Pharmacological profile of deucrictibant, a small molecule bradykinin B2 receptor antagonist in clinical development for hereditary angioedema

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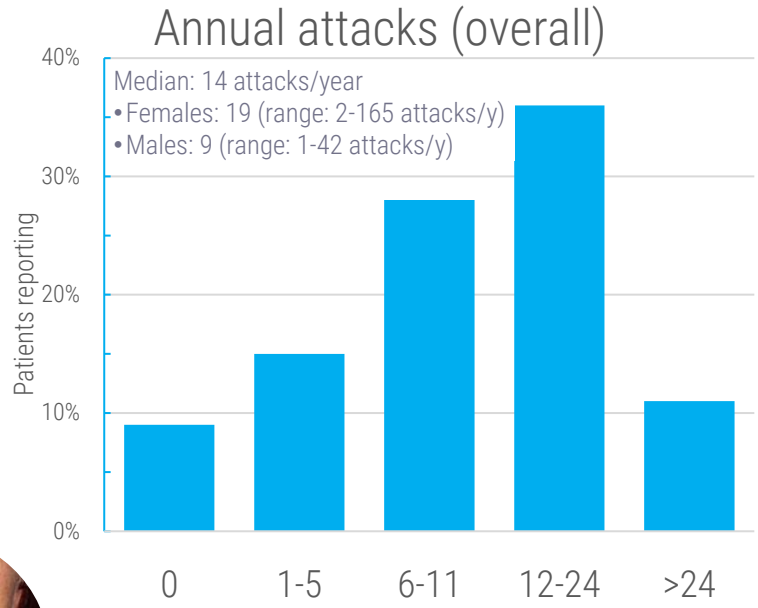
HAE: A rare, life-long genetic condition with significant burden from unpredictable, debilitating, and potentially lethal attacks of swelling

- Unpredictable frequency, location, timing, and severity
  - Multiple types of triggers
  - If untreated, attacks last multiple days
- Attacks are commonly painful, leading to hospitalization or multiple sick days
  - Half of people living with HAE experience a potentially life-threatening laryngeal attack at least once in their lifetime
- 1:10,000 to 1:50,000 Individuals affected by HAE globally
  - At least 6,600 people living with HAE in the U.S.
  - At least 8,900 people living with HAE in Europe
  - Globally, under-diagnosed/treated

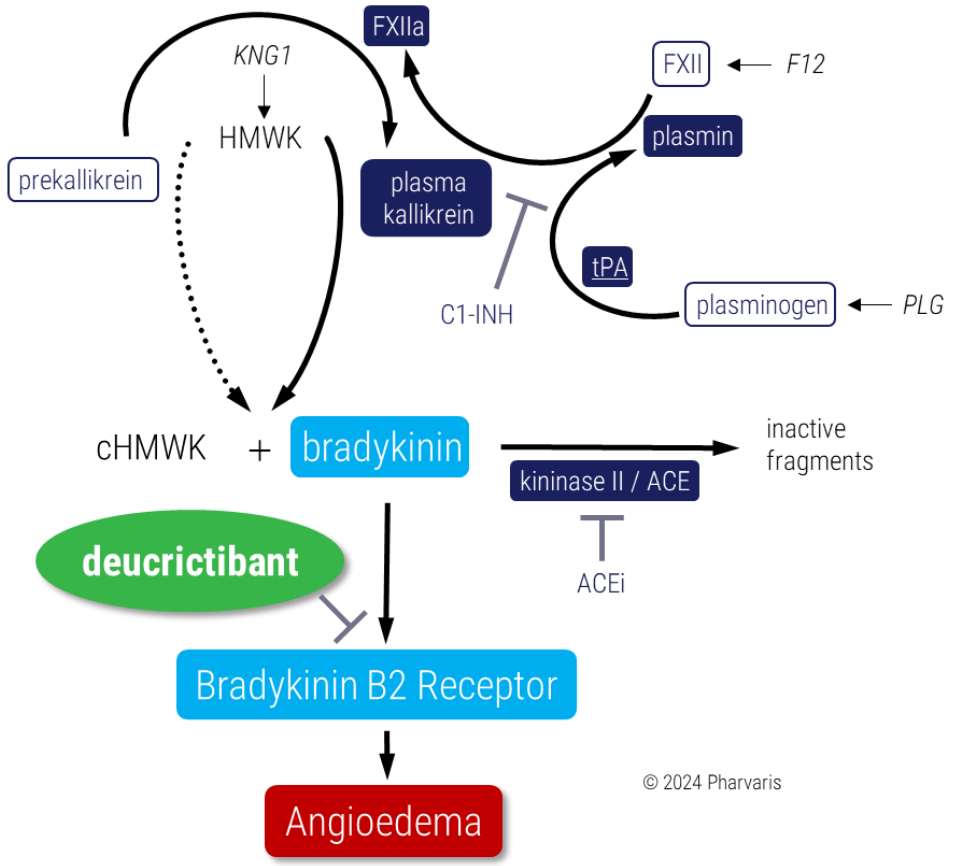


Source: Nordenfelt et al, Acta Derm. Venereol 2016: 96: 540-545; Busse 2020 J Allergy Clin Immunol Pract; Bork et al 2021 J Allergy Clin Immunol

Excess levels of bradykinin lead to swelling characteristic of angioedema attacks

Hereditary	HAE due to C1INH deficiency	**HAE Type 1**
		HAE Type 2
	HAE with normal C1INH	**HAE-FXII**
		HAE-PLG
		HAE-KNG
		HAE-HSST
		HAE-ANGPT
		HAE-MYOF
		HAE-unknown
Acquired	C1INH deficiency (AAE C1-INH)	**Lymphoproliferative disorders, B-cell malignancies**
		Autoimmune disorders
		Other disorders
	Drug-induced	**ACE-inhibitor**
		Other
	Idiopathic	**Histamine independent**
		Histamine dependent

***bold** = known or potential role for bradykinin involvement in disease*



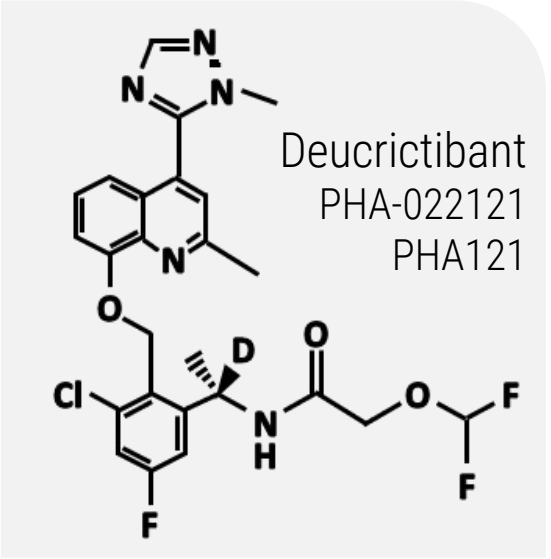
Source: Busse 2020 J Allergy Clin Immunol Pract; Bork et al 2021 J Allergy Clin Immunol; Zanichelli et al 2012 Allergy; Longhurst et al 2016 Clin. Exp. Immunol.; Otani, Banerji 2017 Immunol. Allergy Clin. N. Am.; Bova et al 2018 Int. Arch. Allergy Immunol.; Petersen, "Prophylaxis of angioedema attacks due to acquired C1-Inhibitor deficiency with PHA121, a novel oral bradykinin B2 receptor antagonist" C1-Inhibitor Workshop 2023 (https://2023.haenetworkshop.hu/program/index.php, https://www.linkedin.com/feed/update/urn:li:activity:7060638305842778112/); Shi et al 2021 Clin Immunol. 230 (doi.org/10.1016/j.clim.2021.108819), Reshef et al., 2024 J Allergy Clin Immunol, doi.org/10.1016/j.jaci.2024.03.024.

