PHARVARIS

Tailored drug development for patients living with HAE

Satellite Symposium Kinin 2022, June 7

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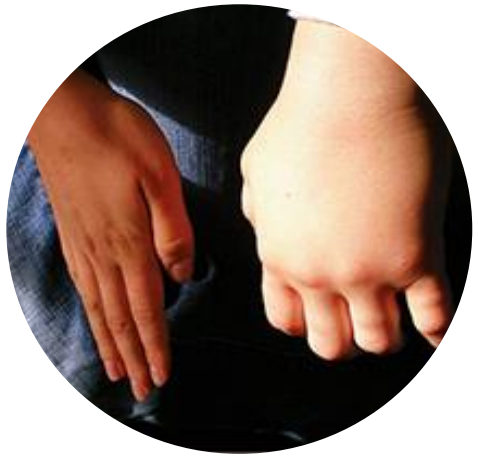
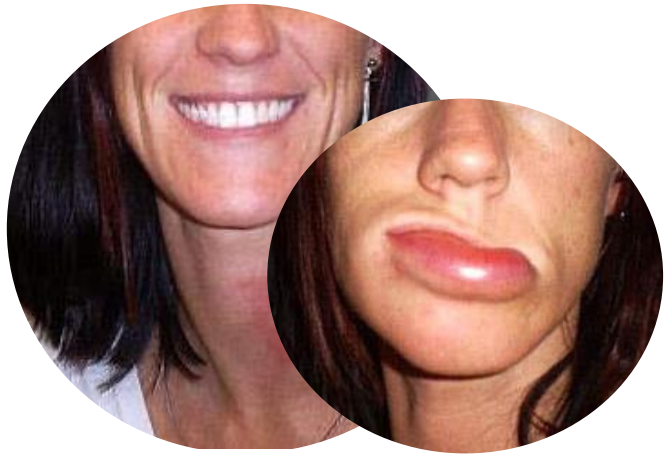
Hereditary angioedema (HAE) is a rare, life-long condition characterized by attacks of swelling

- Rare and potentially life-threatening genetic condition
- 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



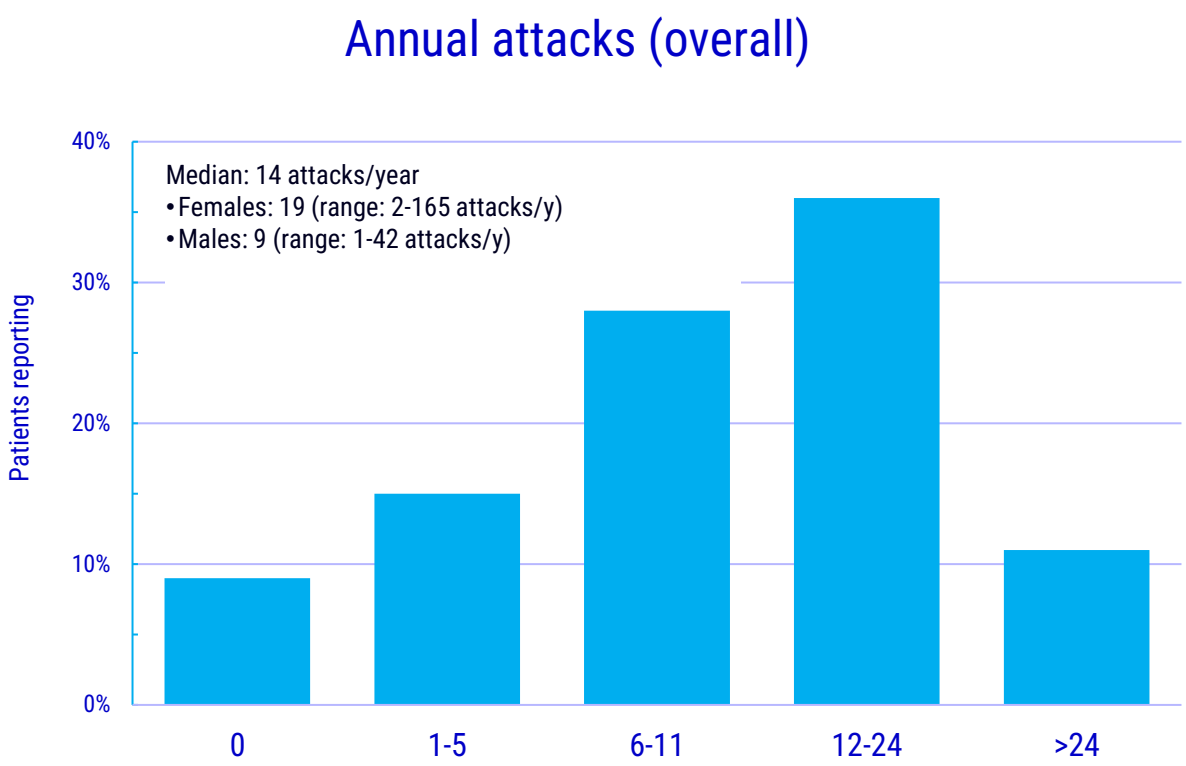


Nordenfelt et al, Acta Derm. Venereol 2016: 96: 540-545

HAE attacks are unpredictable, debilitating and potentially lethal

Attacks are unpredictable in 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



