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Cardiovascular safety of the orally administered bradykinin B2 receptor antagonist, deucrictibant (PHA121, PHA-022121)

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Introduction

Deucrictibant (PHA121, PHA-022121) is an orally bioavailable potent competitive antagonist of the human bradykinin B2 receptor. Deucrictibant is under development for the treatment and prevention of hereditary angioedema (HAE) attacks. Here we present the assessment of the cardiovascular safety of deucrictibant based on preclinical and early clinical studies.

Methods

The preclinical cardiovascular safety of deucrictibant was assessed using *in vitro* cardiac ion channel and off-target receptor screenings, and *in vivo* acute and chronic studies in non-human primates (NHPs) as the pharmacologically responsive species. Occurrence of cardiovascular events was monitored in Phase 1 studies and the Phase 2 on-demand RAPIDe-1 study of deucrictibant and continues to be monitored in ongoing clinical trials in HAE.

Results

Cardio-electrophysiology

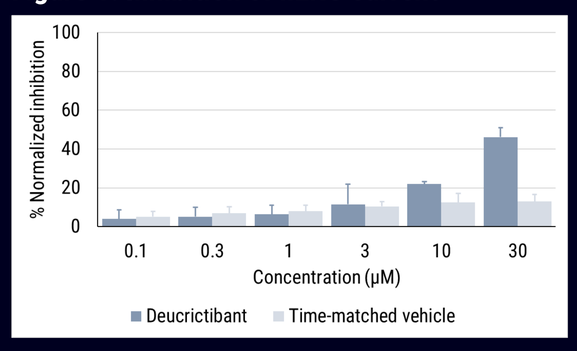
Deucrictibant did not significantly inhibit 8 cardiac ion channels in an automated patch clamp screening assay (inhibition <25% at 10 µM; Table 1).

Table 1: Inhibition of cardiac ion channels

Ion channel	% Normalized inhibition by deucrictibant
hNav1.5	6.0
hKv4.3/KChIP2	24.4
hKv1.5	3.9
hKCNQ1/mink	-5.1
hERG	17.3
hCav1.2	5.3
hKir2.1	10.7
hHCN4	0.8

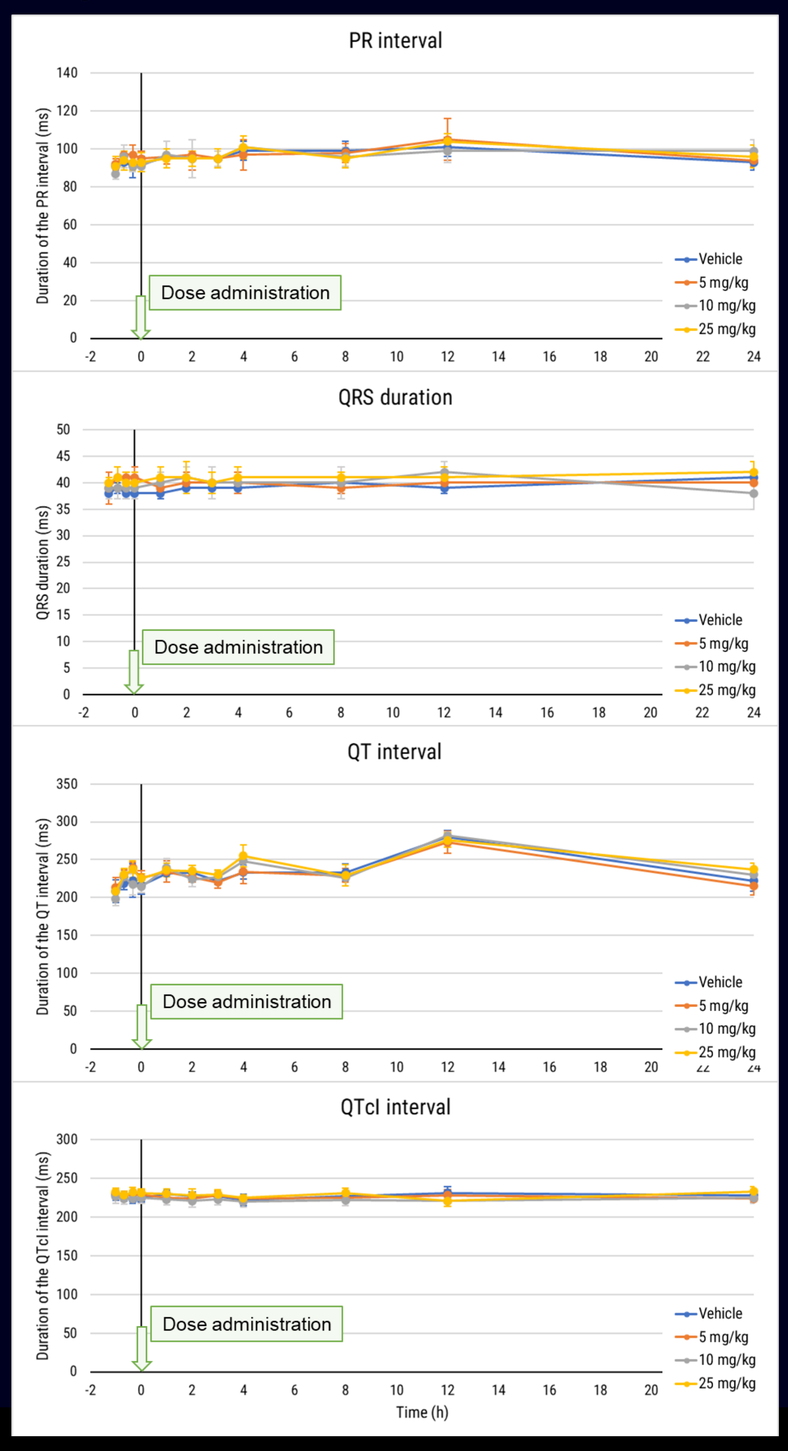
In a manual whole-cell patch clamp GLP study, hERG current was not notably affected by deucrictibant (IC_{50} >30 µM; Figure 1).

