PHA-022121: Efficacy in a Monkey Bradykinin Challenge Model Translated to Human

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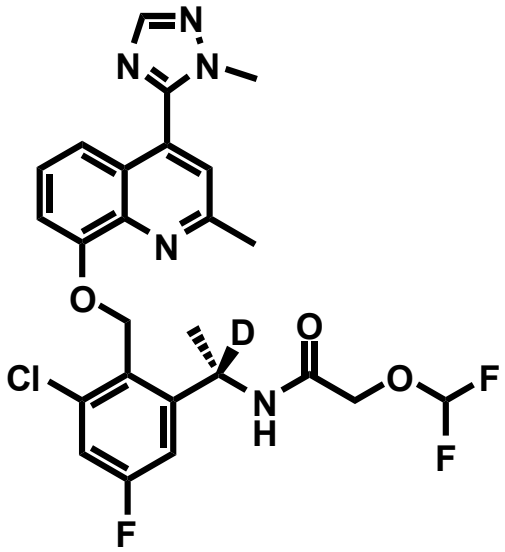
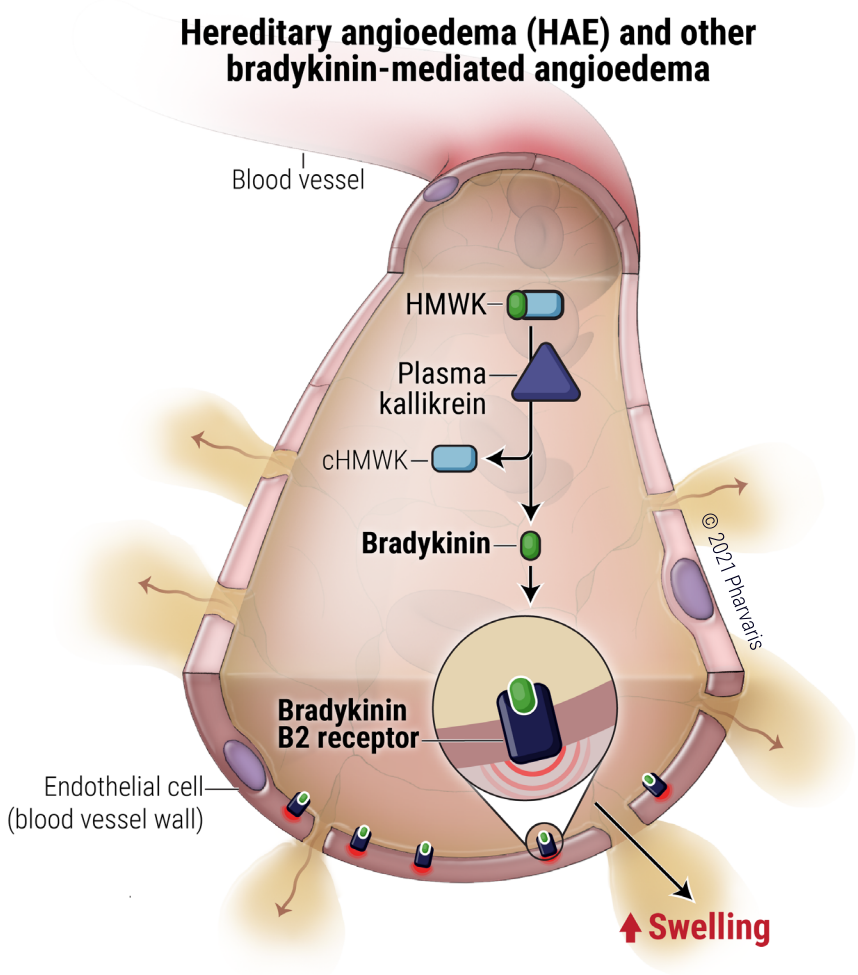
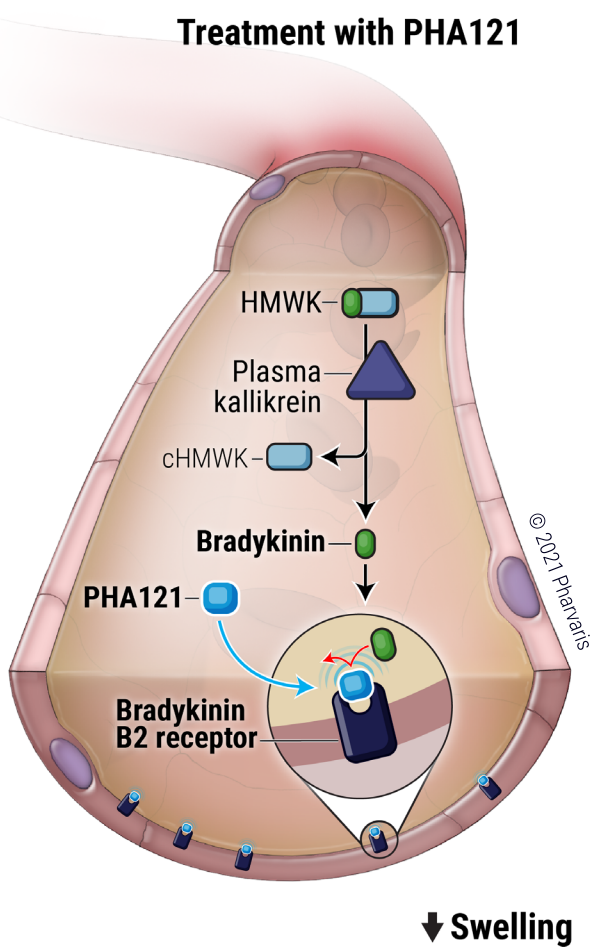
PHA-022121 (PHA121) is a potent and selective oral bradykinin B2 receptor antagonist



