The NHP Bradykinin Challenge Model Predicts Human Deucrictibant Efficacious Doses

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Key takeaways

- The BK-challenge model in non-human primates (NHP) successfully predicted deucrictibant PK/PD in humans.
- Post-hoc predictions of human PK based solely on preclinical data were close to the observed clinical PK data of deucrictibant.
- Combining PK and PK/PD predictions provided predictions of time above efficacy exposure targets in humans consistent with clinical efficacy observed in Phase 2 clinical trials for prophylactic and on-demand treatment of hereditary angioedema (HAE) attacks.
- The BK challenge in NHP could be used as a surrogate model to predict human efficacious doses for bradykinin B2 receptor antagonists in HAE.

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

Introduction

- Deucrictibant is an orally bioavailable competitive antagonist of the bradykinin B2 receptor in clinical development for prophylaxis and on-demand treatment of bradykinin-mediated angioedema attacks, including Hereditary Angioedema (HAE) [1-5].
- 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 non-human primates (NHP) [6].
- The pharmacokinetic/pharmacodynamic (PK/PD) relationship was quantified and the translational predictivity of the BK-challenge model in NHP was investigated.

Objective

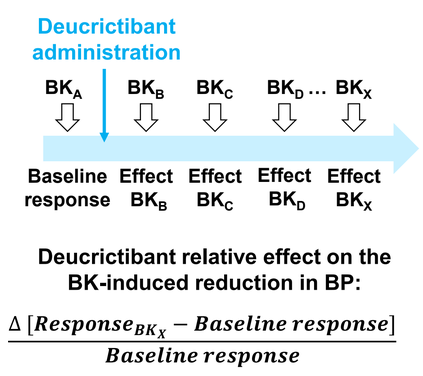
- Estimate the PK/PD relationship of deucrictibant in NHP and compare with its potency estimates in the BK-challenge in humans.
- Perform post-hoc predictions of deucrictibant human PK based solely on preclinical data and compare with clinical PK.
- Predict time above the plasma concentrations corresponding to 50% (EC_{50}) and 85 % (EC_{85}) of the maximum pharmacodynamic effect for deucrictibant at the dose levels investigated in prophylactic and on-demand Phase 2 studies in HAE patients.

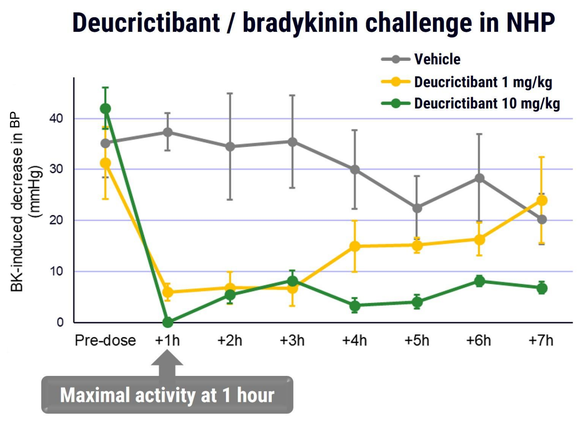
Methods

BK-challenge model in NHP

- 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 (0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, and 10 mg/kg), and the reduction in BP after repeated BK challenges was measured by telemetry.
- The difference in BP reduction during the BK challenges before and after deucrictibant administration was used to compute the % change in BP from pre-dose.
- Figure 1 provides information on the setup of the experiment, the calculation of the BK-induced reduction in BP, and provides the deucrictibant-mediated effect on BK-induced decrease in BP over time for two of the five dose levels of deucrictibant tested.
- The PK/PD relationship was established using PK data from a satellite study in NHP, and the relationship was quantified using a maximal effect model with R software (v4.2.2) and the nlme (v3.1.160) package.
  - The human EC_{50} and EC_{85} were derived from the NHP BK-challenge relationship following scaling by the protein binding in plasma.
  - The predicted human EC_{50} and EC_{85} were compared to those observed in a BK challenge study in healthy human participants [9].

