The Bradykinin Challenge Model Translates across Rat, Monkey, and Human

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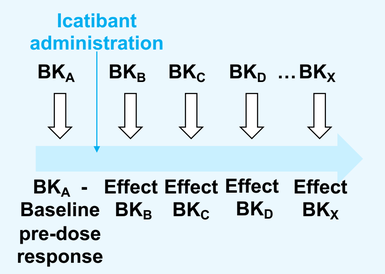
Introduction

- Pharmacokinetic and pharmacodynamic (PK/PD) properties of bradykinin B2 receptor antagonists can be assessed in in vivo bradykinin (BK) challenge models.
- In these models, BK is repeatedly administered as a short intravenous (iv) infusion to cause hemodynamic changes such as a reduction in blood pressure (BP). By administering a bradykinin B2 receptor antagonist prior to the BK challenge, the potential of such an agent to prevent the BK-mediated hemodynamic effects can be assessed.
- The BK challenge model has been used in monkeys [1] and in human healthy participants [2,3]. These models have been used in drug development for prediction of human efficacy but are resource-intensive and require complex set-ups.
- Recently, a BK challenge model in humanized bradykinin B2 receptor transgenic (Tg) rats was developed to provide a new, cost-effective option to evaluate the pharmacological response of bradykinin B2 receptor antagonists [4].
- It was previously not investigated whether the BK challenge model in Tg rats could serve as a replacement for the monkey BK challenge model for the quantitative nonclinical prediction of the in vivo response of bradykinin B2 receptor antagonists in humans.
- We investigated the translational value of the BK challenge model across Tg rats, cynomolgus monkeys, and humans by comparing the PK/PD relationships of icatibant, a marketed bradykinin B2 receptor antagonist, in all three species.

Materials and Methods - BK Challenge Model

- The effects of icatibant on the repeated BK-induced reduction in BP was determined in BK challenge studies in male Tg Sprague Dawley rats [4] and male cynomolgus monkeys [1].
- The relative change from the baseline response to BK was calculated to show the antagonistic properties of the test compound (**Figure 1**).

Figure 1. BK challenge pharmacodynamic endpoint

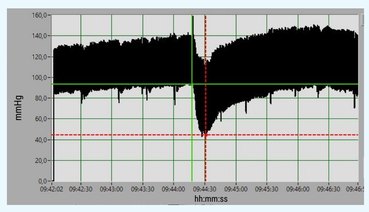


Icatibant relative effect on the BK-induced reduction in BP:

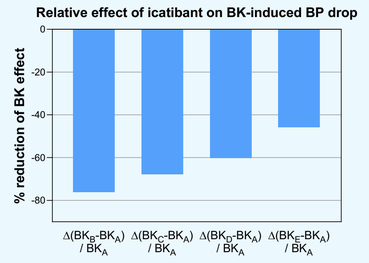
$$\frac{\Delta\ Response_{BK_X} - Baseline\ response}{Baseline\ response}$$

BK: Bradykinin challenge; BP: blood pressure

Typical tracing depicting hypotensive effects of BK following intra-arterial injection



Typical time-dependent pharmacodynamic effect of icatibant on BK-induced BP drop



Pharmacokinetic Data and PK/PD Analysis Methodology

PK/PD data overview

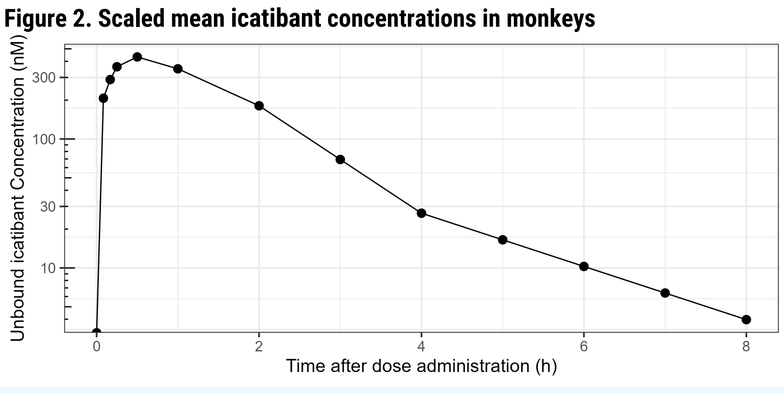
Humanized bradykinin B2 receptor Tg rats