- Antagonist potency at the recombinant human bradykinin B2 receptor Kb 150 pM
- Highly selective over approx 170 molecular targets, including bradykinin B1 receptor
- Activity in primate and human bradykinin (BK) challenge model

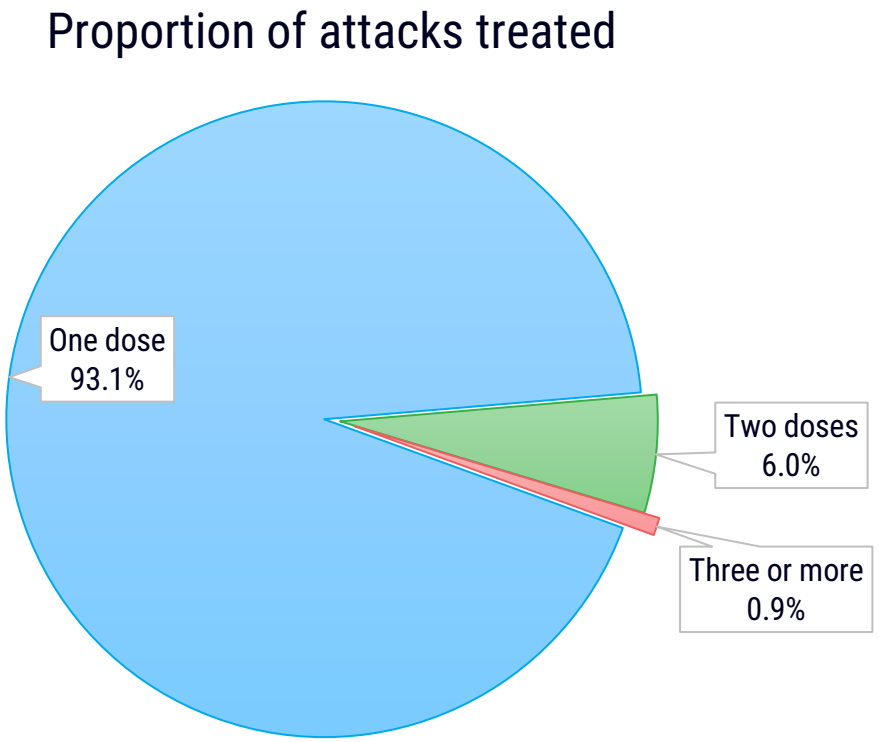
HAE is caused by excess levels of bradykinin
PHA121 is designed to block signaling by bradykinin