Figure 1. BK challenge pharmacodynamic endpoint





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

Prediction of human PK and simulation of time above exposure targets (EC_{50} and EC_{85})

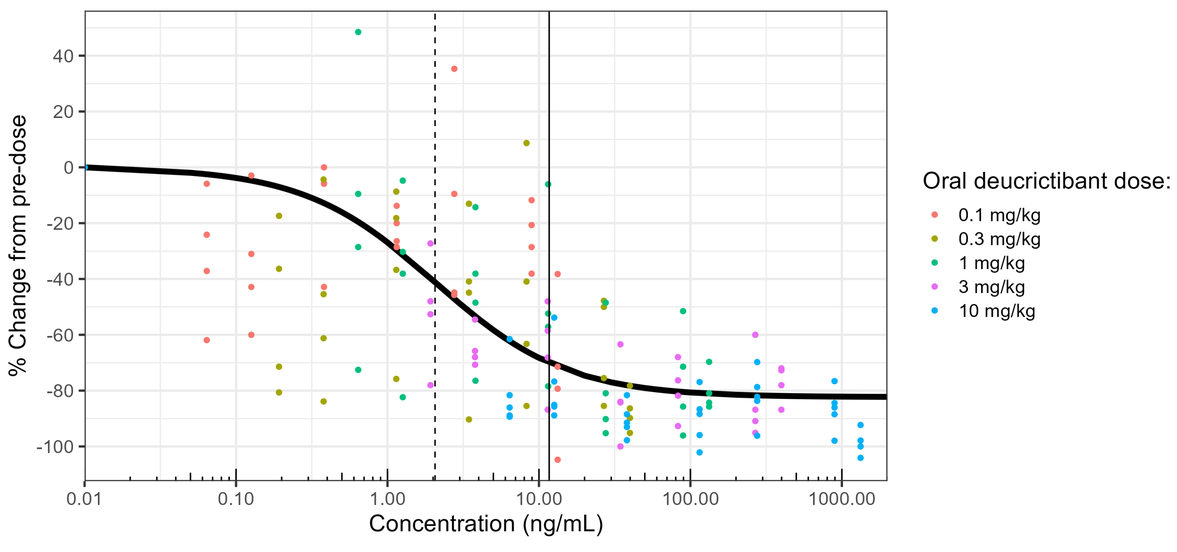
- A one-compartment first-order elimination PK model was constructed based on in vitro data and animal in vivo PK data.
  - Human hepatic metabolic clearance was predicted from in vitro hepatocyte and in vivo preclinical plasma clearance data (rat and NHP).
  - Human volume of distribution was predicted from in vivo preclinical data and mechanistic distribution models.
  - Human oral bioavailability scenarios were based on oral bioavailability studies in rat and NHP.
  - A relatively fast absorption rate (ka) of 2.0/h was used to account for the quick absorption of deucrictibant observed in preclinical in vivo PK studies.
- The time above the EC_{50} and EC_{85} were simulated at the doses investigated in prophylactic and on-demand Phase 2 HAE clinical trials [7-8].
  - The prophylactic Phase 2 HAE clinical trial CHAPTER-1 studied dose levels of 10 and 20 mg twice daily (BID) [8].
  - The on-demand Phase 2 HAE clinical trial RAPIDe-1 studied dose levels of 10, 20 and 30 mg [7].

Results

BK-challenge model in NHP

- The five selected deucrictibant dose levels covered a wide range of concentrations, in which a clear maximal response was observed at the higher concentrations (Figure 2).
- A robust PK/PD relationship was estimated in NHP.
- The scaled human EC_{50} and EC_{85} were comparable to those derived from a BK-challenge model in healthy human participants [9] (Table 1).
- The translational predictivity of the EC_{50} was excellent, with a predicted/observed ratio of 1.18-fold.
- A similar maximal pharmacodynamic effect (E_{max}) was quantified, even though differences exist in the experimental setup between species.