- Icatibant was administered as an iv bolus at 5 dose levels (0.005 – 1 mg/kg) to anesthetized Tg rats.
- The response on the BK-mediated drop in diastolic BP was measured for each BK challenge.
- Plasma exposures to icatibant were determined directly in the study animals closely after each BK challenge.

Cynomolgus monkeys

- Icatibant was administered as a subcutaneous injection at 0.6 mg/kg to freely moving monkeys.
- The response on the BK-induced drop in mean arterial BP was measured by telemetry for each BK challenge.
- The plasma exposure to icatibant after 0.2 mg/kg subcutaneous administration to satellite cynomolgus monkeys was linearly scaled up to the dose used in the monkey BK challenge (0.6 mg/kg).
- Mean plasma concentrations at times corresponding to PD collections were used during PK/PD analysis (**Figure 2**).

Figure 2. Scaled mean icatibant concentrations in monkeys



Humans - healthy participants

- Population PK/PD analysis parameters for icatibant on a BK challenge study in healthy participants were retrieved from NDA 22-150 [5]. While multiple PD endpoints were explored, EC_{50} and maximal effect (E_{max}) values were similar for diastolic and mean BP PD endpoints. Only the diastolic BP was used for translational comparisons.
- The published human PK/PD parameters were rewritten to a % change from pre-dose to match the PD endpoint used in rats and monkeys.

PK/PD analysis

- The PK/PD relationship on the BP data was quantified in Tg rats and cynomolgus monkeys using a maximal effect model with R software (v4.2.2) and the DoseFinding (v1.0.5) package.
- Unbound plasma concentrations (in nM) versus % change from the pre-dose response was modelled as an E_{max} model to account for the impact of differences in unbound fraction across species .
- The estimated maximal inhibition (E_{max}) and unbound EC_{85} parameters were then compared across species. The EC_{85} was selected as a relevant metric to compare icatibant in vivo potency across species because of
  - its relevance to predict efficacy in its primary indication, hereditary angioedema (HAE) [6].
  - the impact of the Hill coefficient (H) on the ratio between EC_{50} versus EC_{85}, which limits the cross-species comparison of EC_{50} estimates.
- EC_{85} calculations were calculated with Equation 1 [7].

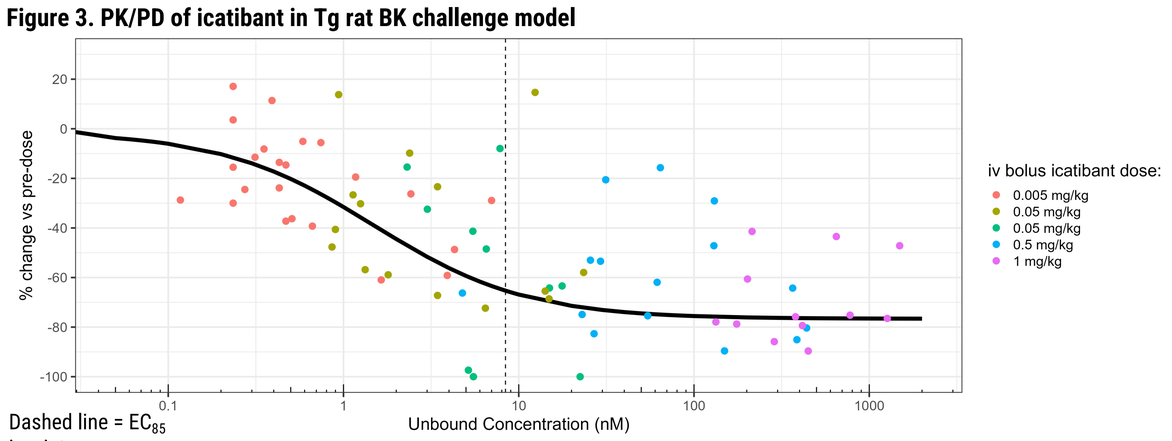
Equation 1. $$EC_{85} = \left(\frac{85}{100-85}\right)^{1/H} \times EC_{50}$$

