

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

Abstract ID 117125

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Introduction

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

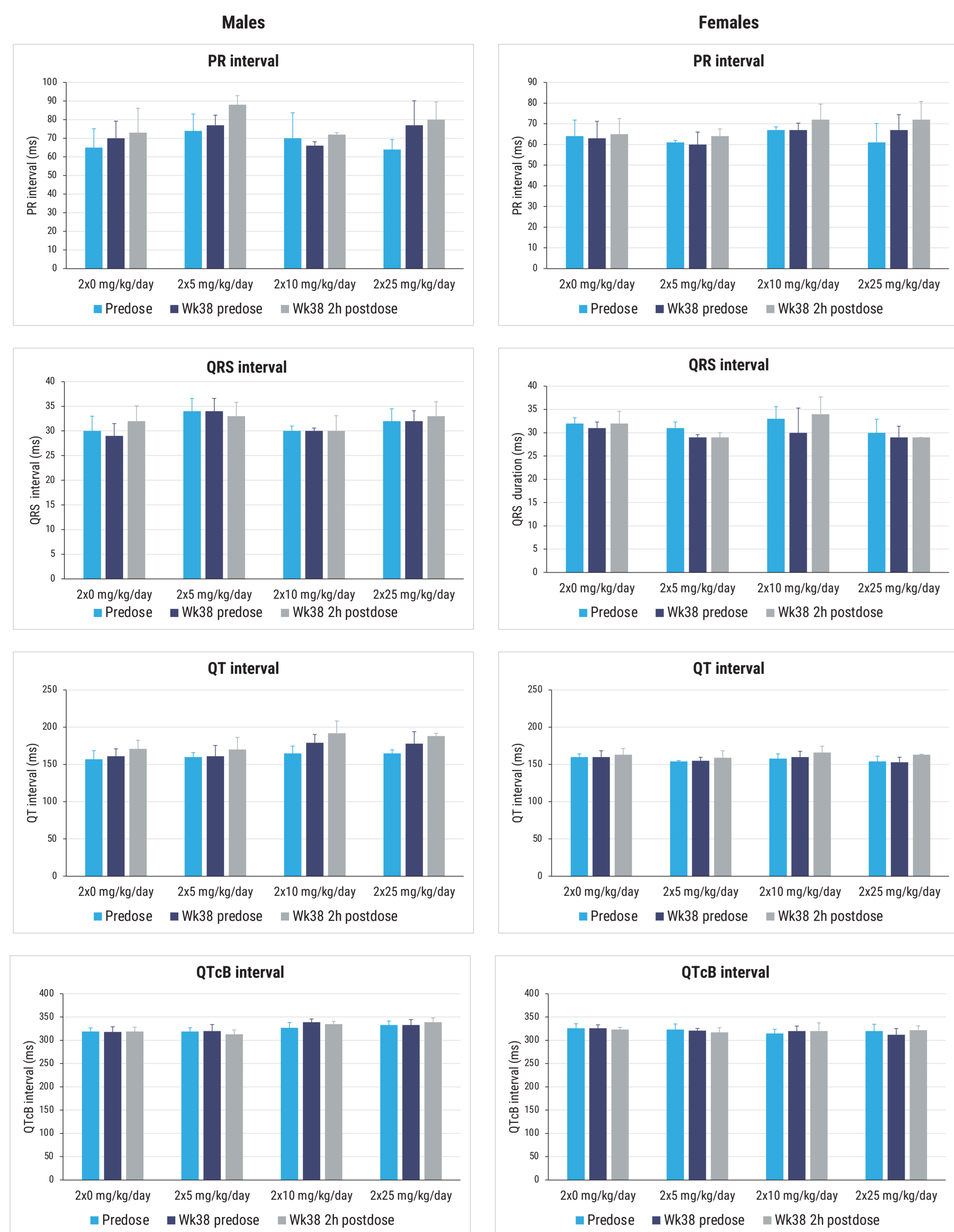
Results

Nonclinical studies in non-human primates (NHP)

Cardio-electrophysiology

• Daily oral administration of deucricitbant 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 deucricitbant on ECG intervals after repeat-dosing to NHPs