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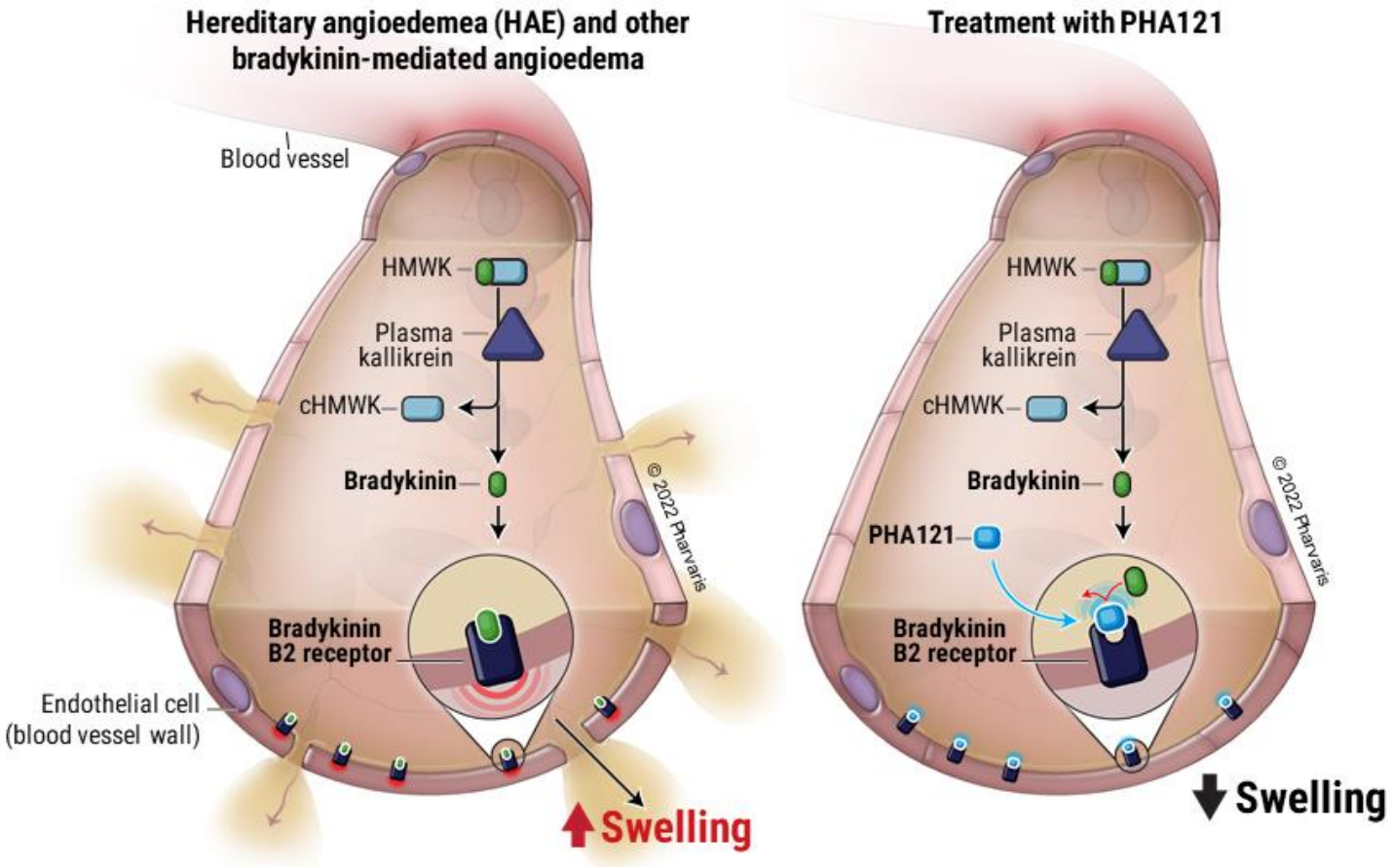
Bradykinin B2 receptor blockade is a clinically proven effective treatment of HAE attacks



