INTRODUCTION

Cebiranopadol is a novel first-in-class analgesic. It acts as a nociceptin/orphanin FQ peptide (NOP) and opioid peptide (OP) receptor agonist with central analgesic activity. Cebiranopadol is currently in clinical development for the treatment of chronic pain conditions.

A human abuse potential study was performed in accordance with the FDA Draft Guidance on Assessment of Abuse Potential of Drugs to evaluate the abuse potential of single doses of cebiranopadol (200, 400 and 800 μg), relative to hydromorphone immediate release (HMO IR) [8 and 16 mg] and placebo in non-dependent recreational opioid users. The primary endpoint for the abuse-related effects was Emx for drug liking “at this moment” measured using a Visual Analog Scale (VAS).

OBJECTIVE

To evaluate the potential correlation between cebiranopadol plasma concentrations and VAS rating for drug liking “at this moment” in comparison with HMO IR.

METHODS

The analysis of VAS for drug liking “at this moment” was performed for cebiranopadol and HMO IR. A total of 45 subjects (39 completers and 6 non-completers) were included. Three subjects were excluded due to major protocol violations. Drug liking “at this moment” was measured using a scale ranging from 0 (strongly dislike) to 100 (strongly like) and was recorded at 0.5, 1, 1.5, 2, 3, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 24, 36 and 56 hours post-dose for each treatment. Blood samples for PK were drawn pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 10, 12, 24, 36 and 56 hours post-dose for each treatment.

A two-compartment model previously developed for cebiranopadol using data from Phase I and Phase II studies was updated using PK data from this study. The pharmacokinetic model was re-run using the PK dataset from this study and the model parameters were re-estimated.

Two PK/PD models for VAS scores for drug likeing “at this moment” were implemented separately for cebiranopadol and HMO IR. Given the distribution of the data, VAS for drug liking “at this moment” was treated as an ordered categorical variable and was binned in three categories:

- VAS score <40: Category 0 - drug disliking
- VAS score >=40 and <=60: Category 1 - placebo range
- VAS score >60: Category 2 - drug liking

The final PK/PD models for HMO IR and cebiranopadol were logit models in which the drug effect was described using an Emax model with Hill coefficient. In order to facilitate the minimization, the parameter describing the placebo effect was assumed to be equal to the maximum drug effect (Emax). For HMO IR, an effect compartment described the delay between dose administration and effect. Inter-individual variability was to be estimated on the parameter for population mean baseline logit probability 2 to have a VAS score >40 and <60 in both models. The final parameter estimates for both models are presented in Table 1.

RESULTS

The mean profile of VAS scores for drug liking “at this moment” versus time is shown in Figure 1. Initially the VAS scores were grouped in 10 categories (Figure 2 left panel) but since with this categorization the amount of information available for some categories was very limited, the VAS scores were grouped in 3 categories (Figure 2 right panel).

The final PK/PD models for HMO IR and cebiranopadol were based on logit models in which the drug effect was described using an Emax model with Hill coefficient. In order to facilitate the minimization, the parameter describing the placebo effect was assumed to be equal to the maximum drug effect (Emax). For HMO IR, an effect compartment described the delay between dose administration and effect. Inter-individual variability was to be estimated on the parameter for population mean baseline logit probability 2 to have a VAS score >40 and <60 in both models. The final parameter estimates for both models are presented in Table 1.

The two models were validated by means of bootstrap (n=300) and visual predictive check (Figure 3).

The validated models were used to predict the mean time varying probability to have a VAS score higher than 60 after the administration of placebo, cebiranopadol 200 μg, 400 μg, 800 μg, and 1600 μg, HMO IR 8 mg and 16 mg and to predict which hypothetical dose of cebiranopadol could lead to comparable effect as the two doses of HMO IR investigated during this study (Figure 4).

CONCLUSIONS

VAS for drug liking “at this moment” was considered as an ordered categorical variable. A logit model fitted adequately the binned VAS score for both cebiranopadol and HMO IR and an Emax model was selected to describe the drug effect for both drugs.

Based on simulations, a dose of cebiranopadol higher than the dose considered as limit of the good tolerability as single dose (800 μg) and as repeated dose administration after titration (1600 μg) would need to be investigated to approach the same maximum probability of having a VAS score higher than 60 as shown by HMO IR 8 mg and this value would be reached approximately 5 hours later for cebiranopadol than for HMO IR.

Our investigation shows that modelling and simulation could successfully support the evaluation of abuse potential.

References

3. NONMEM 7.2 Available at: http://www.iconplc.com/technology/products/nonmem/