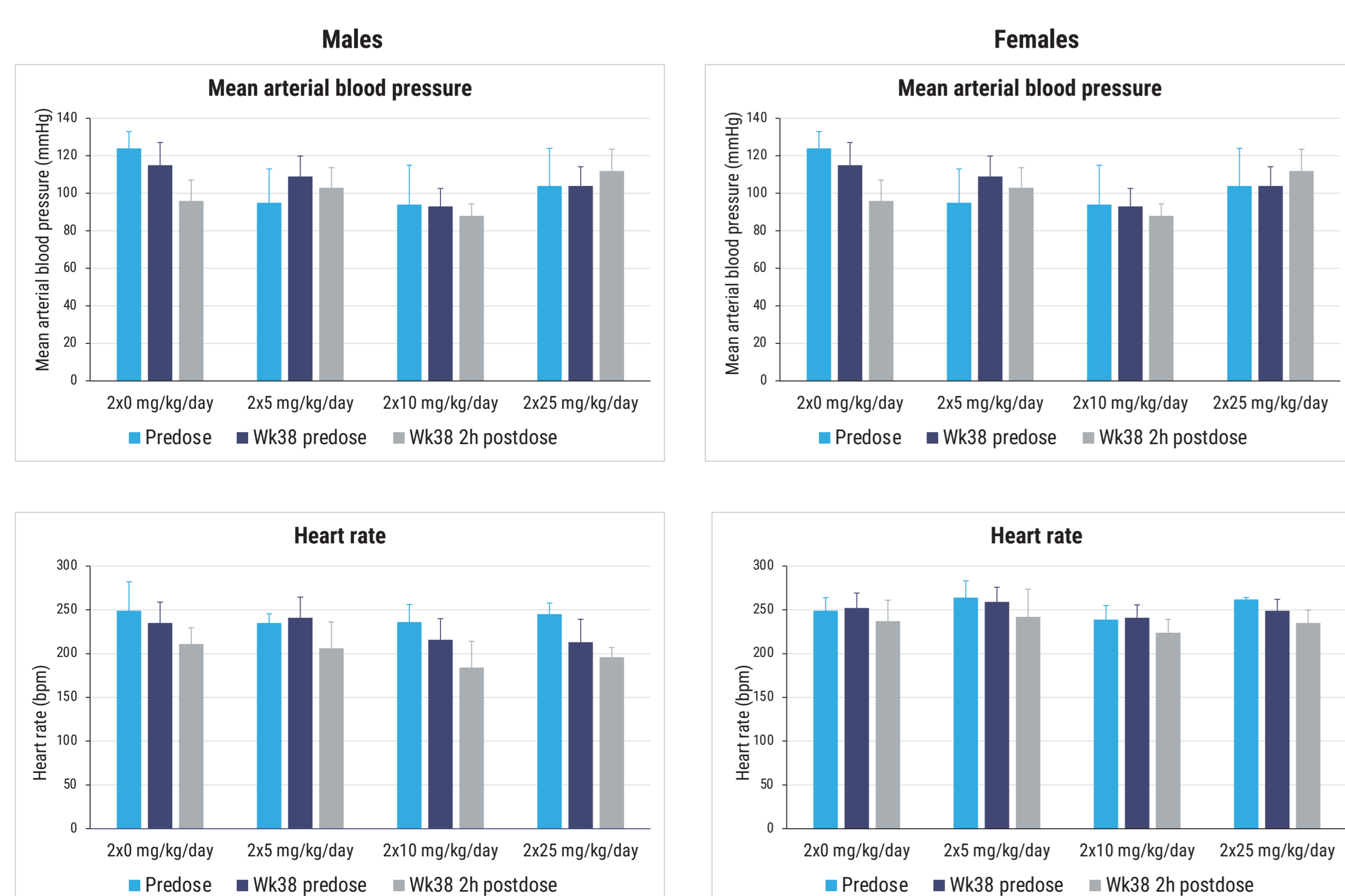


Data are presented as mean values ± SEM for n = 4 for each dose group and sex.

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 deucricitbant 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 deucricitbant. 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 evaluated¹. The QT interval was corrected for HR (QTc) using the Bazett method². At termination, heart weight and macroscopic and microscopic evaluations were performed.

• In clinical studies with deucricitbant, 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 deucricitbant 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 deucricitbant 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 deucricitbant 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

