Cardiovascular Safety of Repeated Oral Administration of the Bradykinin B2 Receptor Antagonist Deucrictibant

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Introduction

- Deucrictibant is an orally bioavailable, potent, competitive antagonist of the human bradykinin B2 receptor.
- Deucrictibant is under development for the prevention and treatment of hereditary angioedema (HAE) attacks. Here we present the assessment of the cardiovascular (CV) safety of deucrictibant after repeated dosing based on data from preclinical and early clinical studies.

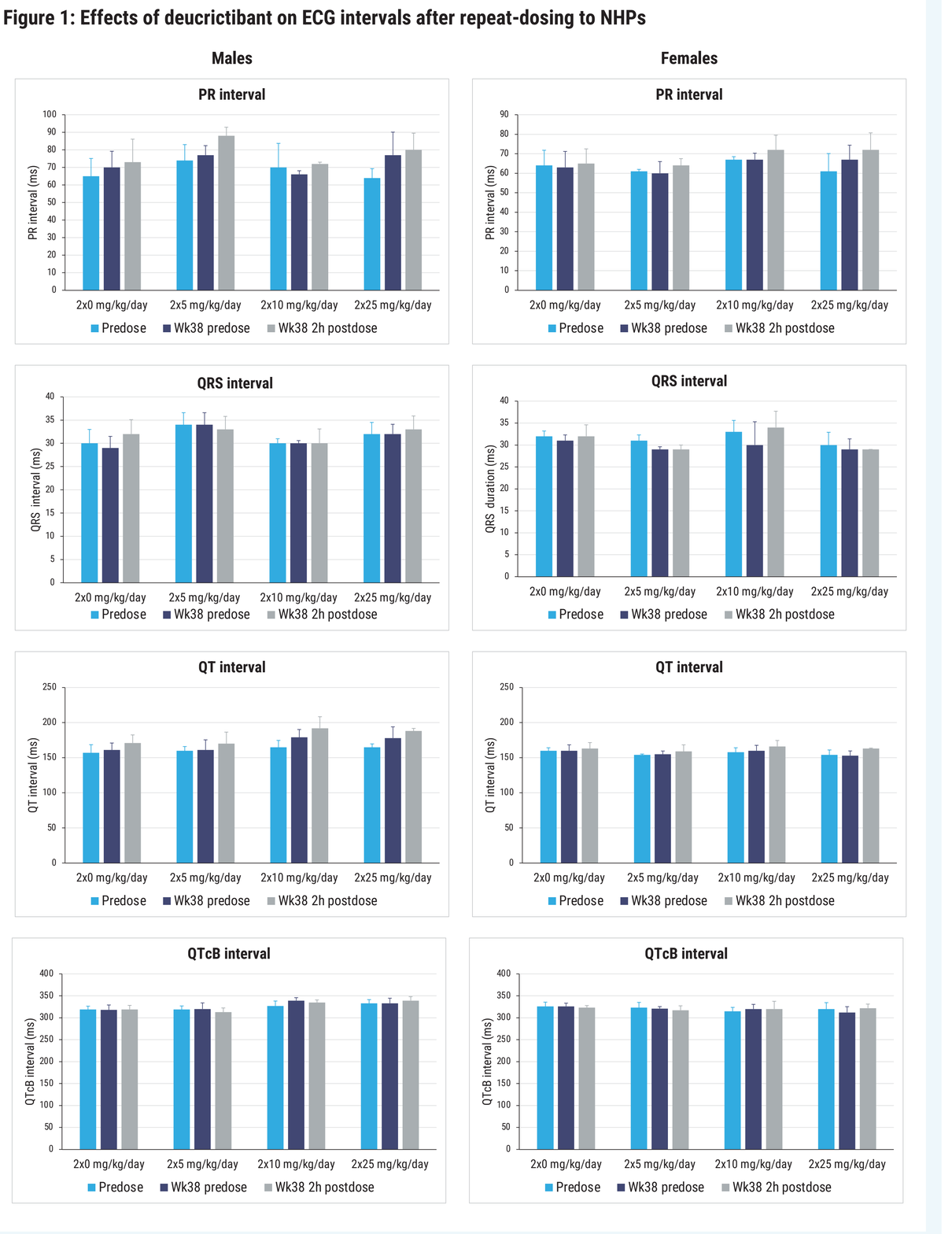
Results

Nonclinical studies in non-human primates (NHP)

Cardio-electrophysiology

- Daily oral administration of deucrictibant to male and female NHPs for up to 39 weeks did not affect the duration of the ECG intervals (**Figure 1**) or ECG waveforms morphology (data not presented).