Notes: HMWK: high-molecular-weight kininogen; cHMWK: cleaved high-molecular-weight kininogen; FXII(a): Factor XII(a); ACE(i): angiotensin-converting enzyme (inhibitor); tPA: tissue plasminogen activator; KNG1: gene encoding HMWK; PLG: gene encoding plasminogen; FXII: gene encoding FXII; ANGPT: gene encoding angiopoietin; MYOF: gene encoding myoferlin; HSST: gene encoding heparan sulfate sulfotransferase; SCLS: systemic capillary leak syndrome

Targeting the culprit in HAE: bradykinin

Deucrictibant: A novel, orally bioavailable bradykinin B2 receptor antagonist for bradykinin-mediated angioedema

- Potent and selective inhibitor of the bradykinin B2 receptor
- The first orally available bradykinin B2 receptor antagonist
- The compound contains a deuterium that was introduced into a metabolic soft spot, to stabilize the molecule.
- Currently in late-stage development for hereditary angioedema

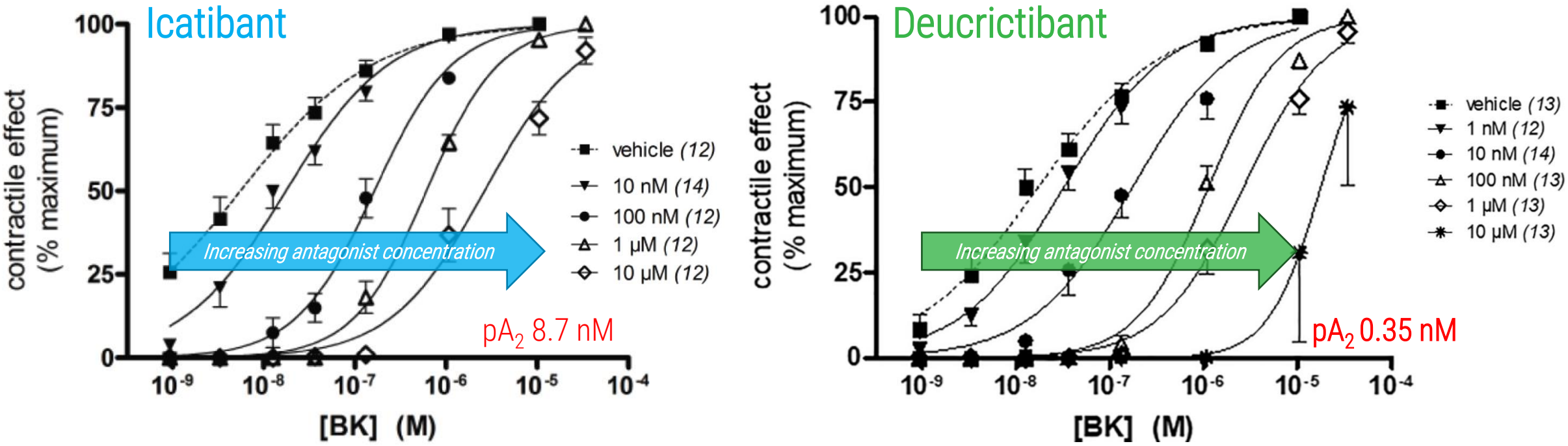


We aspire to develop **novel, oral alternatives** that **improve** the **standard of care** for people living with HAE and other bradykinin-mediated diseases

Source: Lesage et al, Frontiers in Pharmacology 2020, doi: 10.3389/fphar.2020.00916; Lesage et al, Int. Immunopharmacology 2022, doi.org/10.1016/j.intimp.2022.108523; https://ir.pharvaris.com/static-files/0361cd85-6000-490b-932b-d305e1f3ca1b; https://ir.pharvaris.com/static-files/81a9499d-0769-4b89-8ecd-8ace5ca521d3; https://ir.pharvaris.com/static-files/33217945-6893-4f49-8a93-c80ea6fb2a31; https://doi.org/10.1016/j.jaci.2019.12.094 ; Maurer et al., 2023 AAAAI, https://ir.pharvaris.com/static-files/351671e4-35b8-4bc3-a50d-ef96e17059ab; Riedl et al., 2024 AAAAI, https://ir.pharvaris.com/static-files/42de033b-052a-4067-ad10-2c946c9aa2c7

Deucrictibant is a competitive inhibitor of the bradykinin B2 receptor

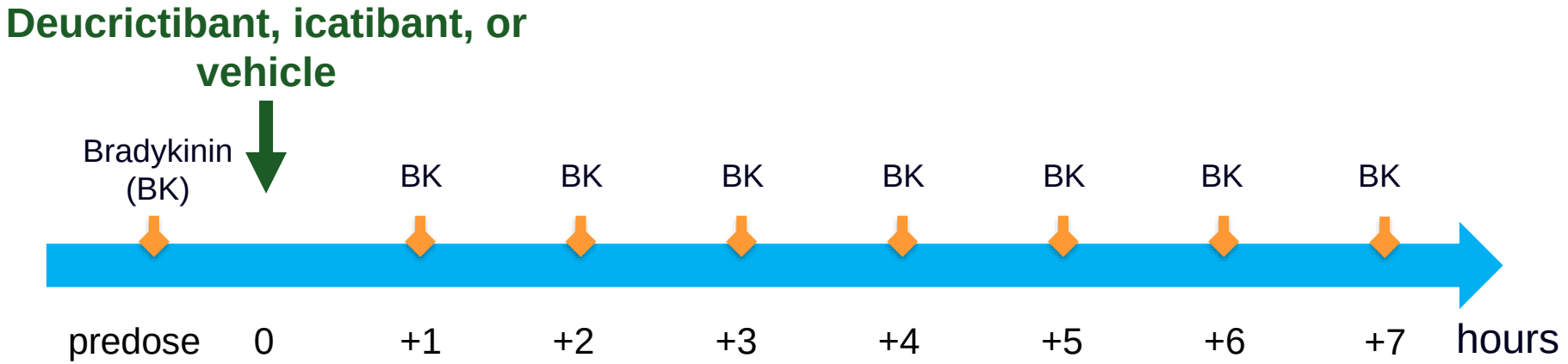
Competitive antagonism of bradykinin-induced contraction
(human umbilical vein preparation)

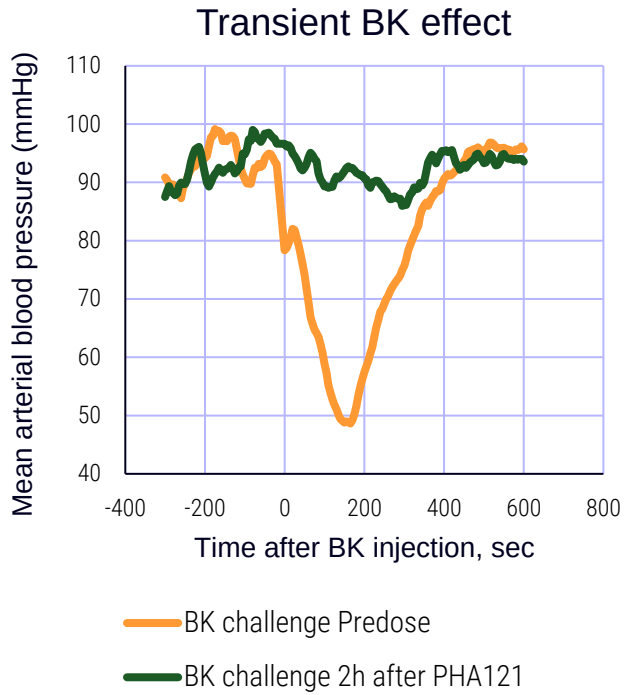


deucrictibant is 25-fold more potent than icatibant at the endogenous human B2 receptor

