The Bradykinin Challenge Model In Non-Human Primates Successfully Predicted Efficacious Doses of Deucrictibant in Humans

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Introduction

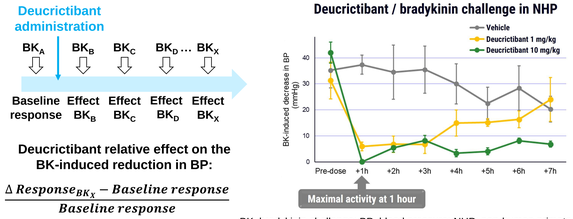
- Deucrictibant is an orally bioavailable competitive antagonist of the bradykinin B2 receptor in clinical development for prophylaxis and on-demand treatment of hereditary angioedema (HAE) attacks [1-3].
- During its preclinical development, the ability of deucrictibant to inhibit bradykinin (BK)-induced reduction in blood pressure (BP) via antagonism of bradykinin B2 receptor activity was assessed in a BK challenge model in monkeys [1].
- In this study,
  - the pharmacokinetic/pharmacodynamic (PK/PD) relationship was established in monkeys, and the predictivity of the monkey PK/PD to humans was explored
  - post-hoc predictions of human PK and efficacious doses of deucrictibant in HAE patients were performed based on solely preclinical data
  - these predictions were compared with clinical data from Phase 1 trials and Phase 2 trials for prophylactic and on-demand treatment of HAE attacks.

Materials & Methods – BK Challenge Model in Monkeys

BK challenge model in cynomolgus monkeys

- BK was administered intravenously to freely moving cynomolgus monkeys to elicit a baseline, transient reduction in BP (~30 to 40 mmHg). Oral deucrictibant was then administered at 5 dose levels, and the reduction in BP after repeated BK challenges was measured by telemetry.
- The difference in BP reduction before and after deucrictibant administration was used to compute the % change in BP vs. pre-dose (Figure 1).
- The PK/PD relationship was established using PK data from a satellite study in monkeys, and quantified using a maximal effect model with R software (v4.2.2) and the DoseFinding (v1.0.5) package.

Figure 1. BK challenge pharmacodynamic endpoint



BK: bradykinin challenge; BP: blood pressure; NHP: non-human primate

Materials & Methods – PK Analysis and Human Predictions

Prediction of human PK

- A one-compartment first-order elimination PK model model was constructed based on in vitro data and animal PK data. Human PK parameters (clearance, volume of distribution, absorption rate, oral bioavailability) were estimated to provide predictions of the PK profile in humans.

Prediction of efficacious dose range in humans for HAE

- The human EC_{50} and EC_{85} were derived from the monkey BK challenge.
- The predicted human EC_{50} and EC_{85} were compared to those observed in a BK challenge in healthy human participants [4].
- Human dosing regimens that would cover the EC_{50} or EC_{85} for 20-24 hours (prophylactic treatment) and 5-10 hours (on-demand treatment) were predicted.
- The predicted human doses were compared to efficacious doses observed in prophylactic and on-demand Phase 2 HAE clinical trials [2-3].

Results

BK challenge model in cynomolgus monkeys

- A robust PK/PD relationship was shown in monkeys (Figure 2).
- The scaled human EC_{50} and EC_{85} were comparable to those derived from a BK challenge model in healthy human participants [4] (Table 1).

Figure 2. PK/PD relationship of deucrictibant in the BK challenge model in monkey

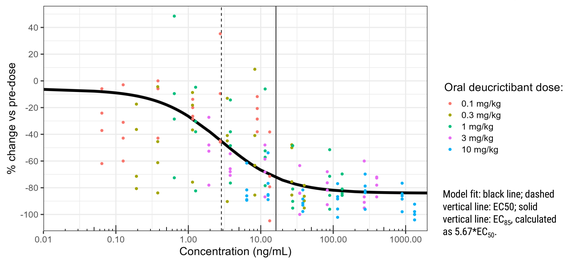


Table 1. Monkey PK/PD model parameters and scaled vs. observed human EC_{50} and EC_{85}

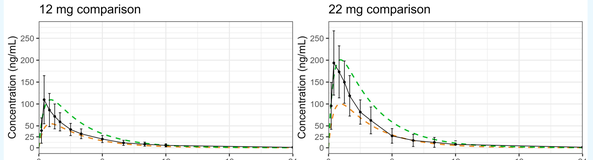
Cynomolgus monkey			Predicted human levels		Observed human levels (healthy participants)		
E_{MAX} (%)	EC_{50} (ng/mL)	EC_{85} (ng/mL)	EC_{50} (ng/mL)	EC_{85} (ng/mL)	E_{MAX} (%)	EC_{50} (ng/mL)	EC_{85} (ng/mL)
-78 ± 4	2.9 ± 0.7	16.2	3.5 ± 0.9	20.1	-74 ± 3	2.4 ± 0.6	13.8

Results

Prediction of human PK

- Predictions of the PK of deucrictibant in humans based on an assumed range of bioavailabilities (F) between 30-60% provided globally accurate prediction of the PK data in human Phase 1 trials at doses of 12 and 22 mg [4] (Figure 3).
- The rapid absorption in humans was slightly underestimated in the PK model.