Results

Humanized bradykinin B2 receptor transgenic Tg rats

- A robust PK/PD relationship was established for icatibant in Tg rats. The plasma concentrations reflected the full inhibition range of BK-induced changes in diastolic BP (**Figure 3**).
- The variability in the PD responses across animals is inherent to the complexity of the model readout and the significant inter- and intra-individual changes in response to BK challenges.

Figure 3. PK/PD of icatibant in Tg rat BK challenge model

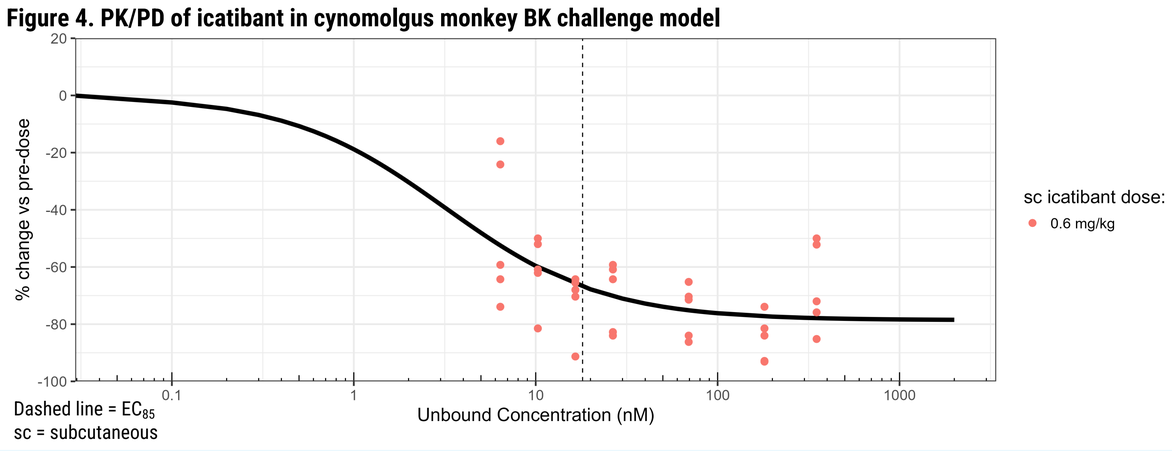


Dashed line = EC_{85}
iv = intravenous

Cynomolgus monkeys

- Clear PK/PD response observed for icatibant on the mean arterial BP in monkeys (**Figure 4**).
- As the BK challenge study in monkeys had not been specifically designed to explore low- or sub-efficacious doses, there are only sparse data below the unbound 5 nM level of icatibant.
- This data gap increases the uncertainty of the exact value of the EC_{50}, but the EC_{85} approximation is more reliable.