Source: Lesage et al, *Frontiers in Pharmacology* 2020, doi: 10.3389/fphar.2020.00916; Lesage et al, Int. *Immunopharmacology* 2022, doi.org/10.1016/j.intimp.2022.108523

Development of translational bradykinin challenge model in monkey



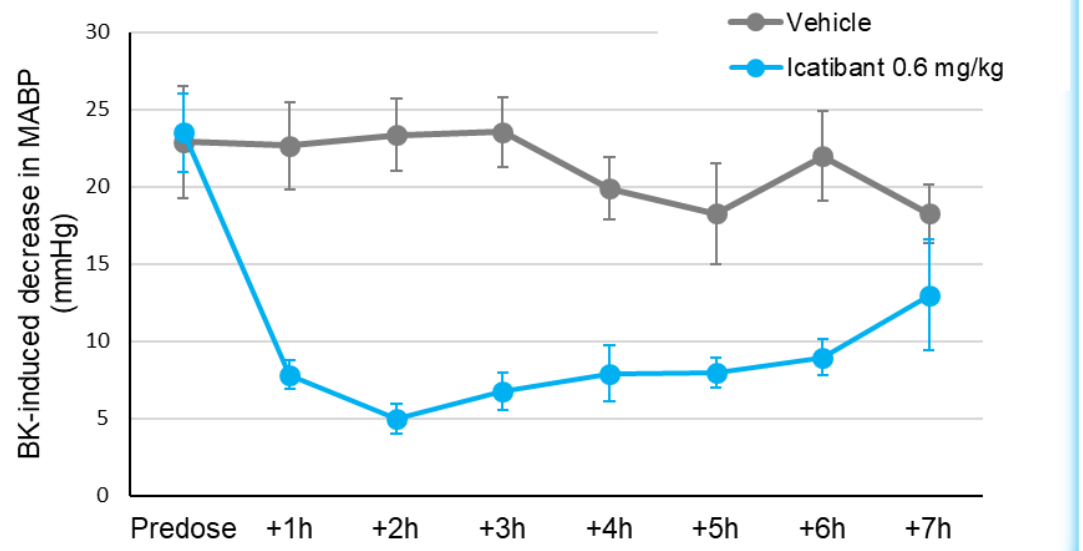


- Conscious, freely moving monkeys
- BK bolus was administered iv using infusion line and remote-control pump
- Mean arterial blood pressure (MABP) was measured using telemetry
- BK induced a transient MABP decrease of 20-40 mmHg

Source: Lesage et al, Kinin 2022, https://ir.pharvaris.com/static-files/f6622f7e-e405-4901-9bc9-5051a3588126

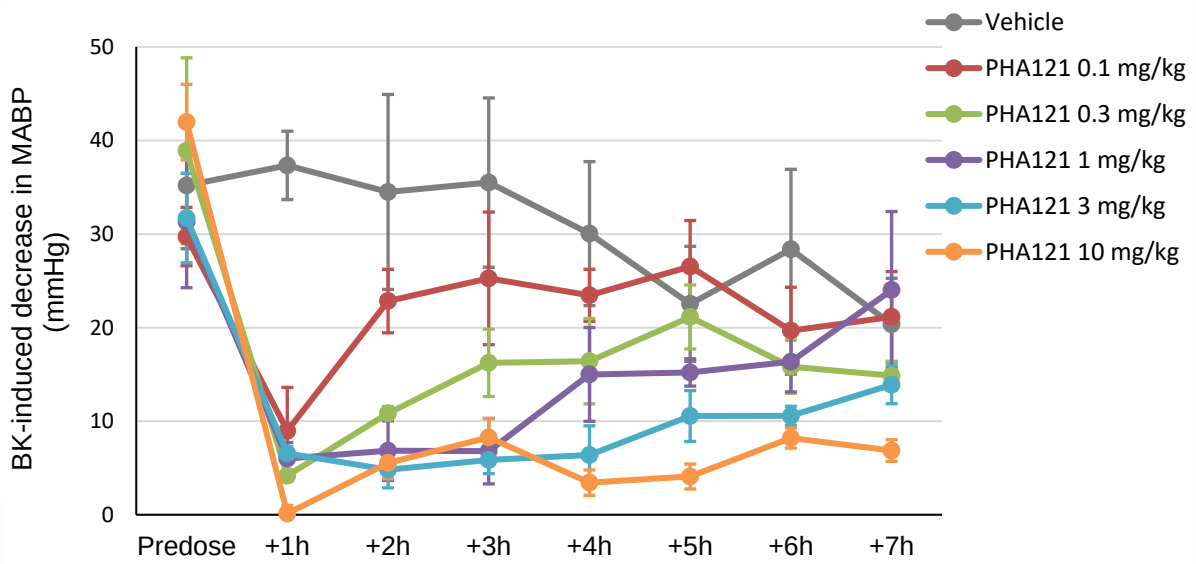
In preclinical in vivo studies, oral deucrictibant inhibits challenge by bradykinin with longer duration and faster achievement of peak of effect than SC icatibant