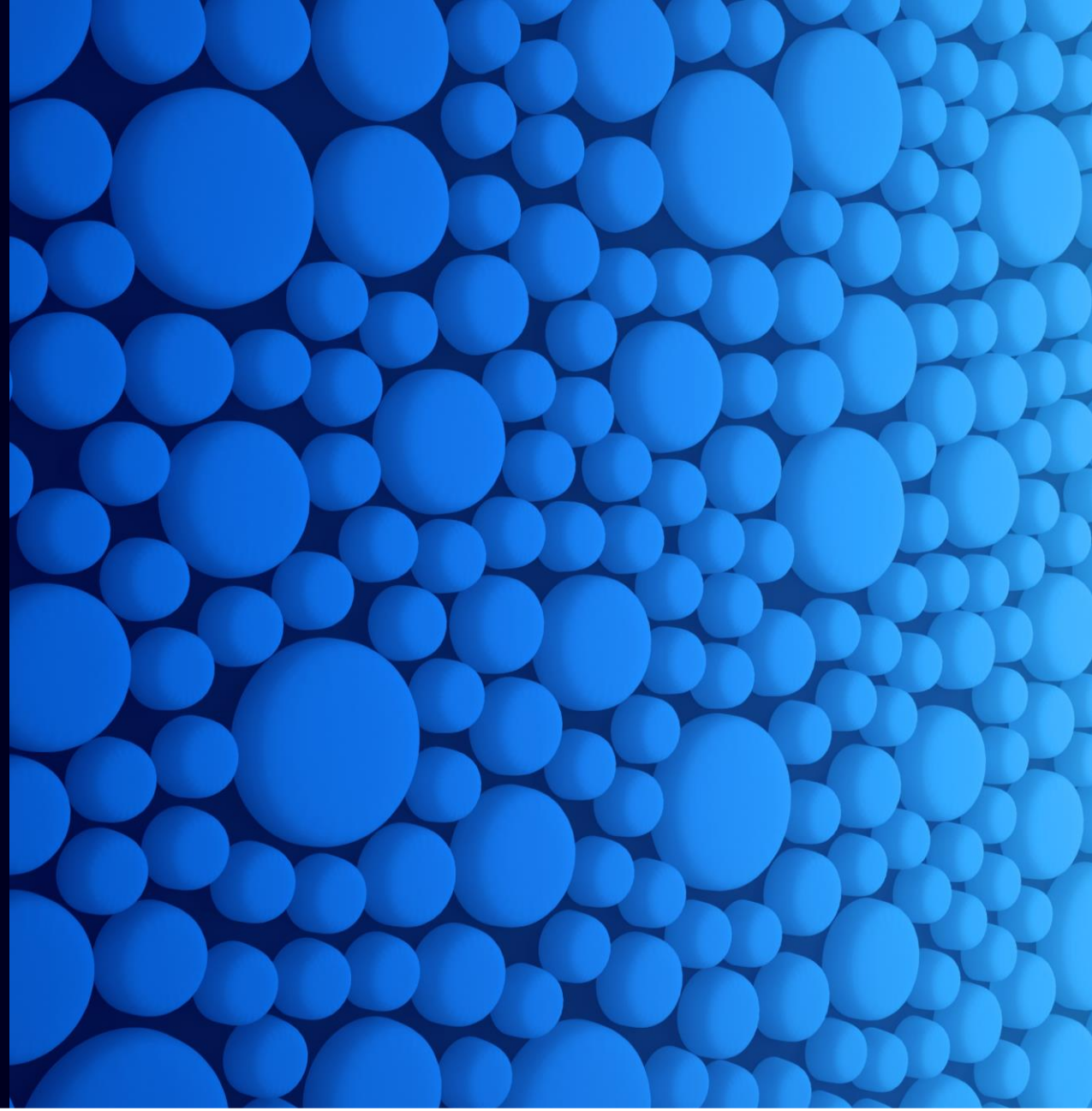
HMWK: high-molecular-weight kininogen; cHMWK: cleaved high-molecular-weight kininogen

Excess bradykinin is the cause of signs and symptoms of swelling during an HAE attack

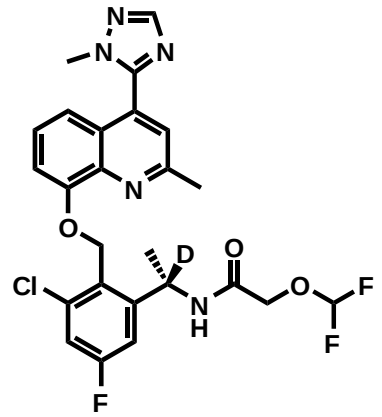
Icatibant is a bradykinin B2 receptor antagonist, a marketed and proven effective treatment of HAE attacks

PHA121 is designed to block signaling by bradykinin

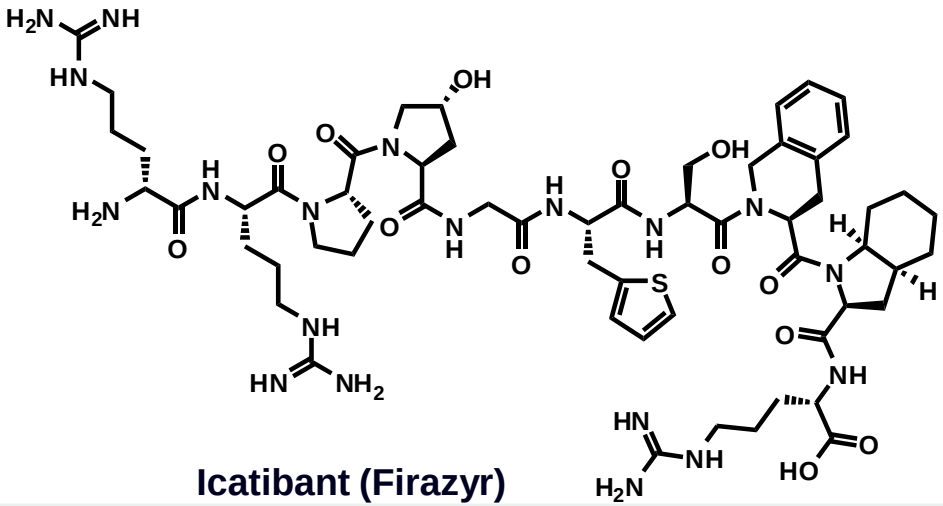
Targeting the culprit in HAE: bradykinin



PHA121 (PHA-022121)



