Supplemental document 1 to:

Neurocognitive effect of biased μ-opioid receptor agonist oliceridine, a utility function analysis and comparison with morphine

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Supplemental document 2 to:

Neurocognitive effect of biased μ-opioid receptor agonist oliceridine, a utility function analysis and comparison with morphine

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Pharmacokinetic-pharmacodynamic analysis: methods and utility functions

Data fitting was done by a sequence of estimation steps: ITS (Iterative Two-Stage; to get initial estimates for SAEM), SAEM (Stochastic Approximation Expectation Maximization) for speed and less biased parameter estimates relative to FOCE, and IMP (Importance Sampling Expectation; to obtain standard errors). To avoid degenerate sampling by SAEM and non-positive-definite matrices at the IMP step, first inter-occasion variability parameters were explored, next shared variability parameters (for the three pharmacodynamic endpoints), and finally interindividual variability parameters were explored. Variances that were biased down to zero or had a more than 100% relative standard error (RSE) were set to zero or a small value of 0.01 to have efficient sampling for the SAEM method. For the pharmacokinetic models, both the parameterizations with volumes and clearances and with volumes and rate constants were performed.

Three types of data were analyzed simultaneously by the maximum likelihood method in NONMEM because of the assumed probability distribution for the latency data. The special reserved variable (CDF_L) was used to allow correct assessment of the normalized prediction discrepancies by NONMEM.

To account for uncertainties in the probability estimates, one sampling importance resampling step was performed after the Importance Sampling (IMP) step using NONMEM and the "table_resample" utility. 4,000 samples and 1,000 resamples were drawn.[1] The standard deviations of the samples for all parameters were compared with their standard errors from

the Importance Sampling (IMP) step to check their validity. Standard errors for derived parameters such as potency ratios, as well as pharmacokinetic parameter estimates for the volume of compartment 2 (V_2), clearance from compartment 1 (CL_1) and intercompartmental clearance CL_2, were also obtained using this approach. Finally, these samples were used to create 1,000 utility curves and to obtain confidence intervals for the typical utility curves. To get acceptable computation speed, the equations for the pharmacokinetic/ pharmacodynamic model were implemented in a custom-made C++ program with the output of the table_resample program as its input.

Reference

1. Dosne AG, Bergstrand M, Harling K, Kartlsson MO: Improving the estimation of parameter uncertainty distributions in nonlinear mixed effects models using sampling importance resampling. J Pharmacokinet Pharmacodyn 2016; 43:583-96