HMWK: high-molecular-weight kininogen; cHMWK: cleaved high-molecular-weight kininogen

Inhibition of bradykinin-induced hemodynamic effects is a validated surrogate efficacy assessment

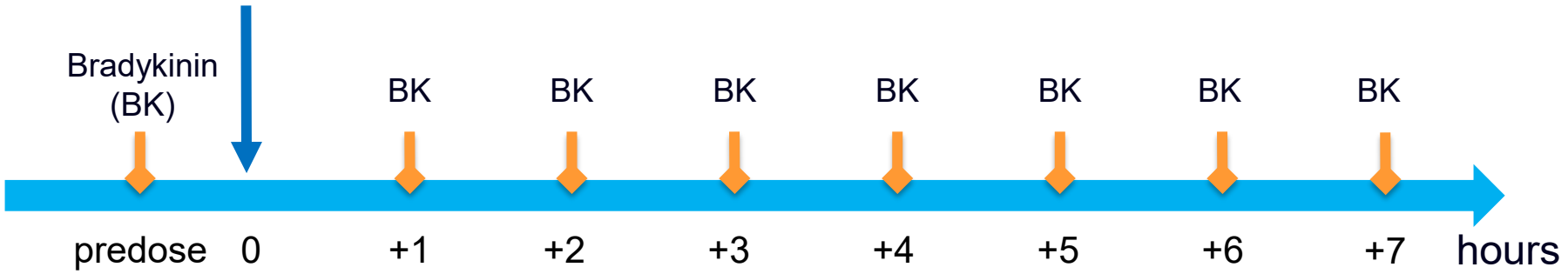


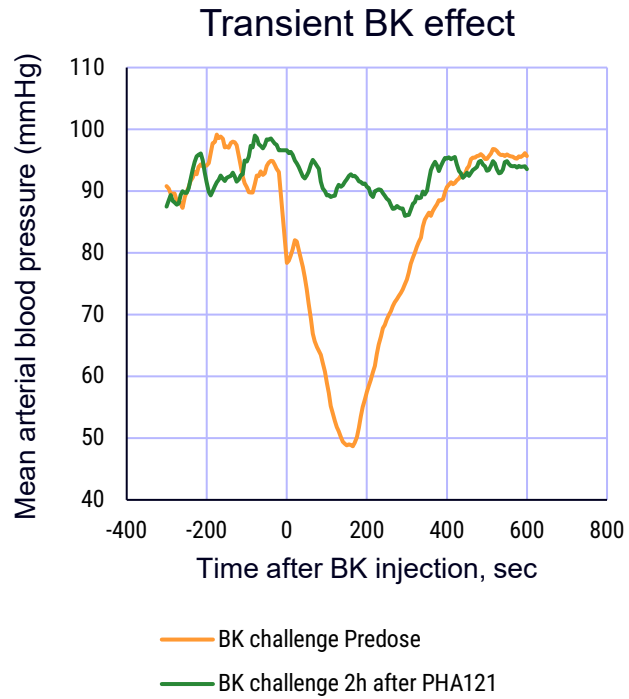
- Used to select the dose in the original development program for icatibant, as reviewed by FDA and EMA
- Clinical dose established with the BK challenge has demonstrated successful resolution of HAE attacks in randomized clinical trials and over 10 years of data post-approval
- Icatibant Outcome Survey: Longitudinal survey over 10 years; more than 5000 HAE attacks treated with 30 mg SC

Maurer et al 2020: Long-term effectiveness and safety of icatibant for the on-demand treatment of hereditary angioedema attacks: 10 years of the icatibant outcome survey (EAACI Poster #1118, June 6-8, 2020): https://clinicaltrials.gov/ct2/show/NCT01034969; https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022150Orig1s000ClinPharmR.pdf

