A NOVEL MODEL-BASED METHODOLOGY FOR THE EVALUATION OF ABUSE POTENTIAL

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INTRODUCTION

- Cebranopadol 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. Cebranopadol is currently in clinical development for the treatment of chronic pain conditions.

- A human abuse potential study[1] was performed in accordance with the FDA Draft Guidance on Assessment of Abuse Potential of Drugs[2] to evaluate the abuse potential of single doses of cebranopadol (200, 400 and 800 µg) relative to hydromorphone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 Emax for drug liking "at this moment" measured using a Visual Analogue Scale (VAS).

OBJECTIVE

To evaluate the potential correlation between cebranopadol 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 cebranopadol 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 cebranopadol 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 liking "at this moment" were implemented separately for cebranopadol 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 probability to observe each specific VAS score value was modeled using a logit model as a function of drug exposure according to the equation:

$$logit[P(VAS_{ij} \leq m)] = \sum_{k=0}^{m} \beta_k + \theta_{PLC} + f_d(C_{ij}) + \eta_i$$

Where:

- VAS_{ij} = VAS score for subject i at time j
- θ_{PLC} = Placebo effect
- $P(VAS_{ij} \leq m)$ = probability that the VAS score, VAS_{ij}, for subject i at time j is ≤ m (m ϵ [0,2))
- $f_d(C_{ij})$ = drug effect with C_{ij} = plasma concentration for subject i at time j
- β_k = population mean baseline logit probability
- η_i = inter-individual random effect
- logit(p) = log(p/(1-p))

- The functional form describing the relationship between drug exposure and VAS score was a sigmoid Emax function as described in the equation:

$$DrugEffect = \frac{Emax * C_{ij}^{\gamma}}{EC_{50}^{\gamma} + C_{ij}^{\gamma}}$$

Where:

- Drug Effect is the drug effect for either cebranopadol or HMO IR in terms of drug liking
- Emax is the maximal cebranopadol or HMO IR effect in terms of maximum drug liking
- C_{ij} is the plasma concentration for subject i at time j
- EC_{50} is plasma concentration associated with 50% of the maximal effect.
- γ is the Hill coefficient

- After model validation, simulations were performed using the PK and PK/PD models to identify the doses of cebranopadol leading to comparable drug liking as HMO IR.

- All model evaluations in these analyses were performed using NONMEM[3] Version 7.2. R Version 3.0.1 was used for dataset creation and exploratory and diagnostic plots.

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); 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).

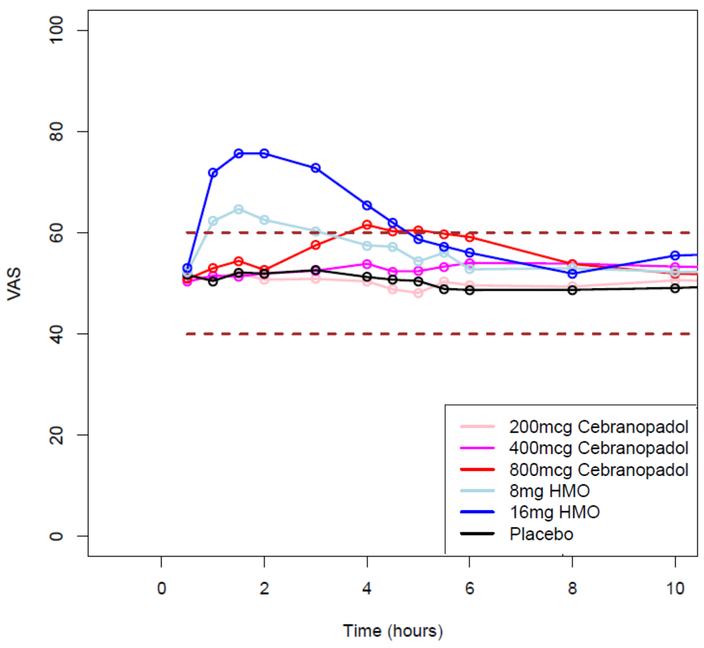

Figure 1 Mean curves for VAS drug liking "at this moment" vs. time up to 10 hours stratified by treatment. The dashed lines indicate the placebo range

- The final PK/PD models for HMO IR and cebranopadol 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 HMO IR exposure and effect. Inter-individual variability could 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, cebranopadol 200 µg, 400 µg, and 800 µg, HMO IR 8 mg and 16 mg and to predict which hypothetical dose of cebranopadol could lead to comparable effect as the two doses of HMO IR investigated during this study (Figure 4).