Figure 1: Effects of deucrictibant on ECG intervals after repeat-dosing to NHPs

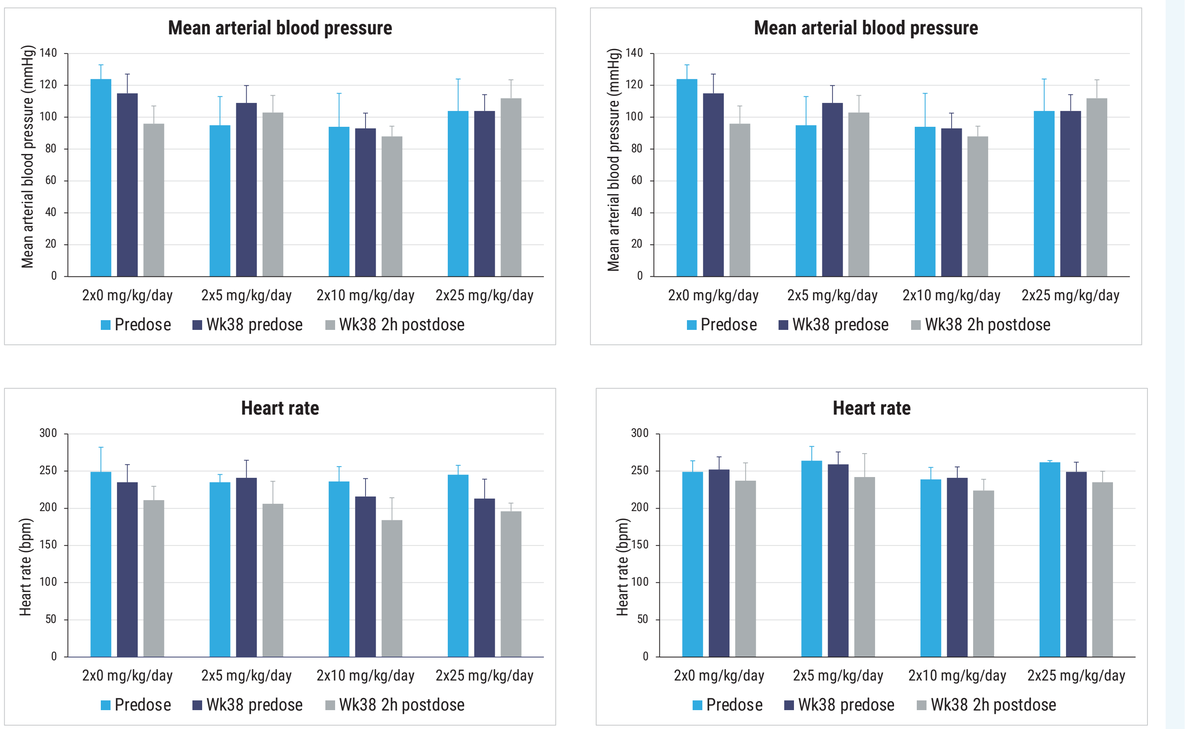


Data are presented as mean values ± SEM for n = 4 for each dose group and sex.

Cardiac hemodynamic parameters

- No evident effects were observed on hemodynamic parameters in NHPs. No relevant changes in heart rate, systolic, diastolic and mean arterial blood pressure were noted after single or repeat oral dosing for up to 39 weeks of daily administration (**Figure 2**).

Figure 2: Effects of deucrictibant on cardio-hemodynamic parameters after repeat-dosing to NHPs



Data are presented as mean values ± SEM for n = 4 for each dose group and sex.

Materials and Methods

- The nonclinical CV safety data presented was collected during the 39-week repeated-dose general toxicity study in non-human primates (NHPs) as the pharmacologically responsive species. The study included 4 groups of treatment (4 animals/group/sex): vehicle control group and 3 dose levels of deucrictibant. Electrocardiograms (ECGs) and blood pressure (BP) data were collected during the pre-dose phase, and on Day 1, Week 25 and Week 38 of treatment, prior to and 2 hours after administration. Recordings were done in conscious animals. Eight-lead ECGs were continuously recorded and analyzed using Ponemah Physiology Platform. Blood pressure was measured by indirect High Definition Oscillometry (HDO). ECG intervals (PR, QRS, QT, QTc, RR), heart rate (HR), ECG waveforms, systolic, diastolic, and mean arterial pressures (mmHg) were evaluated[1]. The QT interval was corrected for HR (QTc) using the Bazett method[2]. At termination, heart weight and macroscopic and microscopic evaluations were performed.
- In clinical studies with deucrictibant, cardiovascular safety was evaluated in healthy participants after 10 days of dosing (Phase 1 study)[3], in participants with HAE after up to 12 weeks of dosing (CHAPTER-1 Phase 2 trial – randomized controlled part)[4] and in the ongoing open-label extension (OLE) part with mean duration of treatment with deucrictibant 40 mg/day reaching approximately 1 year at the date of most recent cutoff (10 June 2024)[5]. Data on vital signs including pulse rate, diastolic and systolic blood pressure were collected at baseline, Week 2, Week 6 and Week 12 for participants receiving placebo, 20 mg/day and 40 mg/day of deucrictibant in the randomized controlled part of the CHAPTER-1 Phase 2 trial (n = 10 to 12 per each dose group).