Icatibant/BK Challenge in monkeys



Maximal activity at 2 h

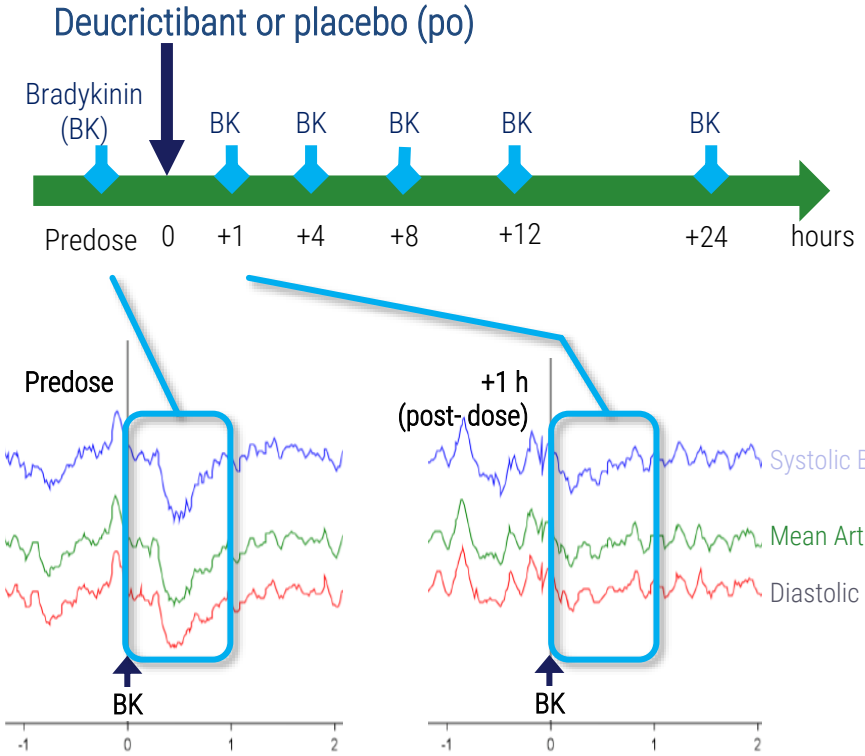
PHA121/BK Challenge in monkeys



Maximal activity at 1 h

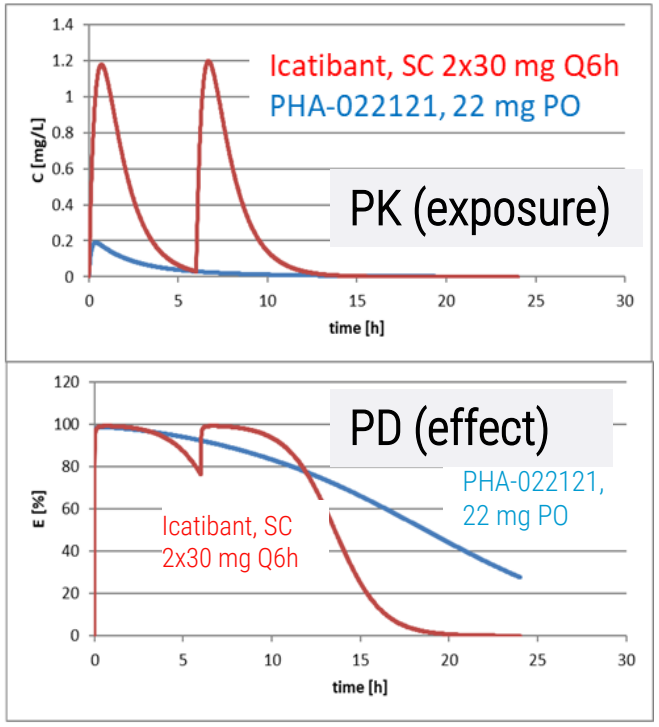
Source: https://education.aaaai.org/sites/default/files/L37%20Lesage_1.pdf ; Lesage et al., 2021, 12th C1-Inhibitor deficiency and angioedema workshop presentation https://ir.pharvaris.com/static-files/76beb63f-4ccf-482a-933d-d2b47ec4e09d

In healthy volunteers, oral pre-treatment with deucrictibant blocks the effect of bradykinin-induced hemodynamic changes



PK/PD modeled using a nonlinear mixed-effect E_{max} model comparing effect (inhibition of the baseline average-to-peak) to PK (two-compartment model, first-order oral absorption)

EC_{50} (ng/mL)	2.4
EC_{85} (ng/mL)	13.8



A **single** deucrictibant dose predicted to provide **similar PD effect** as two injections of icatibant

Source: https://epostersonline.com/acaai2020/node/1369; https://doi.org/10.1016/j.jaci.2019.12.094; https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022150Orig1s000ClinPharmR.pdf

Deucrictibant is 20- to 25-fold more potent than icatibant

Human bradykinin B2 receptor function		Icatibant	Deucrictibant	Deucrictibant potency vs icatibant
		Potency, nM		
In vitro	Recombinant human B2 receptor in CHO cell line	3.19	0.15	21-fold higher
Ex vivo	Endogenous B2 receptor in human umbilical vein	8.71	0.35	25-fold higher
In vivo	Human BK challenge haemodynamic model *	4.08	0.17	24-fold higher

* Potency expressed in nM, considering free fraction in plasma 0.56 for icatibant and 0.038 for deucrictibant, and MW 1,305 for icatibant and 535 for deucrictibant

Picomolar potency of deucrictibant is confirmed in 3 models

Source: Lesage et al, Int. Immunopharmacology 2022, doi.org/10.1016/j.intimp.2022.108523

One disease
Two treatment paradigms

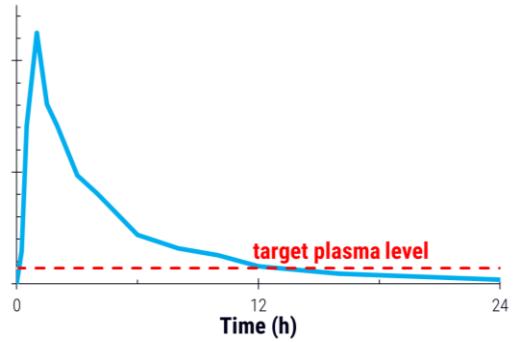
One active ingredient
Two optimized formulations

Our strategy: Manage HAE with two oral products that utilize the same active ingredient for on-demand and prophylactic treatment

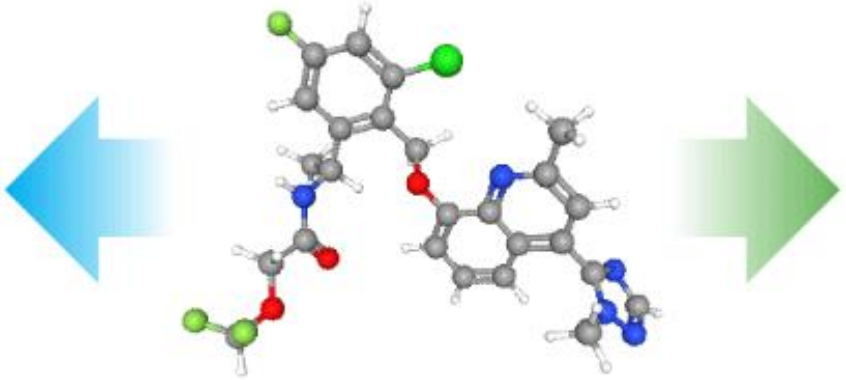
deucrictibant (PHVS416)

Immediate-release capsule

rapid absorption



Aim to provide rapid and reliable symptom relief, through rapid exposure of attack-mitigating therapy in a convenient, small oral dosage form*

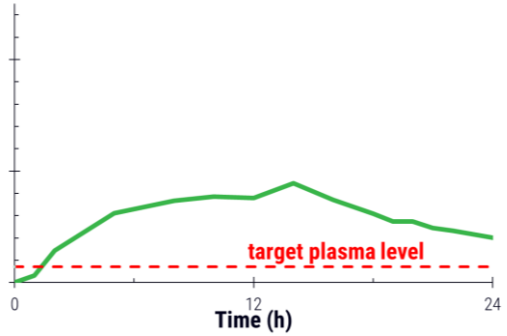


Deucrictibant
PHA-022121
PHA121

deucrictibant (PHVS719)