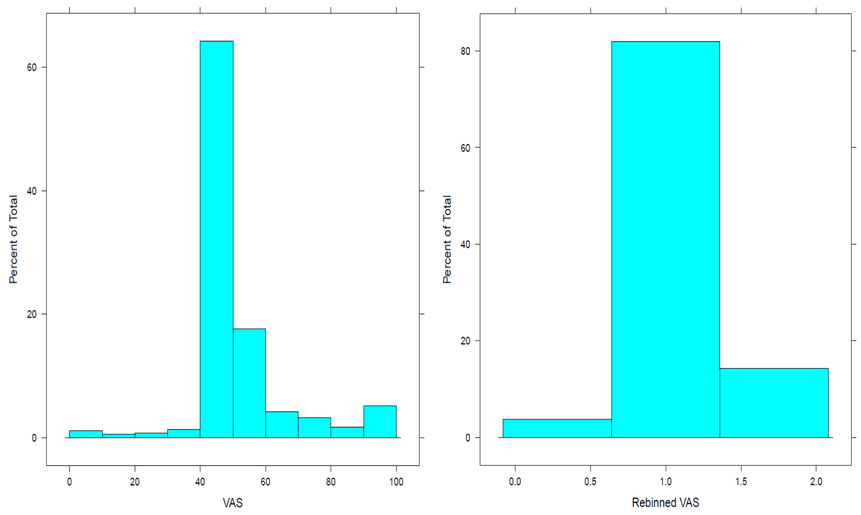

Figure 2 Histogram of VAS for drug liking "at this moment" for all the treatments grouped in 10 categories (left) and in 3 categories (right)

Hydromorphone			Cebranopadol		
Parameter	**Estimate (RSE)**	**Median Bootstrap (90%CI)**	**Parameter**	**Estimate (RSE)**	**Median Bootstrap (90%CI)**
Ke0 (1/h) (delay rate constant)	1.33 (0.5 h) (22%)	1.30 (0.96-2.17)	Ke0 (1/h) (delay rate constant)	-	-
EC_{50}(ng/ml)	2.01 (45%)	2.10 (1.33-25.47)	EC_{50}(ng/ml)	0.27 (28%)	0.25 (0.16-0.83)
γ (Hill coefficient)	1.43 (45%)	1.43 (0.73-3.21)	γ (Hill coefficient)	3.04 (51%)	3.39 (1.51-14.36)
EMAX	6.13 (38%)	6.37 (3.96-25.36)	EMAX	3.68 (46%)	3.58 (1.76-13.48)
Baseline 1	-9.07 (27%)	-9.39 (-28.83- -6.72)	Baseline 1	-7.24 (24%)	-7.19 (-16.90- -5.25)
Baseline 2	5.72 (11%)	5.75 (4.81-7.02)	Baseline 2	7.27 (10%)	7.23 (6.16-8.70)
Inter-individual variability on Baseline 2	0.121 (17%)	0.116 (0.062-0.198)	Inter-individual variability on Baseline 2	0.131 (23%)	0.116 (0.043-0.253)
Residual error	1.54 (16%)	1.44 (0.80-2.61)	Residual error	0.899 (22%)	0.805 (0.249-1.598)

Table 1 Final parameter estimates for hydromorphone and cebranopadol final PK/PD models