Figure 4. PK/PD of icatibant in cynomolgus monkey BK challenge model

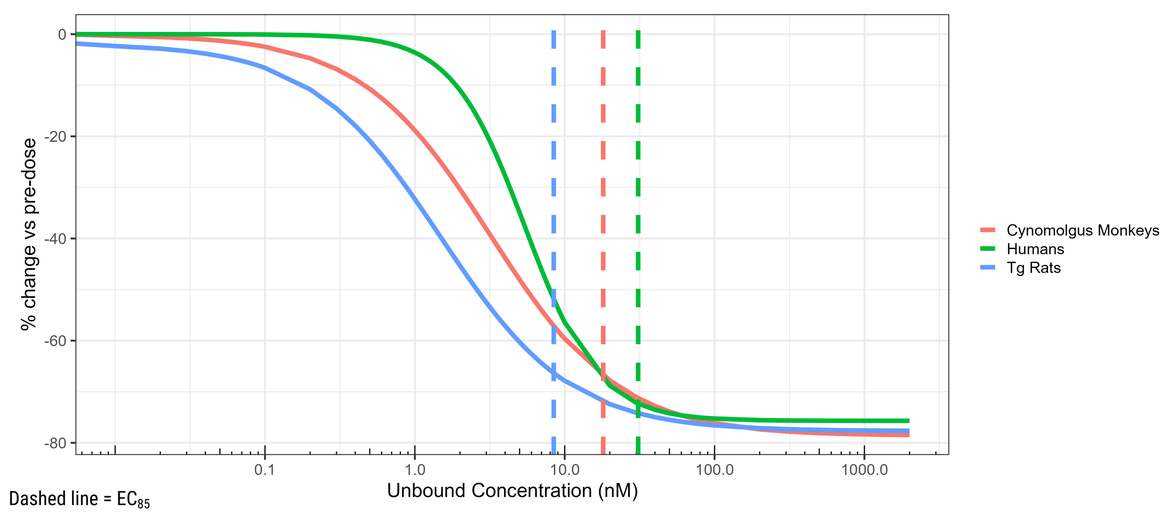


Dashed line = EC_{85}
sc = subcutaneous

Cross-species comparison

- When comparing the PK/PD of icatibant across species, a very close agreement on E_{max} can be observed, and the EC_{85} estimates from Tg rat and monkey BK challenge studies are within 2-fold of the human value (**Figure 5, Table 1**).

Figure 5. Cross-species PK/PD relationship of icatibant on the BK challenge model



Dashed line = EC_{85}

Table 1. Cross-species comparison of PK/PD parameters for icatibant

Species	EC_{50} (unbound nM)	EC_{85} (unbound nM)	E_{max} (%)	Hill coefficient
Humanized bradykinin B2 receptor Tg rats	1.5	**8.4**	-75.3	1.00
Cynomolgus monkeys	3.2	**18.1**	-78.5	1.00
Humans (healthy participants)	5.5	**14.5**	-75.7	1.77

Conclusions

- **Icatibant PK/PD was analysed from BK challenge studies in humanized bradykinin B2 receptor Tg rats, cynomolgus monkeys, and humans and showed a similar PK/PD response in all species.**
- **The BK challenge model in nonclinical species such as Tg rats and monkeys is predictive of PK/PD outcomes in humans. Differences in experimental setup, potency, and modelling approach between Tg rats and other species might have caused some of the observed differences.**
- **The Tg rat BK challenge model can serve as a cost-effective replacement for the monkey BK challenge model for the prediction of the in vivo response of bradykinin B2 receptor antagonists in humans.**

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.** H. Derendorf et al. Bradykinin challenge provides surrogate endpoints for hereditary angioedema treatment using bradykinin B2 receptor antagonists. AAAI 125: P151 (2020). **3.** B. Rosenkranz et al. Efficacy and safety profile of the potent and selective bradykinin B2 receptor antagonist icatibant in healthy volunteers. 26th EAACI Congress, Gothenburg, Sweden, June 9–13, 2007. **4.** J. Skarbaliene et al. Bradykinin challenge model in humanized bradykinin B2 receptor transgenic rat. Bradykinin Symposium, Berlin, Germany, September 5-6, 2024 **5.** US FDA, Clinical Pharmacology review, NDA 22-150, SDN 21, 25 February 2011. **6.** M. Maurer et al. The EC_{85} derived from the oral bradykinin B2 receptor antagonist deucrictibant (PHA121) against bradykinin effects in healthy volunteers predicts the onset and duration of its clinical effects in hereditary angioedema. 13th C1-Inhibitor Deficiency and Angioedema Workshop, Budapest, Hungary, May 4-7, 2023 **7.** https://www.graphpad.com/quickcalcs/ECanything2/ (accessed 13 July 2024).

JB, MJVE, JS: 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.