PHA121



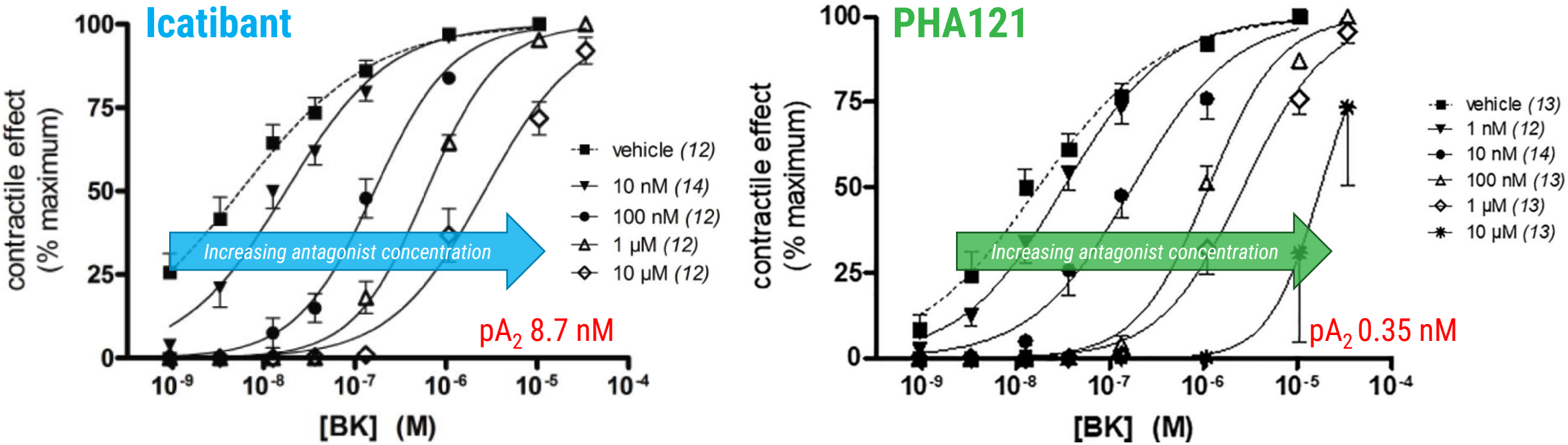
Icatibant (Firazyr)

PHA121

- PHA121 is the first orally bioavailable bradykinin B2 receptor antagonist
- Highly potent and selective B2 antagonist
- 2.4-fold lower molecular weight than icatibant
- Metabolic soft spot has been stabilized by the introduction of a deuterium atom
- Optimized for metabolic stability and exposure in human

PHA121 is a uniquely potent, orally available competitive inhibitor of the bradykinin B2 receptor

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

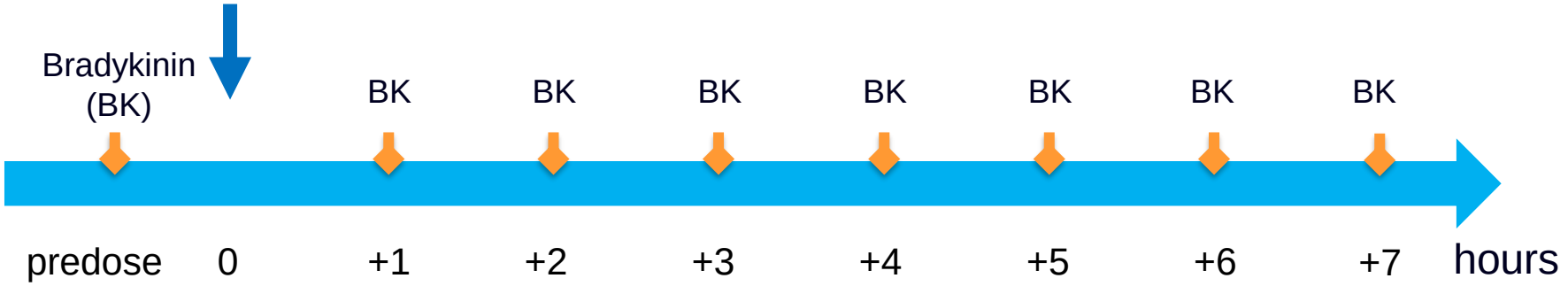


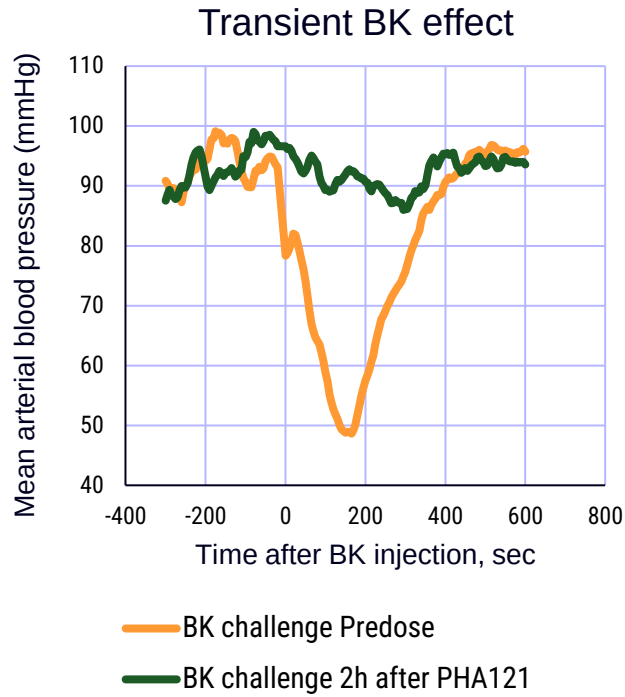
PHA121 is 25-fold more potent than icatibant at the endogenous human B2 receptor