Pharvaris developed a translational bradykinin challenge monkey model

PHA121, icatibant, or vehicle

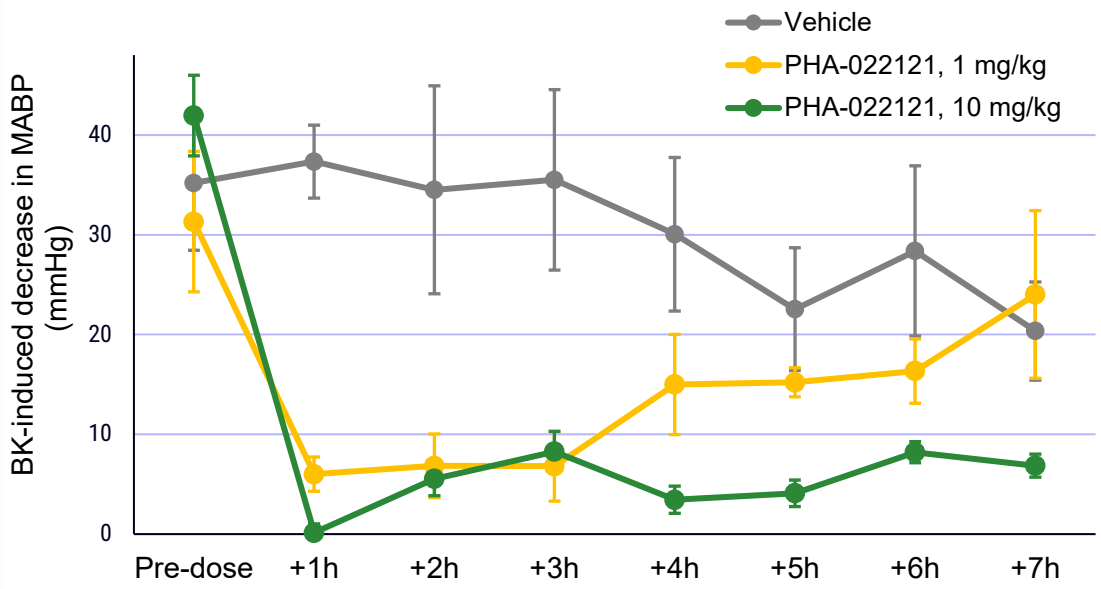




- Modelled after icatibant BK challenge in healthy volunteers (POC Phase I study)
- Mean arterial blood pressure (MABP) was measured using telemetry
- BK iv injected using infusion line and remote-control pump
- BK-induced a transient MABP decrease of 20-40 mmHg

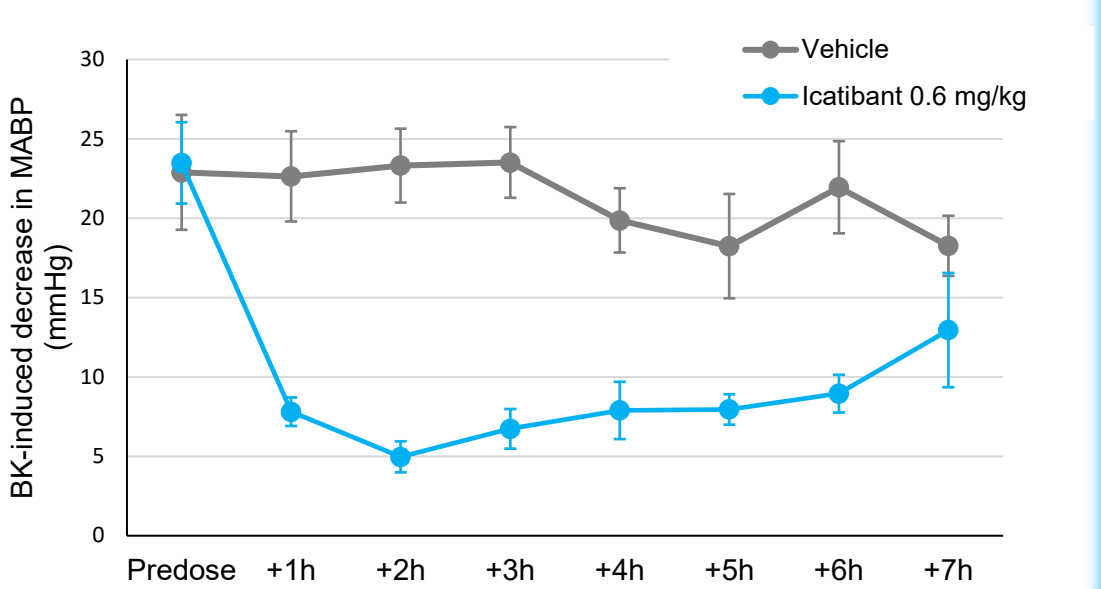
Oral PHA121 inhibits the bradykinin challenge in freely moving monkeys