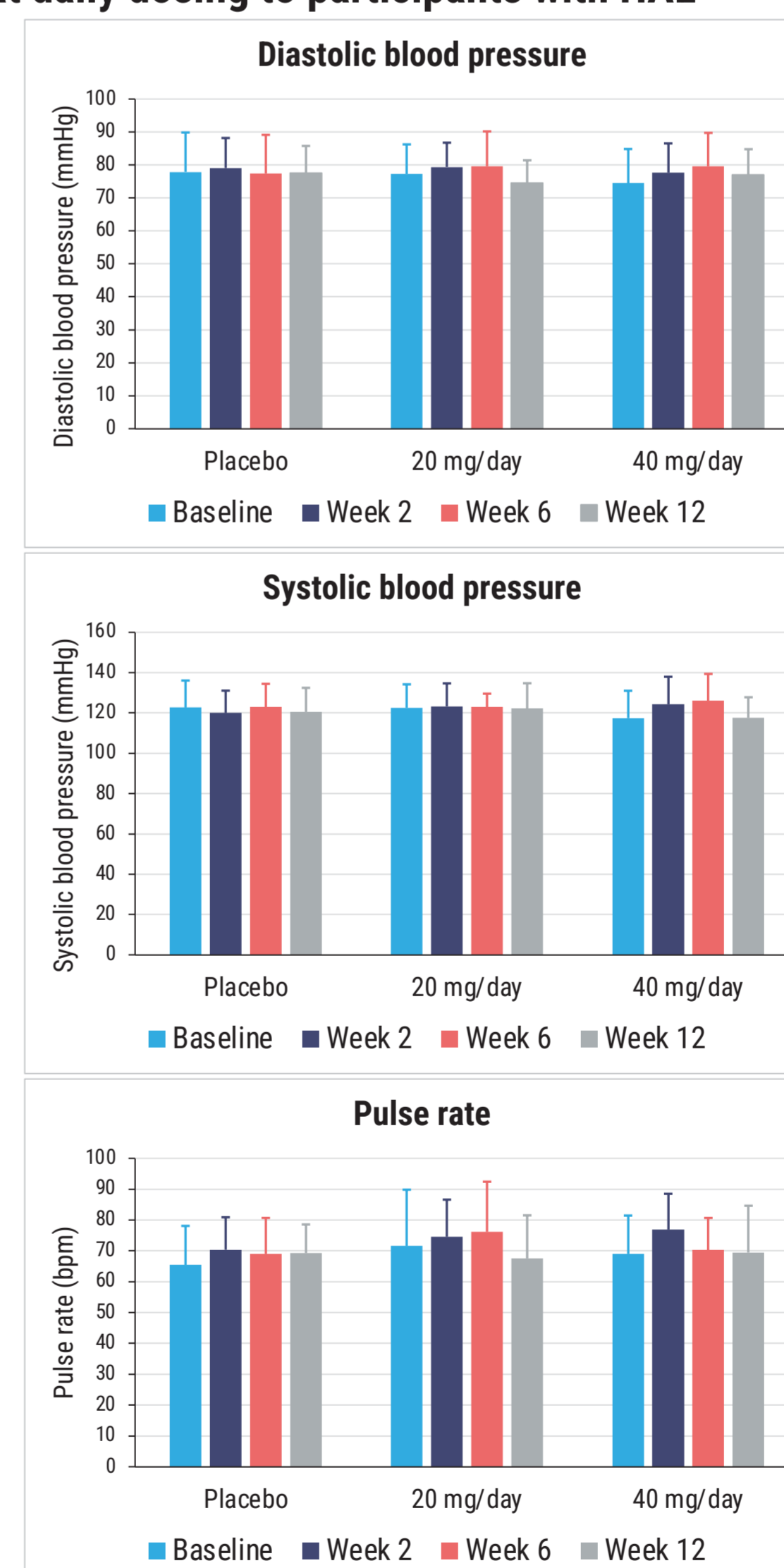
Phase 1 clinical studies

• Deucricitbant 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 deucricitbant 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 deucricitbant 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

• Deucricitbant had no evident effects on cardiac electrophysiology, morphology and hemodynamic parameters in chronic preclinical safety studies in NHP.
• Deucricitbant 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

- Detweiler DK (1989) The mammalian electrocardiogram: Comparative features. In: MacFarlane PW, Lawrie TDV (eds). Comprehensive electrocardiology: Theory and practice in health and disease. Vol. 2, Ch. 36; New York (NY): Pergamon Press, p. 1331-1377.
- Bazett HC (1920) An analysis of the time relations in electrocardiograms. Heart; 7:353-370.
- Groen K et al. (2021) Multiple dose administration of PHA-022121, an orally available, bradykinin B2 receptor antagonist is well tolerated and shows a favorable pharmacokinetic profile for prophylactic treatment of HAE. Poster presentation. European Academy of Allergy and Clinical Immunology (EAACI) Annual Congress, 2021
- Aygören-Pürsün E et al. (2024) Efficacy and safety of oral deucricitbant, a potent bradykinin B2 receptor antagonist, in prophylaxis of hereditary angioedema attacks: results of CHAPTER-1 phase 2 trial. Oral presentation. European Academy of Allergy and Clinical Immunology (EAACI) Annual Congress, 2024
- Riedl MA et al. (2024) Long-term safety and efficacy of oral deucricitbant for HAE prophylaxis. Poster presentation. 7th Bradykinin Symposium, 2024.

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