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*

Translational bradykinin challenge model in monkey

PHA121, icatibant, or vehicle

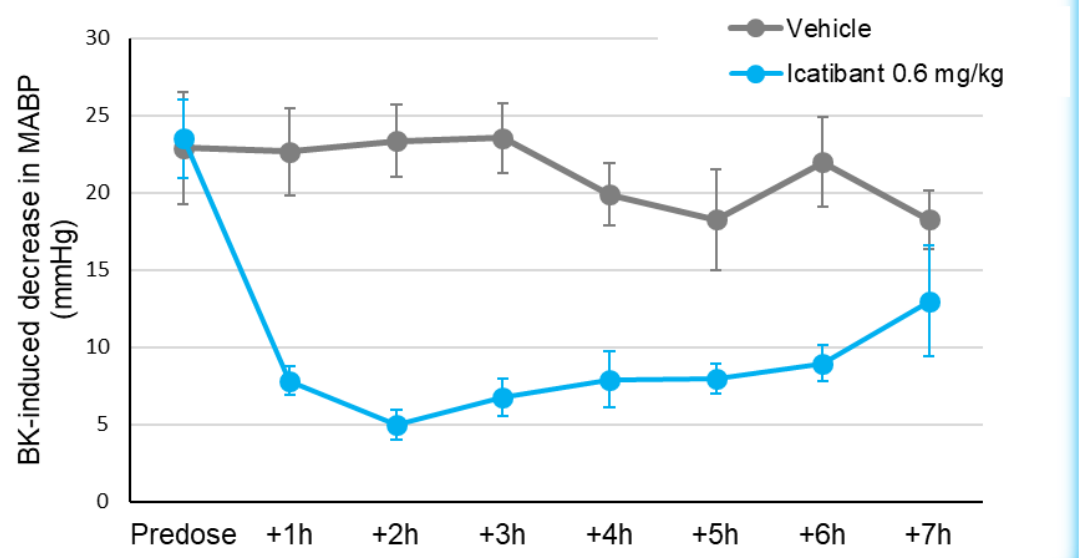




- Modelled after icatibant BK challenge in healthy volunteers (POC Phase I study)
- Mean arterial blood pressure (MABP) was measured using telemetry
- BK iv injected using infusion line and remote-control pump
- BK-induced a transient MABP decrease of 20-40 mmHg

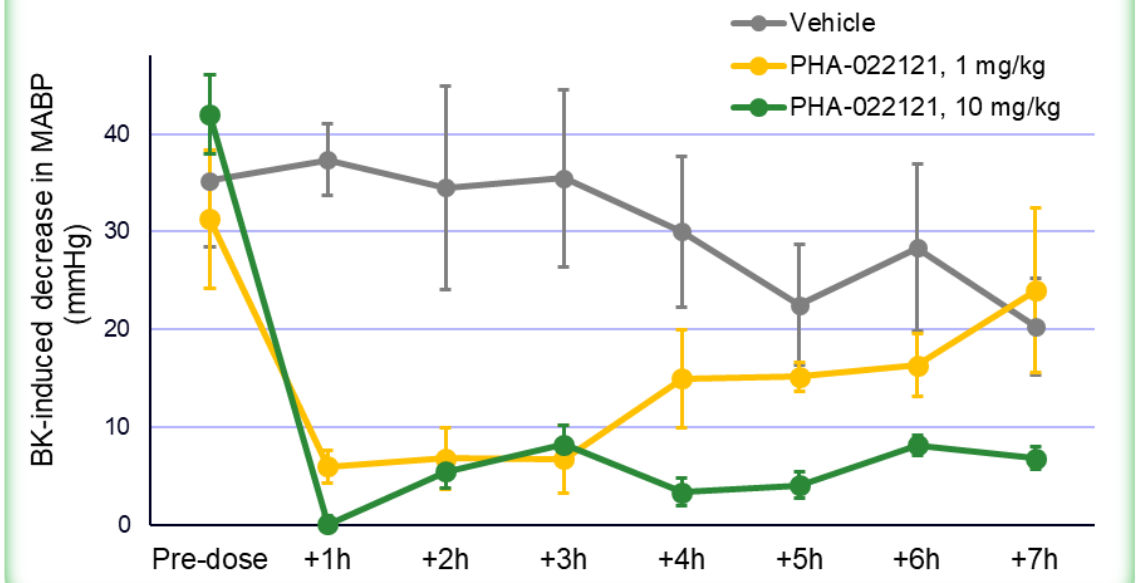
In preclinical in vivo studies, oral PHA121 inhibits challenge by bradykinin with longer duration and faster onset than SC icatibant

