of antidepressant therapies.**

References

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