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Model-Based Drug Development: Optimization of AQUAVAN® Injection Dosing for Minimal-to-Moderate Sedation

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Oral Presentation: Applications

Background: AQUAVAN® (fospropofol disodium) Injection is a water-soluble prodrug of propofol being developed to induce minimal-to-moderate sedation for brief diagnostic and therapeutic procedures. Selection of an appropriate dosing regimen is important to provide sedation to the majority of patients while avoiding deep sedation. The AQUAVAN development program relied on predictive modeling and extensive simulation to guide dose selection. An earlier focus of the program was on selecting a dose that had a rapid onset of sedation, with the majority of patients becoming sedate with a single dose. Dosing in the first study in patients was chosen using the population PK/PD model developed on the healthy volunteers data [Ref 1,2,3]. Two studies in colonoscopy showed good efficacy and fast onset of sedation confirming the utility of the model. However, these studies demonstrated that patients were at deeper levels of sedation than desired. A population PK/PD model of the depth of sedation was developed using clinical measure of sedation from one of these studies (Study 1, n=153) [Ref 4], and was then validated with the data from the second study (n=207). This model became a major tool in shifting the focus of the program to a titration paradigm, selecting the dosing regimens, and design of a dose-ranging study in order to identify the optimal doses for Phase 3.

Methods: Simulations were performed to identify dosing regimens (initial bolus doses, supplemental doses and their timing, and weight adjustment of dosing) that would maximize % of sedated patients while minimizing instances of deep sedation and prolonged deep sedation in patients undergoing colonoscopy. For each dosing scenario, > 16000 patients were simulated; each patient created by the combination of a set of individual PK and PD parameters from a randomly chosen patient in Study 1 with a set of demographic characteristics from another randomly chosen patient in both colonoscopy studies. A Phase 2 pilot study was conducted to test the new dosing regimens and validate model predictions. After the successful completion of the pilot study, the same model was used for simulations of the planned Phase 3 studies.

Results: Simulations suggested the following dosing paradigm to balance efficacy and safety in sedation outcomes: weight-proportional dosing with boundaries at 60 and 90 kg (patients weighing < 60 or > 90 kg are dosed as 60 or 90 kg patients), initial doses of 5-8 mg/kg, and supplemental doses of 25% of the initial administered at 4 and 8 min. Pilot Phase 2 study results for 5-8 mg/kg dose groups showed excellent agreement with apriori simulations while sedation in the sub-therapeutic 2 mg/kg dose group was under-predicted. Simulations of the Phase 3 study demonstrated high probability of success and safety of the selected dosing regimens. Phase 3 studies are ongoing.

Conclusions: The model-based simulations optimized AQUAVAN dosing to provide safe and effective minimal-to-moderate sedation. An excellent agreement of a priori predictions with the sedation results of a model-based designed Phase 2 study added credibility to chosen dosing regimens, and provided confidence in the ability to predict AQUAVAN sedation outcomes in the Phase 3 program.

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