Extended-release tablet

sustained absorption

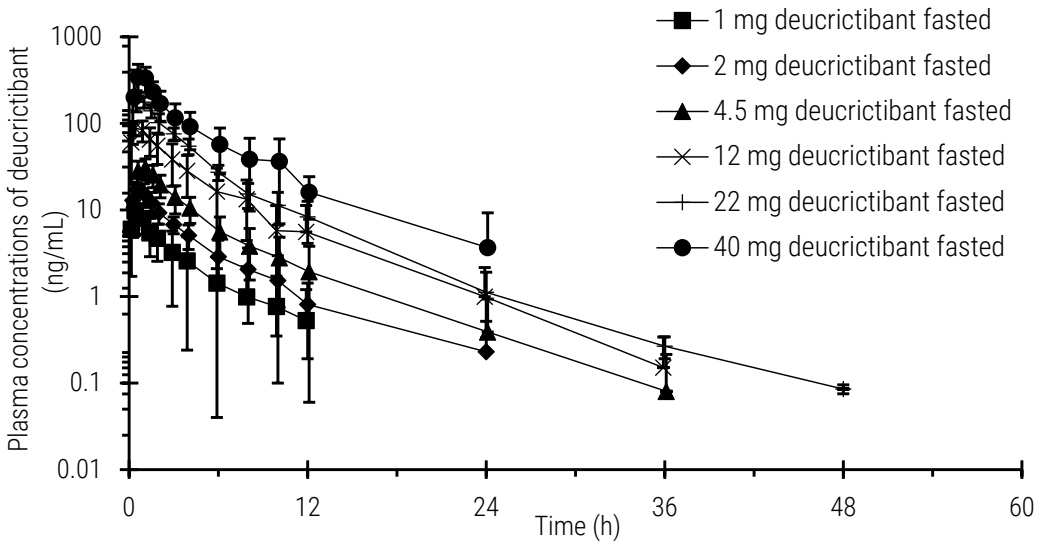


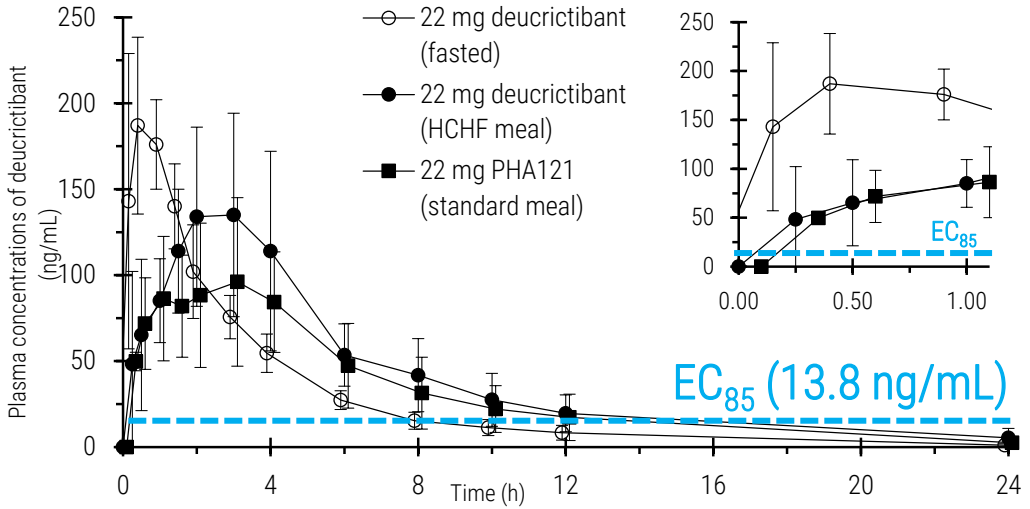
Aim to provide sustained exposure of attack-preventing medicine in a convenient, small oral dosage form*

Deucrictibant has the potential to become the preferred therapy for people living with HAE to manage their condition

*Aspirational; to be confirmed with clinical data

First-in-human Phase 1 study
Deucrictibant PK profile optimally suited for on-demand treatment



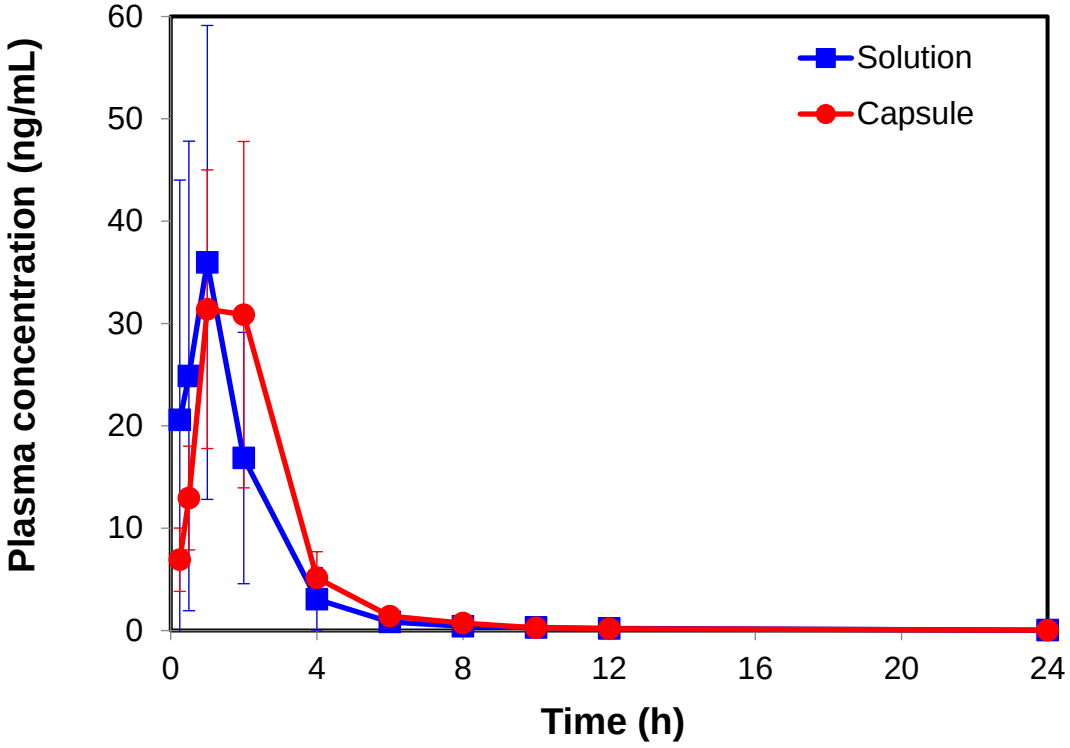


- Rapid absorption, achievement of therapeutic levels (EC_{85}) within 15-30 minutes
- Plasma half-life approximately 3.5 to 5.6 hours, about 3-fold longer than icatibant
- Plasma exposure remained above EC_{85} for 8 to >10 h

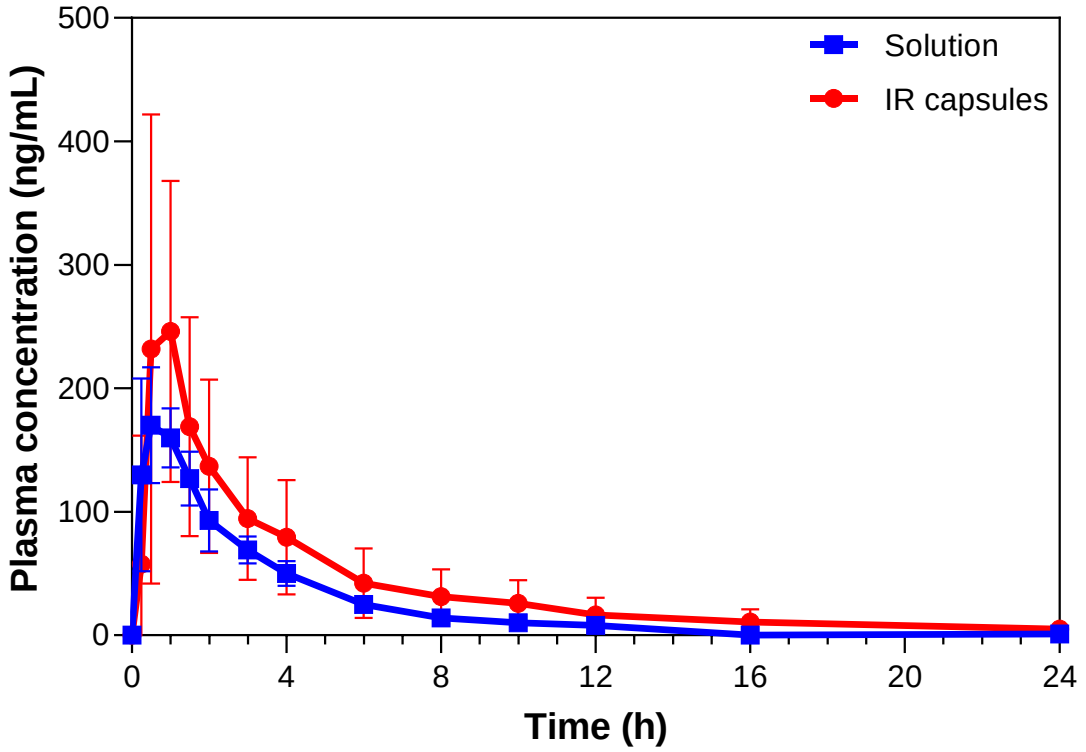
Source: Lu , et al. ACAAI 2020 https://ir.pharvaris.com/static-files/0361cd85-6000-490b-932b-d305e1f3ca1b; Maurer, et al., AAAAI 2023 https://ir.pharvaris.com/static-files/351671e4-35b8-4bc3-a50d-ef96e17059ab ; Crabbé et al., AAAAI 2021 https://ir.pharvaris.com/static-files/a5937e81-635a-4808-b099-3a049c87c51b

In preclinical and clinical studies, the solution formulation showed a similar PK profile as the capsule

Exposure of 3 mg deucrictibant in monkey



Exposure of 20 mg deucrictibant in human



Exposure of deucrictibant in healthy volunteers was assessed in 2 independent trials (C001 and C010) and overlayed here for the purpose of comparison