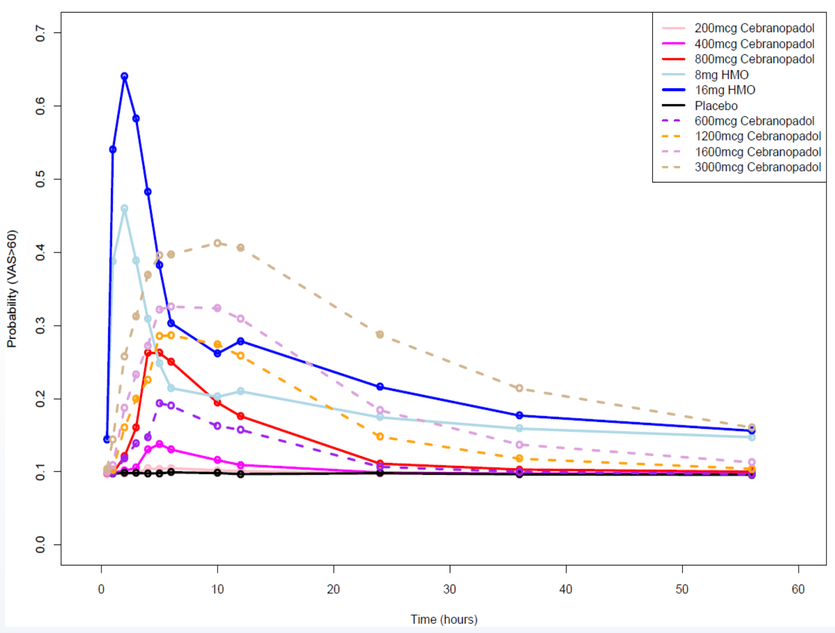

Figure 4 Probability to have a VAS score higher than 60 (drug liking "at this moment") for the treatments administered during the study (solid lines) and for different hypothetical cebranopadol doses (dashed lines)

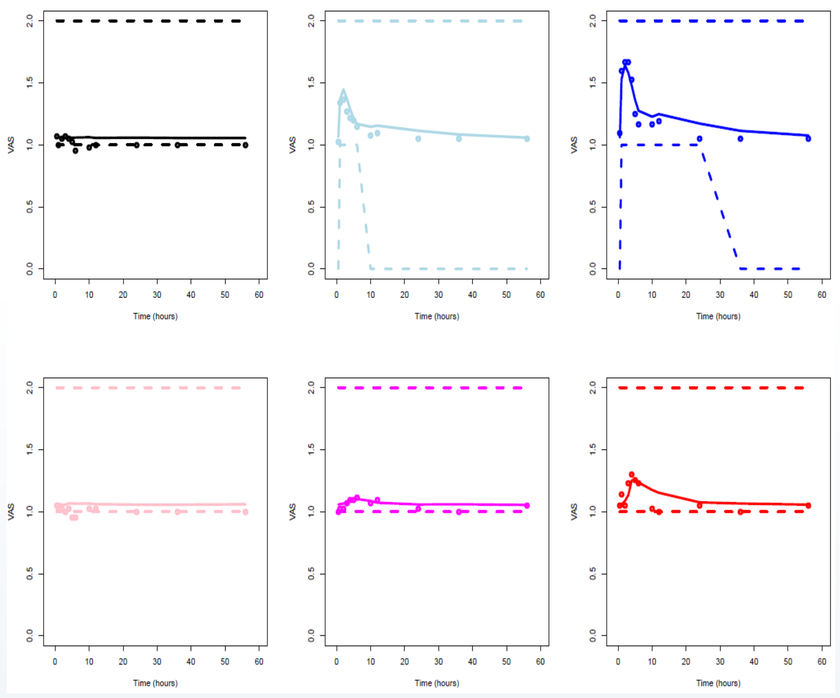

Figure 3 Visual predictive check of the PK/PD models for VAS for drug liking "at this moment" stratified by treatment (colors for treatment as given in Figure 4)

CONCLUSIONS

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

- Based on simulations, a dose of cebranopadol 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 administered 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 cebranopadol than for HMO IR .

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

References

1. Poster presented at the 8th World Congress, World Institute of Pain, New York, USA, 20-23 May 2016, WIP16-0480.
2. Food and Drug Administration Guidance for Industry. Assessment of Abuse Potential of Drugs. Draft guidance, January 2010.
3. NONMEM 7.2 Available at: http://www.iconplc.com/technology/products/nonmem/