Pitolisant for Daytime Sleepiness in Obstructive Sleep Apnea Patients Refusing CPAP: A Randomized Trial

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Online Data Supplement

Additional analysis: Multiple Imputation of missing data

Missing data for the primary efficacy variable, the Epworth Sleepiness Scale (ESS), was imputed using the Last Observation Carried Forward (LOCF) method. Upon request of the reviewer an additional sensitivity analysis was performed, where missing data was allocated using Multiple Imputation (MI). The additional analysis was performed using SAS version 9.2.

Here, 10 datasets were created using the Markov chain Monte Carlo method (PROC MI). The considered variables in the imputation model were the Final ESS, the Baseline ESS, BMI at baseline, age and gender. The method was performed by treatment group. Then, the primary analysis was performed on each of the imputed datasets. The analysis included computation of the mean Final ESS and mean Change in Final ESS per treatment group. In addition, the effect of the treatment on the Final ESS was assessed using a mixed model, while correcting for BMI and ESS at baseline (PROC MIXED). The study center was included as a random factor. Finally, the results of the analyses were combined, providing a valid inference for the parameters (PROC MIANALYZE).

After MI, the mean final ESS score was 9.2 in the pitolisant group and 12.0 in the placebo group, with 95% Confidence Intervals equal to [8.6; 9.9] and [10.6; 13.4] respectively. The primary endpoint, namely the change in ESS from baseline to the end of the intervention was -6.5 (95% CI: [-7.1; -5.9]) in the pitolisant group and -3.7 (95% CI: [-5.0; -2.3]) in the placebo group. For both the Final ESS score and the Change in ESS the confidence intervals did not overlap, which indicates a significant difference between the arms. This was confirmed by the primary analysis, resulting in a significant treatment effect equal to -2.9 (95% CI: [-4.1; -1.7]) ($p<.0001$).

Table E1 and Table E2 compare the results of the analysis after MI with the results obtained after the LOCF method. It is evident that the choice of method to handle missing data has little impact due to the small number of missing values in this study, which was only 3.0% of the Final ESS data. In conclusion, this additional sensitivity analysis confirms the findings of the original analysis.

Table E1. Comparison of Final ESS and Change in ESS obtained after LOCF and MI. The mean and corresponding 95% CI are shown.

		LOCF	**MI**
Final ESS	Treatment	9.24 [8.78; 10.07]	9.23 [8.59; 9.88]
	Placebo	12.07 [10.67; 13.48]	11.99 [10.60; 13.38]
Change in ESS	Treatment	-6.29 [-6.92; -5.66]	-6.48 [-7.10; -5.85]
	Placebo	-3.58 [-4.92; -2.25]	-3.66 [-4.98; -2.35]

Table E2. Comparison of the estimated treatment effect adjusted for ESS and BMI at baseline after LOCF and MI. The mean and corresponding 95% CI are shown.

	LOCF	**MI**
Treatment effect	-2.8 [-4.0; -1.5]	-2.9 [-4.1; -1.7]

Table E3. Major Protocol Deviations in the Double-Blind Phase ITT Population (N=268)

Variable	Pitolisant (N=201)	Placebo (N=67)
Patients with at least one major protocol deviation	**9 (4.5%)**	**3 (4.5%)**
Treatment compliance < 80% at V3, V4, V5, or V6	7 (3.5%)	1 (1.5%)
ESS < 12 at V1 or V2	2 (1.0%)	1 (1.5%)
Abnormal ECG at V2	1 (0.5%)	0
Private hospital went bankrupt*	1 (0.5%)	0
Unauthorized medication	0	1 (1.5%)

Table E4. Amphetamine-like Withdrawal Symptoms – SAFETY Population (N=267)

	Pitolisant (N=200)			Placebo (N=67)		
Variable	PC6-7	V7	Post Treatment	PC6-7	V7	Post Treatment
Dysphoria Number with the symptom (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Fatigue Number with the symptom (%)	0 (0.0%)	1 (11.1%)	1 (11.1%)	1 (12.5%)	1 (11.1%)	1 (11.1%)
Increased appetite Number with the symptom (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (11.1%)	1 (11.1%)
Insomnia or hypersomnia Number with the symptom (%)	0 (0.0%)	1 (11.1%)	1 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Psychomotor retardation or agitation Number with the symptom (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (11.1%)	1 (11.1%)
Vivid and unpleasant dreams Number with the symptom (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Amphetamine-like withdrawal syndrome Number of patients (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

PC6-7= Phone Contact between V6 and V7.