Source: Lesage et al, Kinin 2022, https://ir.pharvaris.com/static-files/f6622f7e-e405-4901-9bc9-5051a3588126 ; Pharvaris, data on file

Deucrictibant formulated as an immediate-release oral soft capsule

20 mg capsule

(example, not the actual product)

- Deucrictibant immediate-release (IR) capsules meet the target product profile for oral on-demand treatment of HAE attacks
  - Rapid absorption with mean plasma levels reaching the threshold of therapeutic exposure (EC_{85}) within 15-30 minutes from deucrictibant administration
  - Mean plasma levels of deucrictibant maintained >EC85 for approx. 8 to >10 hours (10 to 30 mg deucrictibant IR capsule doses)
  - Deucrictibant IR capsules are being used for our Phase 2 and 3 trials for the on-demand treatment of HAE

Source: Maurer, et al., AAAAI 2023 https://ir.pharvaris.com/static-files/351671e4-35b8-4bc3-a50d-ef96e17059ab,

Designing an extended-release (XR) formulation meeting the requirements of prophylaxis

- 24-hour exposure of test item in human requires
  - Slow release dosage form, gradual disintegration over time
  - Test item to be absorbed throughout the entire GI tract, including the colon
  - High oral bioavailability: test item to be highly absorbed in the gut
  - An acceptable peak to trough plasma exposure in PK profile

Evidence of deucrictibant absorption in the gut

Fecal excretion in rat & monkey

	Excretion of deucrictibant, recovery over 24 h in %		Oral bioavailability, Fpo
	Urine	Faeces	
Rat	0.05	2.2	43%
Monkey	<0.01	<0.5	28%

- High oral bioavailability together with little to no deucrictibant excretion in preclinical species, suggest full absorption potential in the GI tract

Source: Lesage, et al., ACAAI 2022 https://ir.pharvaris.com/static-files/c6a3ec57-e2db-41ca-a2c8-f184f4759be4

Low/absent excretion of unchanged deucrictibant in human confirms high extent of absorption in human gastrointestinal tract

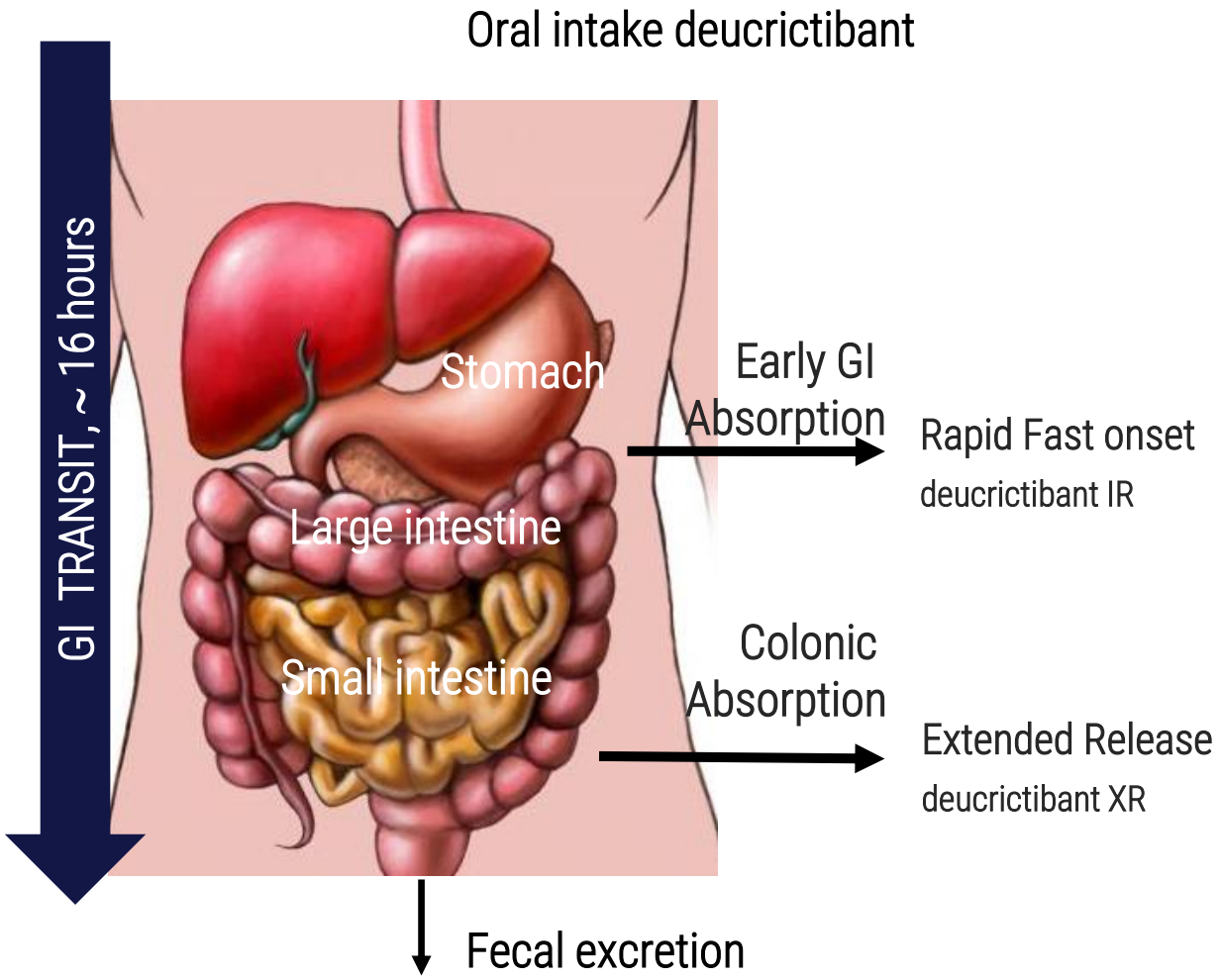
Single dose mass balance study with deucrictibant in human *	Excretion of deucrictibant, recovery over 72 h in %		Oral bioavailability, Fpo
	Urine	Feces	
	0.09	3.2	57%