Figure 1: Inhibition of hERG current



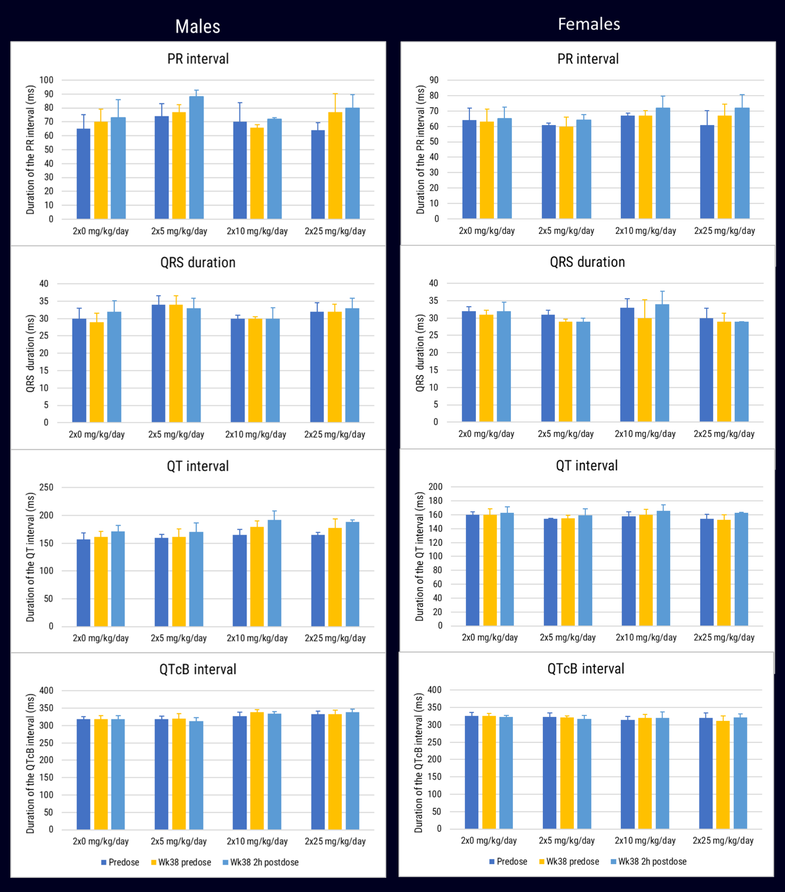
Single oral administration of deucrictibant to male NHPs did not affect the duration of the ECG intervals (Figure 2). No cardiac arrhythmias were observed.

Figure 2: Effects of deucrictibant on ECG intervals after single dosing to male NHPs



Furthermore, repeat oral administration of deucrictibant to male and female NHPs for up to 39 weeks did not affect the duration of the ECG intervals (Figure 3), nor ECG morphology.