PHA121/BK Challenge in monkeys



Maximal activity at 1 h

Icatibant/BK Challenge in monkeys



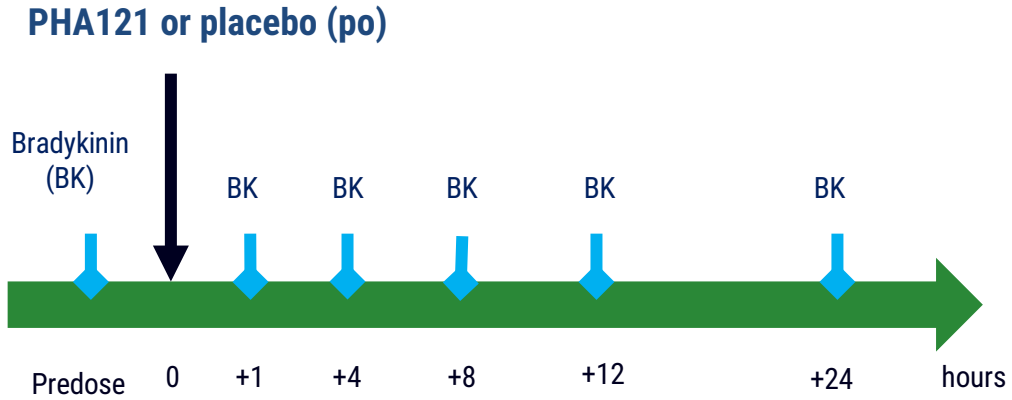
Maximal activity at 2 h

Pre-clinical BK challenge study in freely moving monkeys

- Clear dose-dependent activity
- Longer duration, faster onset of activity for PHA121 than icatibant

https://education.aaaai.org/sites/default/files/L37%20Lesage_1.pdf

Oral pre-treatment with PHA121 blocks the effect of IV bradykinin-induced hemodynamic changes in human studies



Human BK challenge	PHA121	Icatibant
EC_{50} (ng/mL)	2.4	9.5
EC_{85} (ng/mL)	13.8	53.8