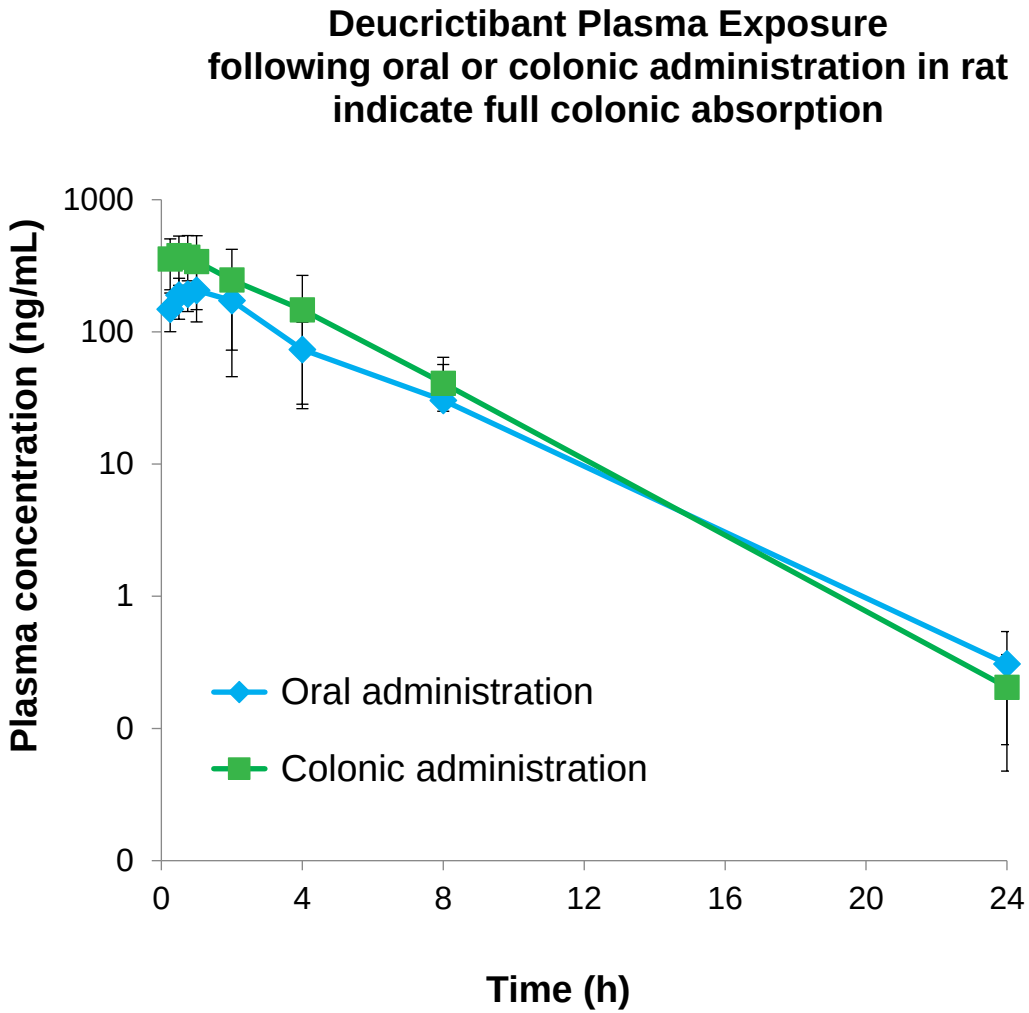
*Single-dose mass balance and absolute bioavailability study with an oral 20 mg dose of deucrictibanr and an oral and intravenous microtracer dose of 14C-deucrictibant in healthy male subjects

- High oral bioavailability together with low fecal excretion of deucrictibant confirmed the assumption of high absorption in the gastrointestinal tract

Source: Lesage, et al., ACAAI 2022 https://ir.pharvaris.com/static-files/c6a3ec57-e2db-41ca-a2c8-f184f4759be4

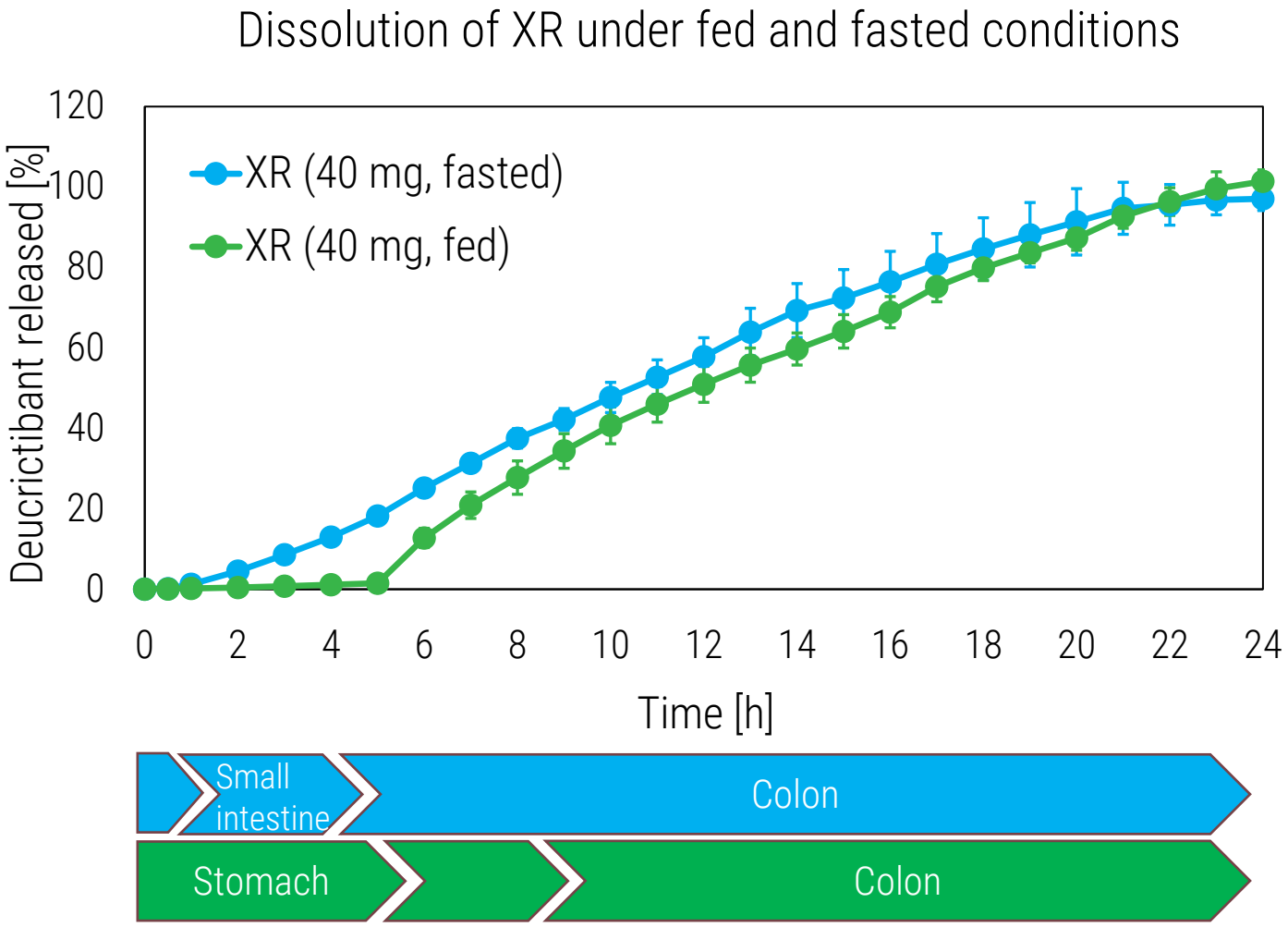
Evidence of colonic absorption in rat indicates feasibility of extended drug release

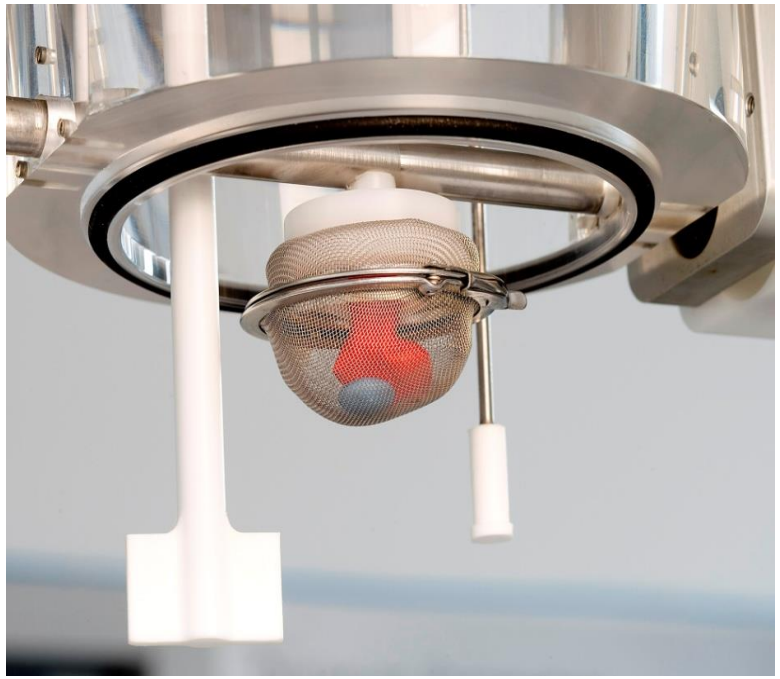




Source: Lesage, et al., ACAAI 2022 https://ir.pharvaris.com/static-files/c6a3ec57-e2db-41ca-a2c8-f184f4759be4