Icatibant/BK Challenge in monkeys



Maximal activity at 2 h

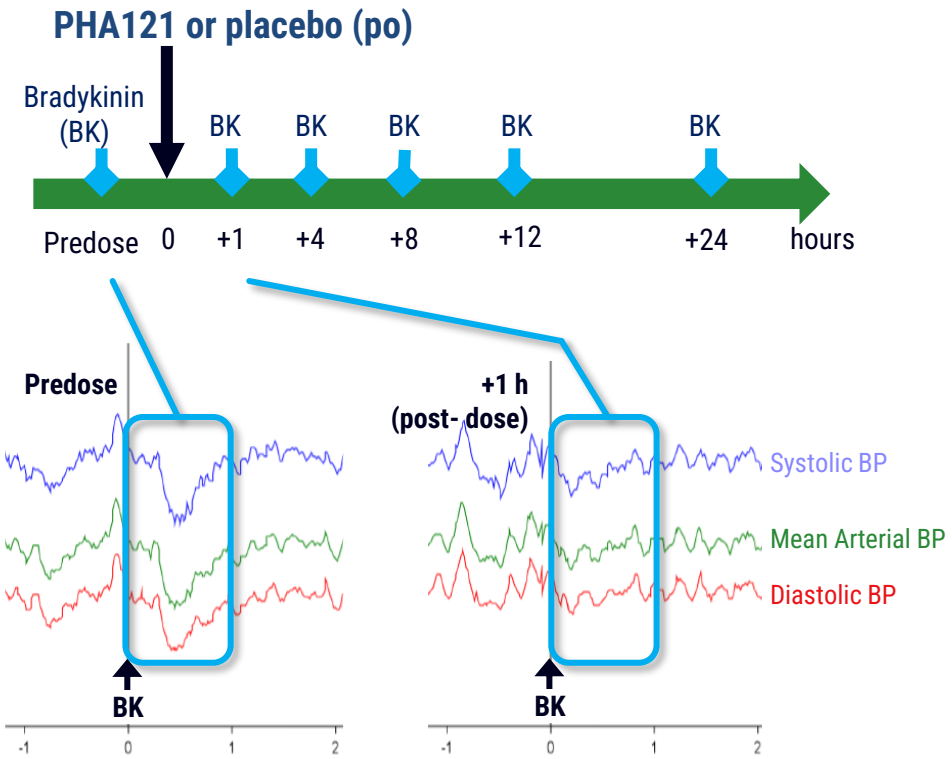
PHA121/BK Challenge in monkeys



Maximal activity at 1 h

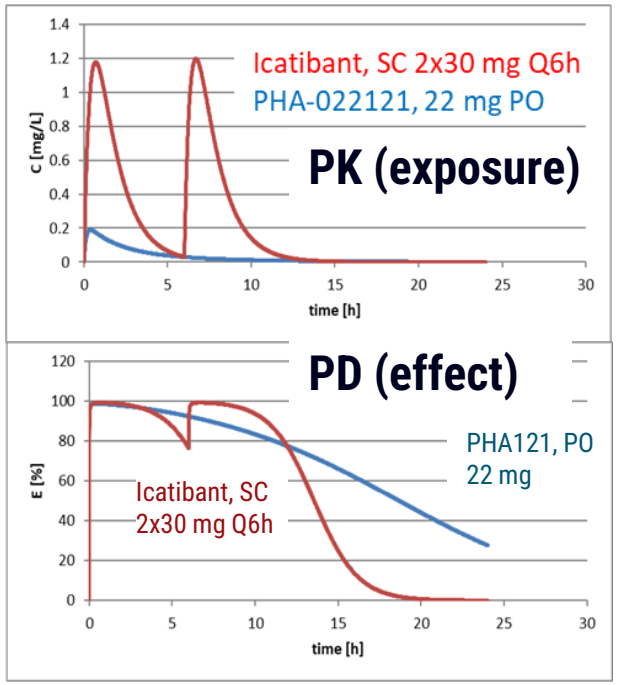
https://education.aaaai.org/sites/default/files/L37%20Lesage_1.pdf

In healthy volunteers, oral pre-treatment with PHA121 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** PHA121 dose predicted to provide **similar PD effect** as two injections of icatibant

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

PHA121 is 20- to 25-fold more potent than icatibant

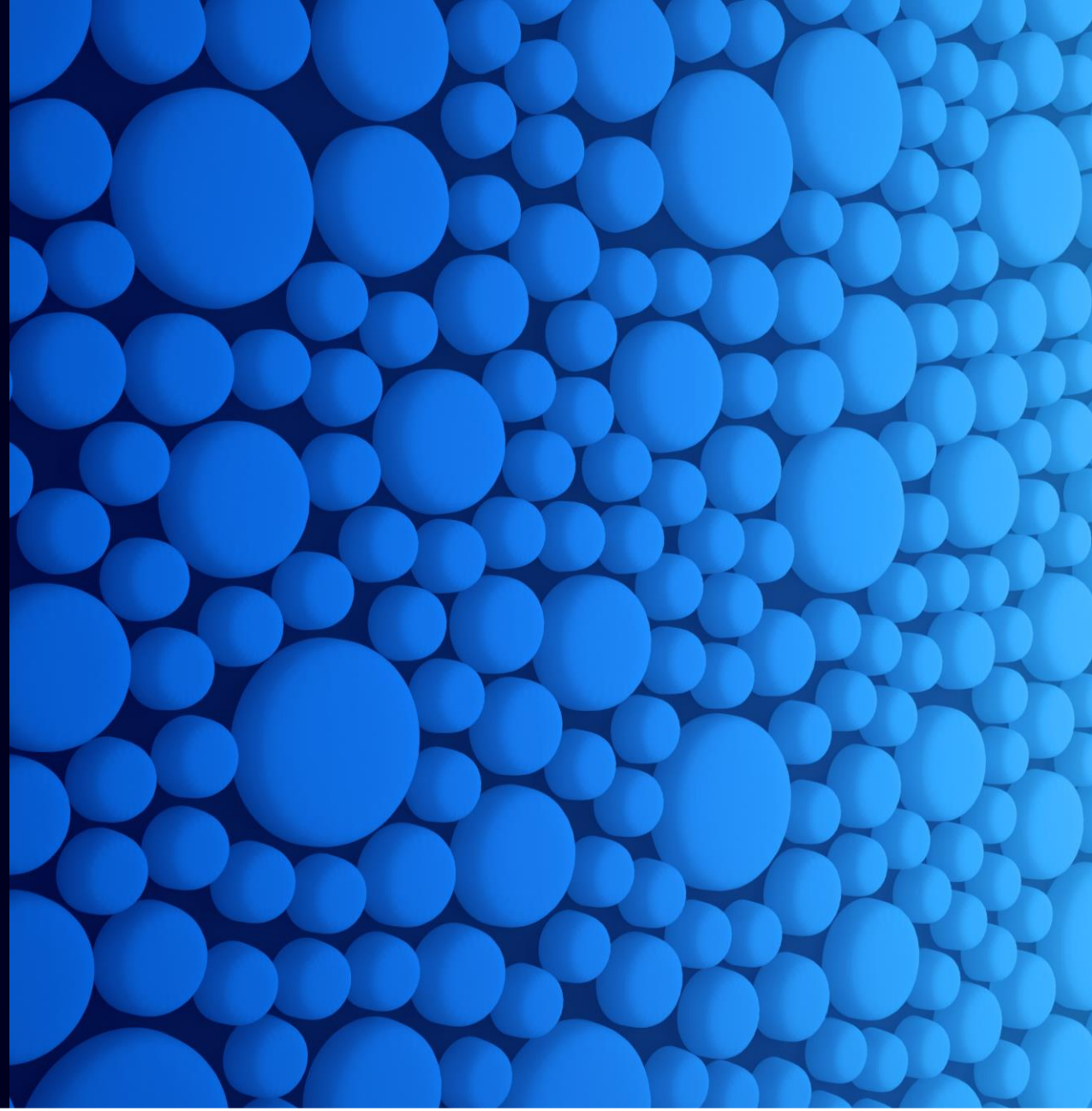
Human bradykinin B2 receptor function		Icatibant	PHA121	PHA121 relative potency vs icatibant
		Potency, nM		
In vitro	Recombinant B2 receptor in CHO cell line	3.19	0.15	21-fold
Ex vivo	Endogenous B2 receptor in human umbilical vein	8.71	0.35	25-fold
In vivo	Human BK challenge haemodynamic model *	4.08	0.17	24-fold