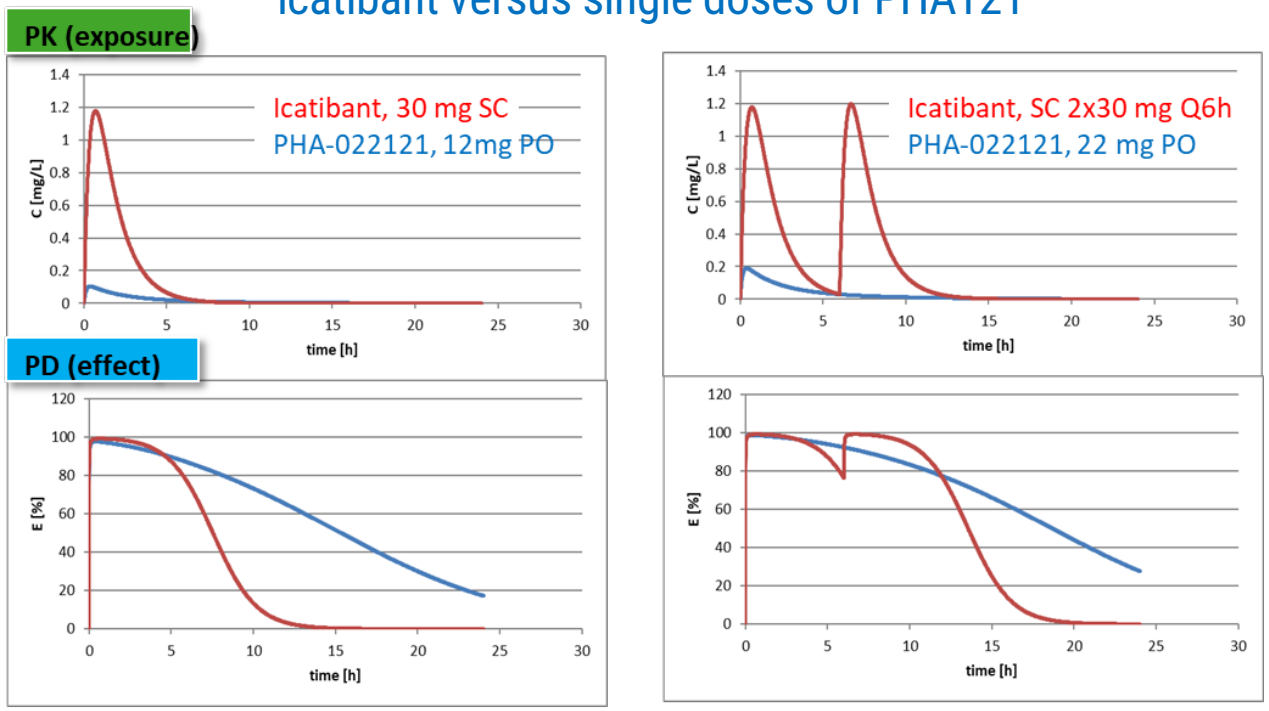
Phase 1 BK challenge study in healthy volunteers

- Potency ~4x higher than icatibant based on plasma concentration from published data
- Potency ~24x more potent than icatibant on Molar basis and taking free fraction in plasma into account (PHA121 0.17 nM vs. icatibant 4.1 nM)
- In vivo potency consistent with in vitro measurement (K_b 150 pM @ recombinant hB2 and pA2 350 nM @ endogenous B2 in human umbilical vein)

https://doi.org/10.1016/j.jaci.2019.12.094; https://epostersonline.com/acaai2020/node/1369

A single PHA121 dose expected to provide a similar pharmacodynamic effect as two injections of icatibant

Simulation of PK/PD resulting from single vs. double doses of icatibant versus single doses of PHA121



Estimated duration of effect (icatibant versus PHA121)

Response	Icatibant 30 mg SC	PHA121 12 mg PO	PHA121 22 mg PO
Time (h) plasma level above EC50 at 75% confidence level			
DBP	6	**11.5**	14
MABP	6	**12**	15.5
HR	6.5	**10**	13
Time (h) plasma level above EC85 at 50% confidence level			
DBP	5.5	7.5	**10**
MABP	5.5	7	**10**
HR	5.5	6.5	**9.5**

DBP: diastolic blood pressure; MABP: mean arterial blood pressure; HR: heart rate

https://epostersonline.com/acaai2020/node/1369

Human BK challenge study: A surrogate marker of clinical efficacy

- Human BK challenge study has been validated in the icatibant development
- In the monkey BK challenge study, PHA121 inhibited BK-induced changes with a faster onset and a longer duration of action as compared to icatibant
- PHA121 tested at two doses (12, 22 mg) in the BK challenge study in healthy volunteers
  - Demonstrated proof-of-mechanism
  - Provided justification of dose selection for on-demand studies
  - Provided guidance for prophylactic development

Based on prior experience with icatibant we expect that an oral dose of <50 mg PHA121 will show similar or better clinical efficacy as icatibant