Results

Cardiac morphology

- Repeat dosing to NHPs for up to 39 weeks did not affect heart weight (**Table 1**), a sensitive measure of muscle mass. Macroscopic and microscopic evaluation of heart and cardiac tissue revealed no treatment-related effects including no signs of ventricular wall thickness.
- The absence of an increase in heart weight, together with the lack of effects on the QRS complex are indicative of the absence of left ventricular hypertrophy, which is consistent with the finding that deucrictibant did not increase BP after long-term administration.

Table 1: Heart weights after 39 weeks of dosing in NHPs

Dose (mg/kg/day)	Males		Females	
	Absolute weight (g)	% vs. body weight	Absolute weight (g)	% vs. body weight
2x0	15.4 ± 4.1	0.390 ± 0.054	13.9 ± 1.69	0.372 ± 0.032
2x5	11.8 ± 1.5	0.331 ± 0.021	10.1 ± 0.6	0.344 ± 0.022
2x10	11.8 ± 1.2	0.344 ± 0.026	12.0 ± 1.6	0.361 ± 0.019
2x25	15.1 ± 2.2	0.383 ± 0.039	11.0 ± 1.9	0.353 ± 0.046

Clinical studies

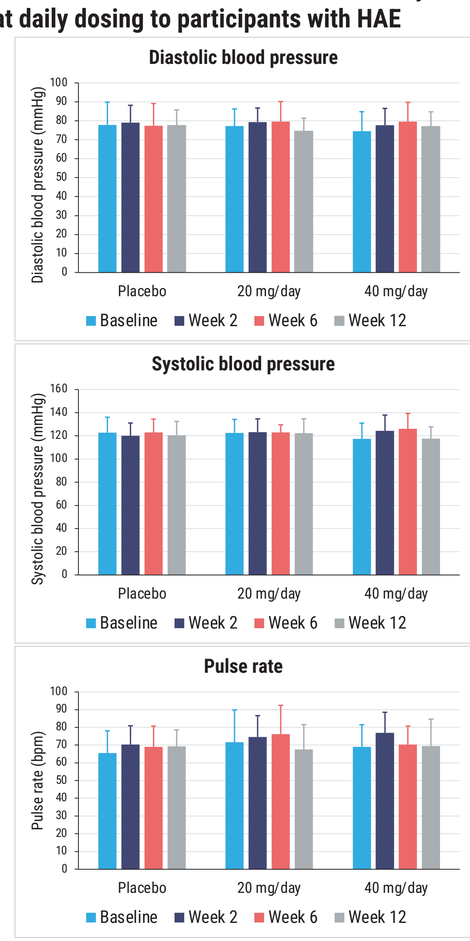
Phase 1 clinical studies

- Deucrictibant was well tolerated in clinical studies conducted to date, and no clinically significant treatment-emergent adverse events were observed in the MedDRA Cardiac disorders System Organ Class (SOC).
- No dose-, time-, or treatment-dependent changes in ECG-intervals or relevant effects on HR and BP were observed across single- and multiple-dose Phase 1 clinical studies.

Phase 2 clinical studies

- There were no treatment-emergent adverse events in the prophylactic clinical Phase 2 study and in the ongoing OLE part with mean duration of treatment with deucrictibant 40 mg/day reaching approximately 1 year at the date of most recent cutoff (10 June 2024).
- No dose-, time-, or treatment-dependent changes in diastolic and systolic BP and pulse rate were observed in participants with HAE dosed daily for 12 weeks (**Figure 3**).

Figure 3: Effects of deucrictibant on cardio-hemodynamic parameters after repeat daily dosing to participants with HAE



Data are presented as mean values ± SD for n = 10 to 12 per each dose group.

Conclusions

- **Deucrictibant had no evident effects on cardiac electrophysiology, morphology and hemodynamic parameters in chronic preclinical safety studies in NHP.**
- **Deucrictibant showed no evident effects on cardiac electrophysiology and hemodynamic parameters in clinical studies in humans completed to date, following prophylactic treatment up to 12 weeks of daily administration in the Phase 2 clinical trial and for a mean of approx. 1 year in the ongoing OLE.**

References

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5. Riedl MA et al. (2024) Long-term safety and efficacy of oral deucrictibant for HAE prophylaxis. Poster presentation. 7th Bradykinin Symposium, 2024.

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

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