Figure 3. Human PK predictions based on preclinical data versus observed clinical PK



Observed values present mean ± standard deviation. F: estimated oral bioavailability

Prediction of efficacious doses for prophylaxis of HAE attacks

- Steady-state simulations of dosing with 10 or 20 mg twice daily (BID) in humans were performed (Figure 4A) to estimate the time spent above the predicted EC_{50} and EC_{85}.
- Both dose levels were predicted to elicit concentrations above the EC_{50} and EC_{85} for up to 24 hours (Table 2), in line with efficacy observed at such dose levels in Phase 2 HAE clinical trial CHAPTER-1 [3].

Table 2. Predicted daily time above PK/PD target for deucrictibant at steady-state based on nonclinical projections

PK/PD target	Predicted time > target at 10 mg BID	Predicted time > target at 20 mg BID
Predicted EC_{50}	22 – 24 h	24 h
Predicted EC_{85}	9 – 17 h	14 – 19 h

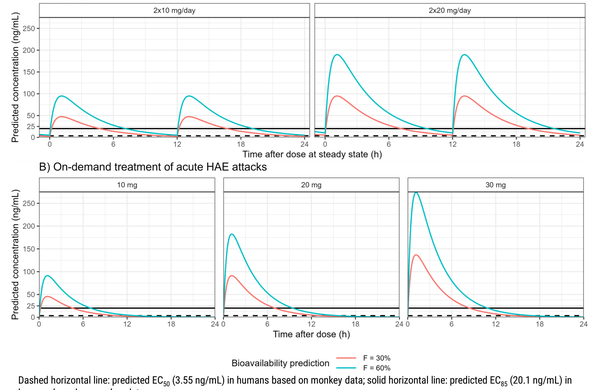
Predicted time > target are based on a range of estimated bioavailabilites between 30 and 60%

Prediction of efficacious doses for on-demand treatment of HAE attacks

- PK predictions suggested doses of 10 to 30 mg deucrictibant would quickly reach efficacious levels and exceed the scaled human EC_{50} for 11 to 17 hours and the EC_{85} for 4 to 11 hours in humans (Figure 4B).
- The same dose levels were found to be effective in treating HAE attacks in on-demand Phase 2 HAE clinical trial RAPIDe-1 [2].

Results

Figure 4. Human PK predictions of the deucrictibant efficacious dose levels based on preclinical data for (A) prophylaxis and (B) on-demand treatment of HAE attacks



Dashed horizontal line: predicted EC_{50} (3.55 ng/mL) in humans based on monkey data; solid horizontal line: predicted EC_{85} (20.1 ng/mL) in humans based on monkey data

Conclusions

- **The BK challenge model in monkey accurately predicted human PK/PD of deucrictibant.**
- **Post-hoc predictions of human PK based solely on preclinical data were close to the observed clinical PK data of deucrictibant.**
- **Efficacious doses of deucrictibant in HAE trials were well predicted, both for prophylaxis and on-demand treatment of HAE attacks.**
- **The BK challenge in monkeys could be used as a surrogate model to predict human efficacious doses for bradykinin B2 receptor antagonists in HAE.**

References

1. A. Lesage et al. PHA-022121, a first in class oral bradykinin B2 receptor antagonist in clinical development: Proof of concept study in a translational monkey bradykinin challenge model. JACI 145: AB346 (2020). **2.** M. Maurer et al. Efficacy and safety of bradykinin B2 receptor inhibition with oral PHVS416 in treating hereditary angioedema attacks: results of RAPIDe-1 phase 2 trial. JACI 151: AB134 (2023). **3.** M. Riedel et al. Efficacy and safety of bradykinin B2 receptor antagonism with oral deucrictibant in prophylaxis of hereditary angioedema attacks: results of CHAPTER-1 phase 2 trial. JACI 153: AB11 (2024). **4.** H. Derendorf et al. Bradykinin challenge provides surrogate endpoints for hereditary angioedema treatment using bradykinin B2 receptor antagonists. AAAI 125: P151 (2020).

This presentation includes data for an investigational product not yet approved by regulatory authorities.

JB, MJVE, PL: employees of Pharvaris, hold stocks/stock options in Pharvaris. **BL**: consultant to Pharvaris, holds stocks/stock options in Pharvaris. **JK**: employee of JCK Consult and consultant to Pharvaris, holds stocks/stock options in Pharvaris. **CG**: employee of AnalytiCon Discovery, holds stocks/stock options in Pharvaris. **AL**: employee of GrayMatters Consulting and consultant to Pharvaris, holds stocks/stock options in Pharvaris; advisor to Kosa Pharma.

RAPIDe-1 and CHAPTER-1 are Pharvaris-sponsored clinical trials. ClinicalTrials.gov identifiers: NCT04618211 and NCT05047185.