In vitro, gradual, near linear dissolution of deucrictibant from XR tablet

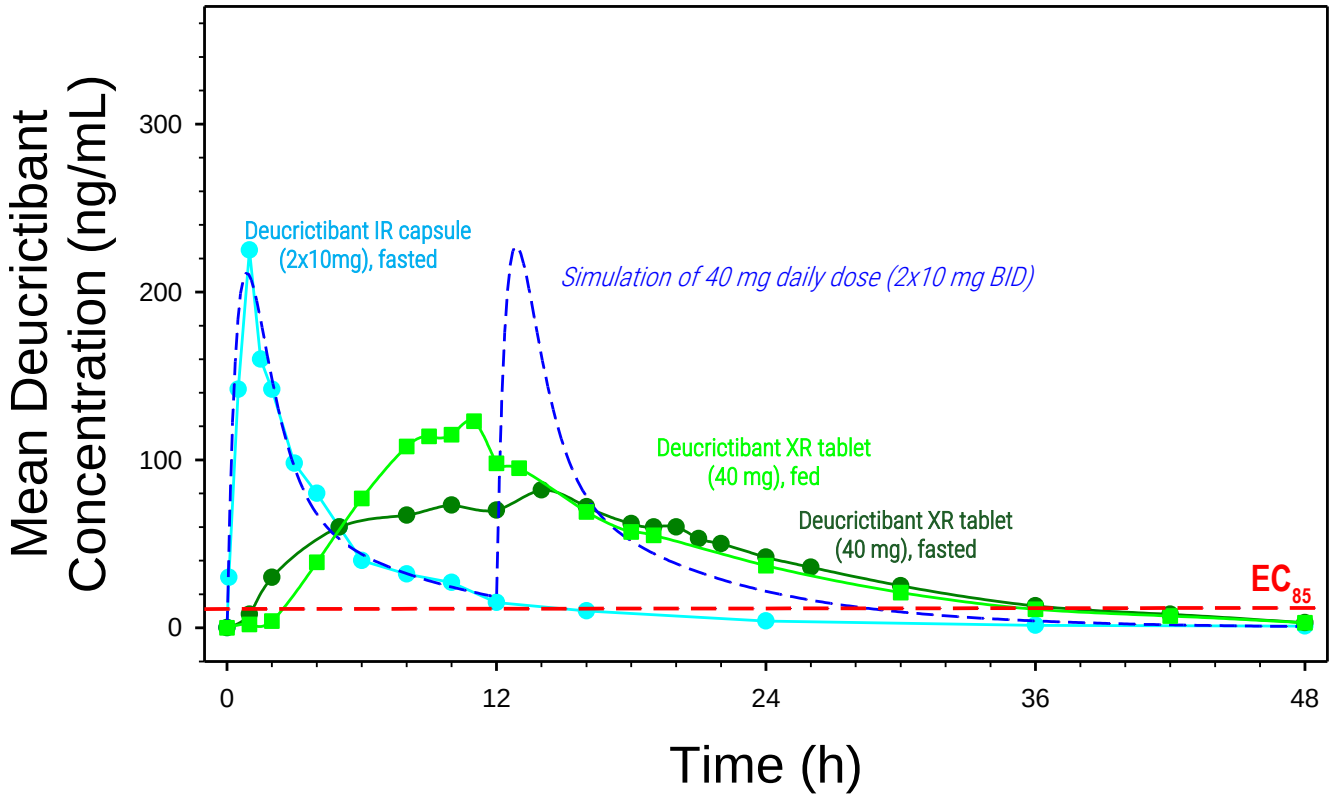




Simulated GI matrix and mechanical stress

Source: Lesage, et al., ACAAI 2022 https://ir.pharvaris.com/static-files/c6a3ec57-e2db-41ca-a2c8-f184f4759be4

As seen in a single-dose Phase 1 PK study, deucrictibant XR demonstrates QD potential: proposed Phase 3 dosage form



- Deucrictibant IR and XR well tolerated
  - No SAEs or severe TEAEs
- Deucrictibant XR maintained exposure above EC_{85} for >24h with and without food
  - Similar AUC_{24h} as 40 mg deucrictibant IR dosed with food

Deucrictibant XR anticipated to maintain higher trough exposure relative to BID deucrictibant IR

Source: Pharvaris, Data on file

Deucrictibant formulated as a film-coated extended-release tablet

(examples, not the actual product)

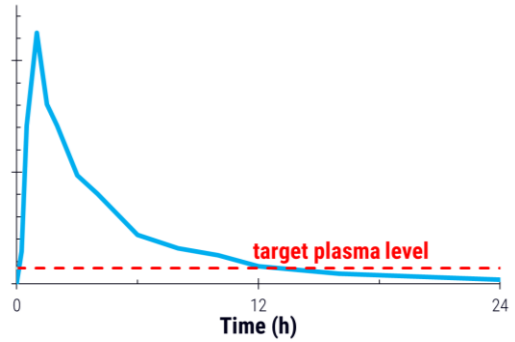
- Deucrictibant extended-release (XR) meets target product profile for oral prophylactic treatment of HAE
  - 24 hours coverage of anticipated therapeutic exposure
  - Deucrictibant XR is anticipated to be used for our Phase 3 trial for prophylactic treatment of HAE

Our strategy: Manage HAE with two oral products that utilize the same active ingredient for on-demand and prophylactic treatment

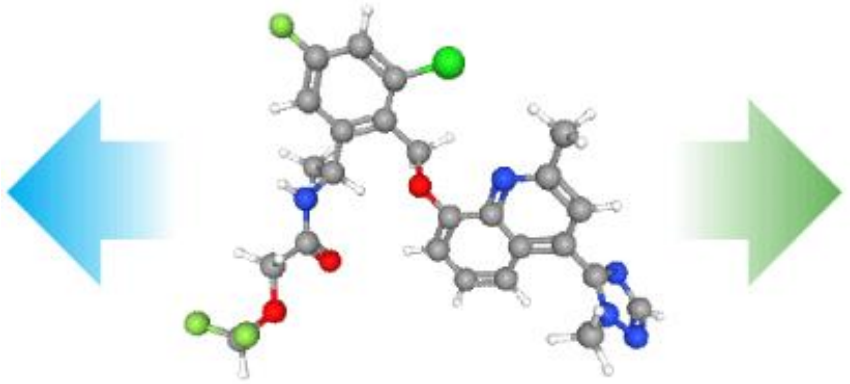
deucrictibant (PHVS416)

Immediate-release capsule

rapid absorption



Aim to provide rapid and reliable symptom relief, through rapid exposure of attack-mitigating therapy in a convenient, small oral dosage form*

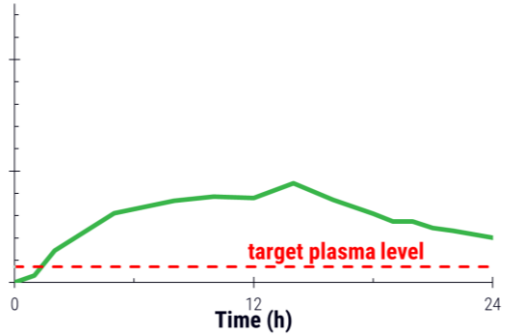


Deucrictibant
PHA-022121
PHA121

deucrictibant (PHVS719)

Extended-release tablet

sustained absorption



Aim to provide sustained exposure of attack-preventing medicine in a convenient, small oral dosage form*

Deucrictibant has the potential to become the preferred therapy for people living with HAE to manage their condition

*Aspirational; to be confirmed with clinical data

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Aspiring to free people from HAE or other bradykinin-mediated diseases