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



BK: bradykinin; PK/PD: pharmacokinetic/pharmacodynamic; NHP: non-human primate

Results

2.89 ng/mL
Predicted human EC_{50} based on BK-challenge in NHP

2.44 ng/mL
Human EC_{50} based on BK-challenge in healthy participants

Table 1. PK/PD model parameters in cynomolgus monkey and predicted vs. observed human EC_{50} and EC_{85}

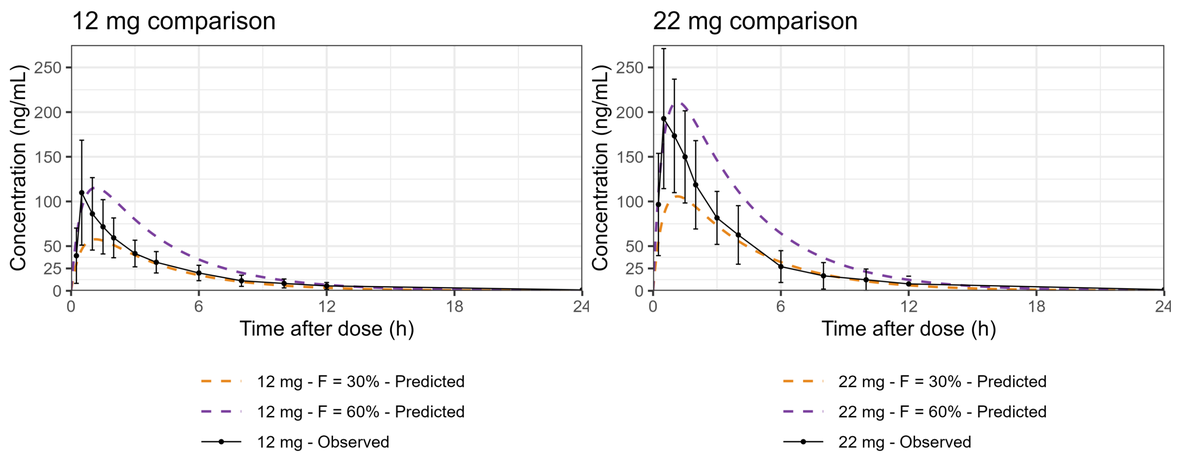
Observed cynomolgus monkey values			Predicted human values		Observed human values (healthy participants)		
E_{MAX} (%)	EC_{50} (ng/mL)	EC_{85} (ng/mL)	EC_{50} (ng/mL)	EC_{85} (ng/mL)	E_{MAX} (%)	EC_{50} (ng/mL)	EC_{85} (ng/mL)
-82.3 ± 3.2	2.06 ± 0.45	11.7 ± 2.6	2.89 ± 0.64	16.4 ± 3.6	-73 ± 2.2	2.4 ± 0.6	13.8 ± 3.6

Mean ± standard error. E_{max}, maximum pharmacodynamic effect; EC_{50}, concentration associated with 50% of E_{max}; EC_{85}, concentration associated with 85% of E_{max}.

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 9 (Figure 3).
- The rapid absorption in humans was slightly underestimated in the translational PK model and was quicker in the observed clinical PK.

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



Observed values present mean ± standard deviation. F: estimated human oral bioavailability based on preclinical data; PK: pharmacokinetic