Figure 3: Effects of deucrictibant on ECG intervals after repeat-dosing to NHPs



Cardio-hemodynamics

No effects were observed on hemodynamic parameters in *in vivo* studies in NHPs. No relevant changes in heart rate and mean arterial blood pressure were noted after single or repeat oral dosing (Figure 4 and 5, respectively). Effects on functional cardiovascular parameters were not assessed in rodents.

Figure 4: Effects of deucrictibant on cardio-hemodynamic parameters after single dosing to male NHPs

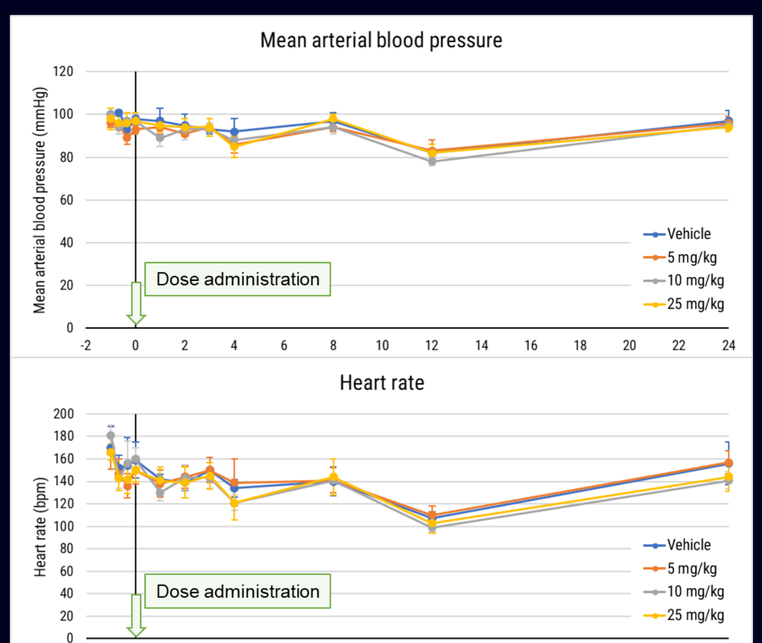
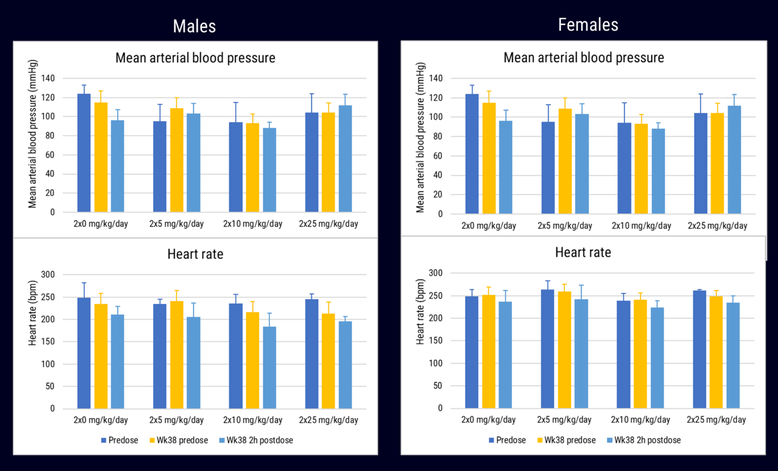


Figure 5: Effects of deucrictibant on cardio-hemodynamic parameters after repeat-dosing to NHPs



Cardiac morphology

Assessment of heart weights (Table 2), a sensitive measure of muscle mass, and microscopic evaluation of cardiac tissue in the 4-, 13- and 39-week toxicology study in NHPs, revealed no treatment-related adverse effects and no signs of ventricular wall thickness after chronic repeat-dose administration.

Table 2: Heart weights after 39 weeks of dosing in NHPs

Dose (mg/kg/day)	Males		Females	
	Actual weight (g)	% vs body weight	Actual 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

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 relevantly increase BP after long-term administration.

Effects in humans

Deucrictibant was well tolerated in clinical studies in humans. No clinically significant treatment-emergent adverse events were observed in the MedDRA Cardiac disorders SOC, nor 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 and the Phase 2 on-demand RAPIDe-1 study.

Conclusions

Deucrictibant showed no effect on cardiovascular function in *in vitro* and *in vivo* preclinical studies, nor in clinical studies in humans completed to date, including acute on-demand and repeat administration up to 10 days at doses anticipated to be used in future late-stage clinical trials and to be potentially marketed upon approval by regulatory agencies.

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

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