Sensitivity Analyses of PANSS Total Score Under Assumption of Missingness

To verify the impact of early dropouts on change in PANSS total score, two sensitivity analyses were conducted to explore the robustness of change from double-blind (DB) baseline and change from open-label (OL) baseline in PANSS total score.

One of these sensitivity analyses is based on multiple imputations (MI) using MMRM approach, and the other is based on a descriptive summary at each post-baseline timepoint using the last observation carried forward (LOCF) approach. The assumption that efficacy profiles of dropouts after discontinuation were similar between earlier dropouts and later dropouts or completers was considered conservative because this methodology tends to minimize the potential improvement in PANSS total score. The results per multiple imputations under the assumption of missing at random (MAR) is considered to be closer to the true estimation of drug effect since it avoids either over-estimating (per observed value) or under-estimating (per LOCF approach) the treatment effect.

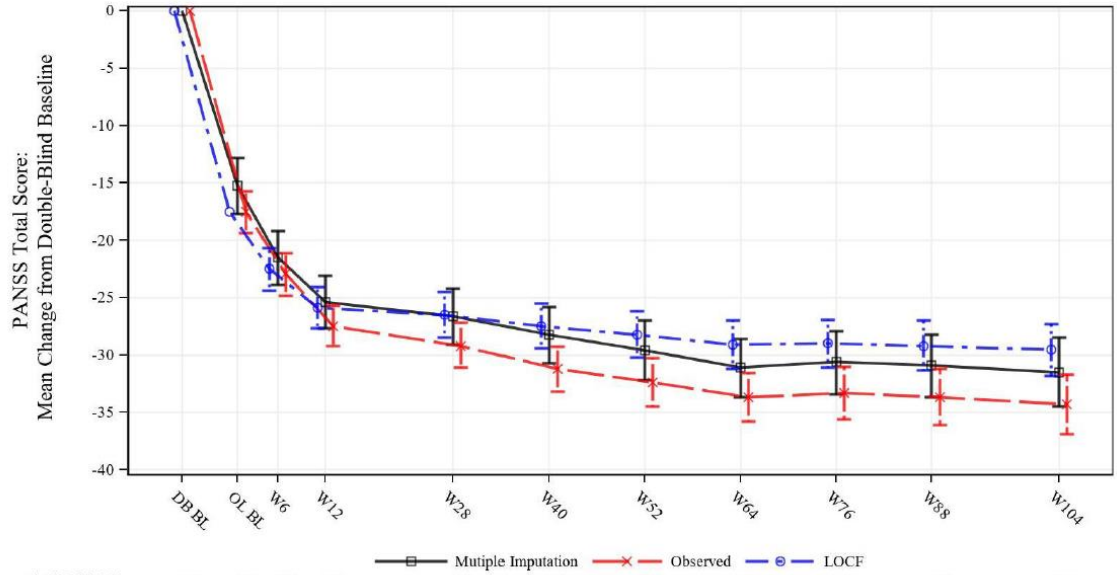
Mean [95% CI] changes from DB and OL Baseline in PANSS total score over time were examined. The results at Week 28, Week 53, and Week 104 are shown in **Table 1**.

Table 1. Mean [95% CI] Change in PANSS Total Score (Safety Population)

Time Point	Observed Case		Multiple Imputation		LOCF	
	Chg from DB BL	Chg from OL BL	Chg from DB BL	Chg from OL BL	Chg from DB BL	Chg from OL BL
Week 28	-29.2 (-31.1, -27.2)	-11.9 (-13.7, -10.0)	-26.6 (-29.1, -24.2)	-10.2 (-12.6, -7.7)	-26.5 (-28.5, -24.5)	-9.2 (-11.1, -7.2)
Week 52	-32.4 (-34.5, -30.3)	-15.6 (-17.8, -13.5)	-29.6 (-32.2, -27.0)	-13.1 (-15.9, -10.3)	-28.2 (-30.2, -26.2)	-10.8 (-13.0, -8.7)
Week 104	-34.3 (-36.9, -31.7)	-18.4 (-21.0, -15.7)	-31.5 (-34.5, -28.5)	-15.0 (-18.2, -11.8)	-29.5 (-31.8, -27.3)	-12.2 (-14.5, -9.8)

Mean [95% CI] changes in PANSS total score over time are shown in **Figure 1** for change relative to DB Baseline and in **Figure 2** for change relative to OL Baseline.