Simulation of time above exposure targets for prophylaxis of HAE attacks

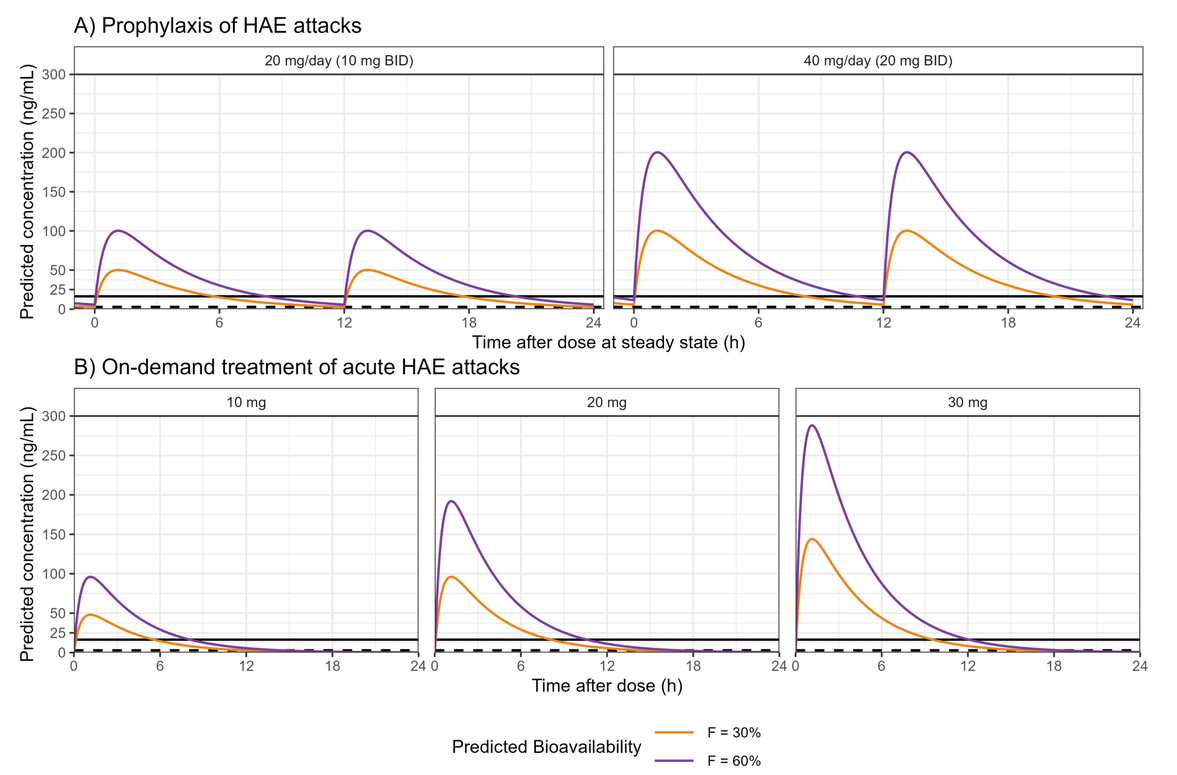
- Both the 10 mg BID and 20 mg BID dose levels were predicted to elicit concentrations consistently above the EC_{50} for 24 hours and above the EC_{85} for up to 21 hours (Table 2)
- Predicted time of exposure targets are in line with efficacy observed at such dose levels in Phase 2 HAE clinical trial CHAPTER-1 [8].

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

PK/PD target	Predicted time > target at 20 mg/day (10 mg BID)	Predicted time > target at 40 mg/day (20 mg BID)
Predicted EC_{50}	24 h	24 h
Predicted EC_{85}	11 – 16 h	16 – 21 h

BID: bis in die (twice daily); EC_{50}, concentration associated with 50% of E_{max}; EC_{85}, concentration associated with 85% of E_{max}; PK/PD: pharmacokinetic/pharmacodynamic

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} (2.89 ng/mL) in humans based on NHP data; solid horizontal line: predicted EC_{85} (16.4 ng/mL) in humans based on NHP data. BID: bis in die (twice daily); HAE: hereditary angioedema

Simulation of time above exposure targets for on-demand treatment of HAE attacks

- PK predictions suggested that doses of 10 to 30 mg deucrictibant would reach efficacious levels within minutes and exceed the scaled human EC_{50} for 12 to 18 hours and the EC_{85} for 5.4 to 12 hours in humans (Figure 4B, Table 3).
- These dose levels were found to be effective in treating HAE attacks in on-demand Phase 2 HAE clinical trial RAPIDe-1 [7].
- The 20 mg dose level was later confirmed to be efficacious in Phase 3 trial RAPIDe-3 for the treatment of on-demand HAE attacks[10].

Table 3. Predicted time above PK/PD target for a single deucrictibant dose based only on nonclinical projections

PK/PD target	Predicted time > target at 10 mg	Predicted time > target at 20 mg	Predicted time > target at 30 mg
Predicted EC_{50}	12 -14 h	14 – 17 h	16 – 18 h
Predicted EC_{85}	5.4 - 8 h	8 - 11 h	9.5 - 12 h

EC_{50}, concentration associated with 50% of E_{max}; EC_{85}, concentration associated with 85% of E_{max}; PK/PD: pharmacokinetic/pharmacodynamic

References

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