Figure 1. PANSS Total Score: Mean Change from DB Baseline (Observed, LOCF, vs. Multiple Imputation)

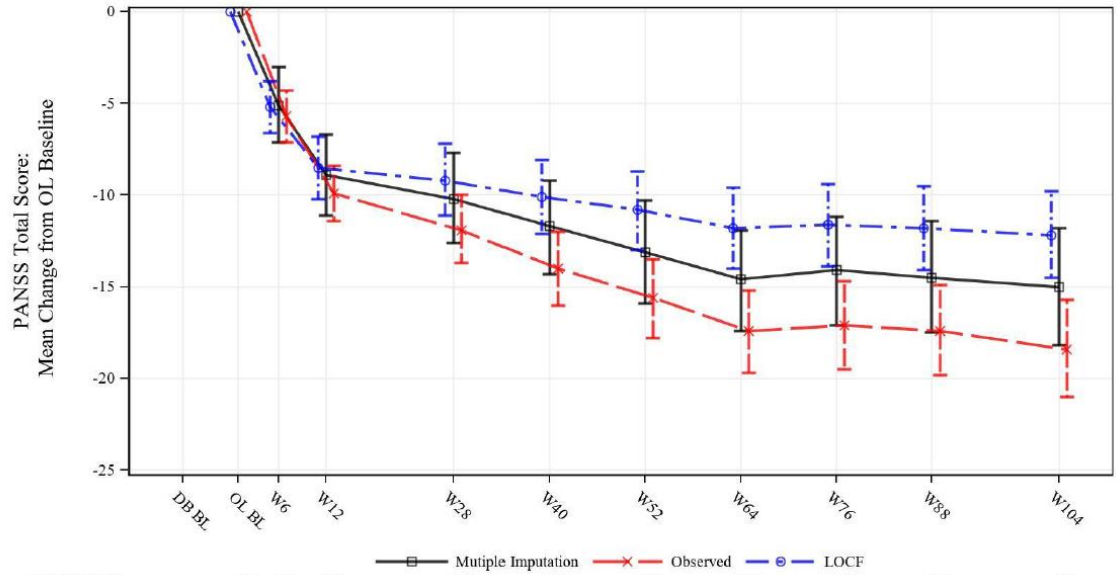


	DB BL	OL BL	W6	W12	W28	W40	W52	W64	W76	W88	W104
# of Subj: MI	271	271	271	271	271	271	271	271	271	271	271
# of Subj: Obs.	271	271	257	239	215	203	189	182	174	163	156
# of Subj: LOCF	271	271	265	267	267	267	267	267	267	267	267

Note: LS means and their 95% CIs from the MMRM model are displayed for multiple imputation approach.

Abbreviation: MI= multiple imputation approach; Obs= observed case; LOCF = last-observation carried forward.

Figure 2. PANSS Total Score: Mean Change from OL Baseline (Observed, LOCF, vs. Multiple Imputation)



	OL BL	W6	W12	W28	W40	W52	W64	W76	W88	W104
# of Subj: MI	271	271	271	271	271	271	271	271	271	271
# of Subj: Obs.	271	257	239	215	203	189	182	174	163	156
# of Subj: LOCF	271	265	267	267	267	267	267	267	267	267

At Week 104, mean [95% CI] change in PANSS total score from DB Baseline was -34.3 [-36.9, -31.7], -31.5 [-34.5, -28.5], and -29.5 [-31.8, -27.3] and mean [95% CI] change from OL Baseline was -18.4 (-21.0, -15.7), -15.0 (-18.2, -11.8), and -12.2 (-14.5, -9.8) for observed value, multiple imputation, and LOCF approach, respectively. Results from the three analysis approaches are generally consistent with each other, and all show consistent and clinically significant improvement over time. Nevertheless, a minor difference among the three approaches was observed in term of magnitude of treatment effect. LOCF results were the most conservative while the analyses based on observed values provided the most optimistic result. Overall, the result per multiple imputation under assumption of missing at random might be the most reasonable estimation of true treatment effect in this long-term study. Results for change from OL Baseline corroborate the above conclusions regarding the magnitude of treatment effect among these three approaches. Based on this summary, it can be confidently concluded that effectiveness in terms of PANSS total score was robust in the current study.