** Potency expressed in nM, considering free fraction in plasma 0.56 for icatibant and 0.038 for PHA121, and MW 1,305 for icatibant and 535 for PHA121*

Picomolar potency of PHA121 is confirmed in the 3 models

1 Disease
2 Treatment paradigms

1 Active ingredient
2 Optimized formulations



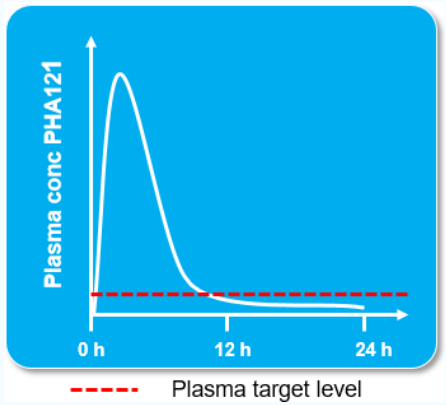
Two innovative formulations to optimize the treatment experience for all types of HAE patients

PHA121

PHVS416

Softgel capsule formulation

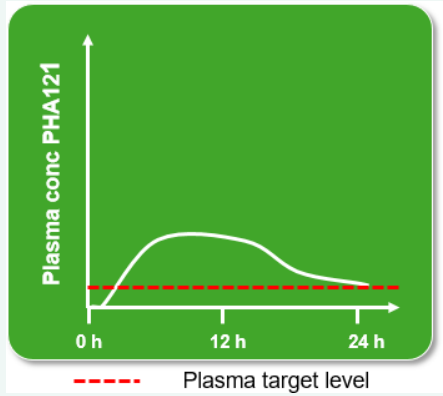
On-demand treatment



Potential to provide fast, easy, and reliable symptom relief for all attacks

PHVS719

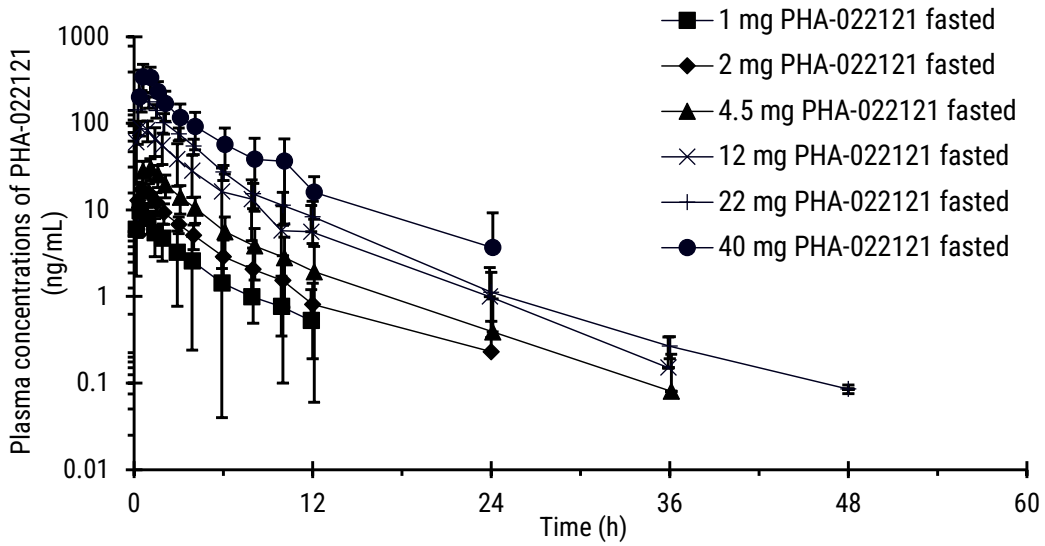
Extended-release tablet formulation

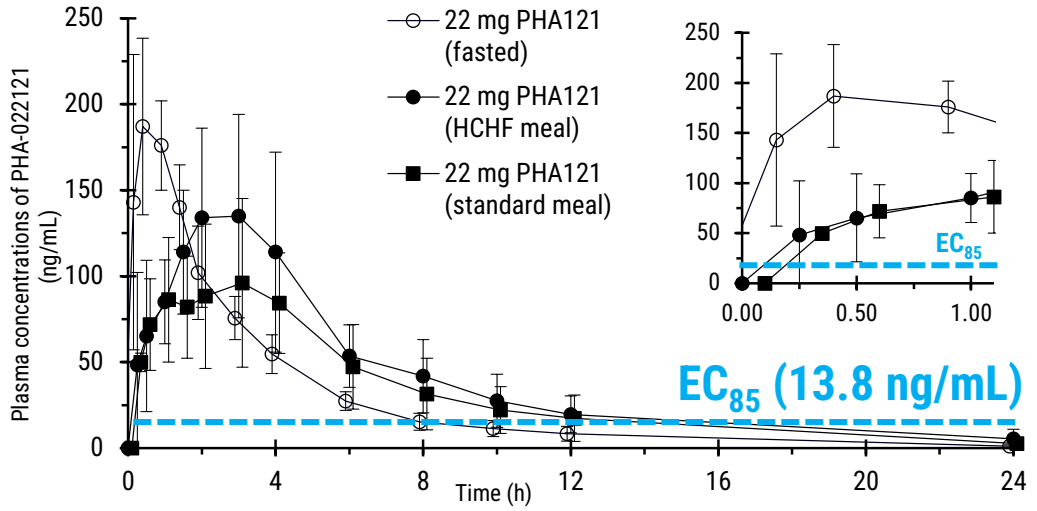


Prophylactic treatment

Aim to maintain compound exposure to prevent attacks, providing an easy and effective way for patients to live

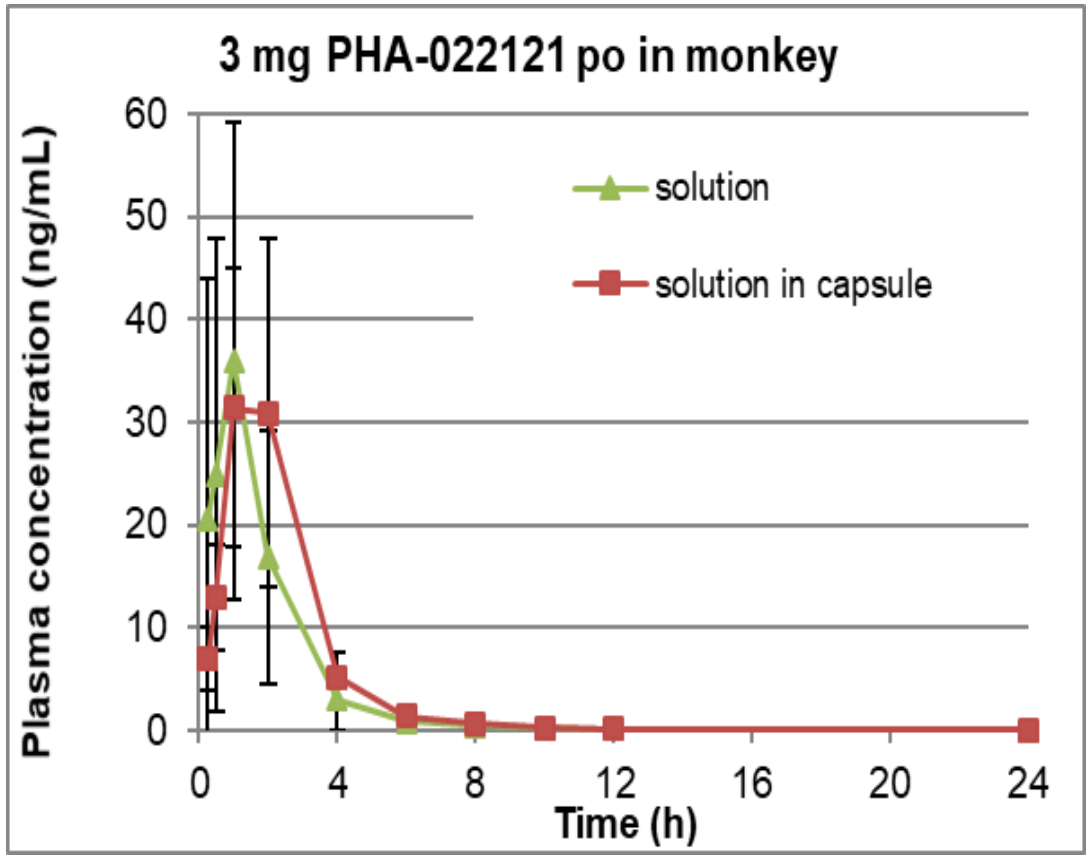
First-in-human Phase 1 study
PHA121 PK profile optimally suited for on-demand treatment





- Fast absorption, reaching anticipated therapeutic exposure (EC_{85}) in less then 15 minutes
- Plasma half-life approximately 3.4 to 5.6 hours, about 3-fold longer than icatibant

In preclinical studies, the solution formulation demonstrated the same PK profile as the capsule



PHVS416: Oral soft capsule containing PHA121

(samples, not the actual product)

- PHVS416 meets target product profile for oral on-demand treatment of HAE attacks
  - Exposure reaches anticipated therapeutic levels within 15 min of intake
  - Anticipated duration of action similar to two injections of icatibant
  - PHVS416 is used for RAPIDe-1, our Phase 2 trial for the on-demand treatment of HAE

Designing an extended-release formulation meeting the requirements of prophylaxis

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

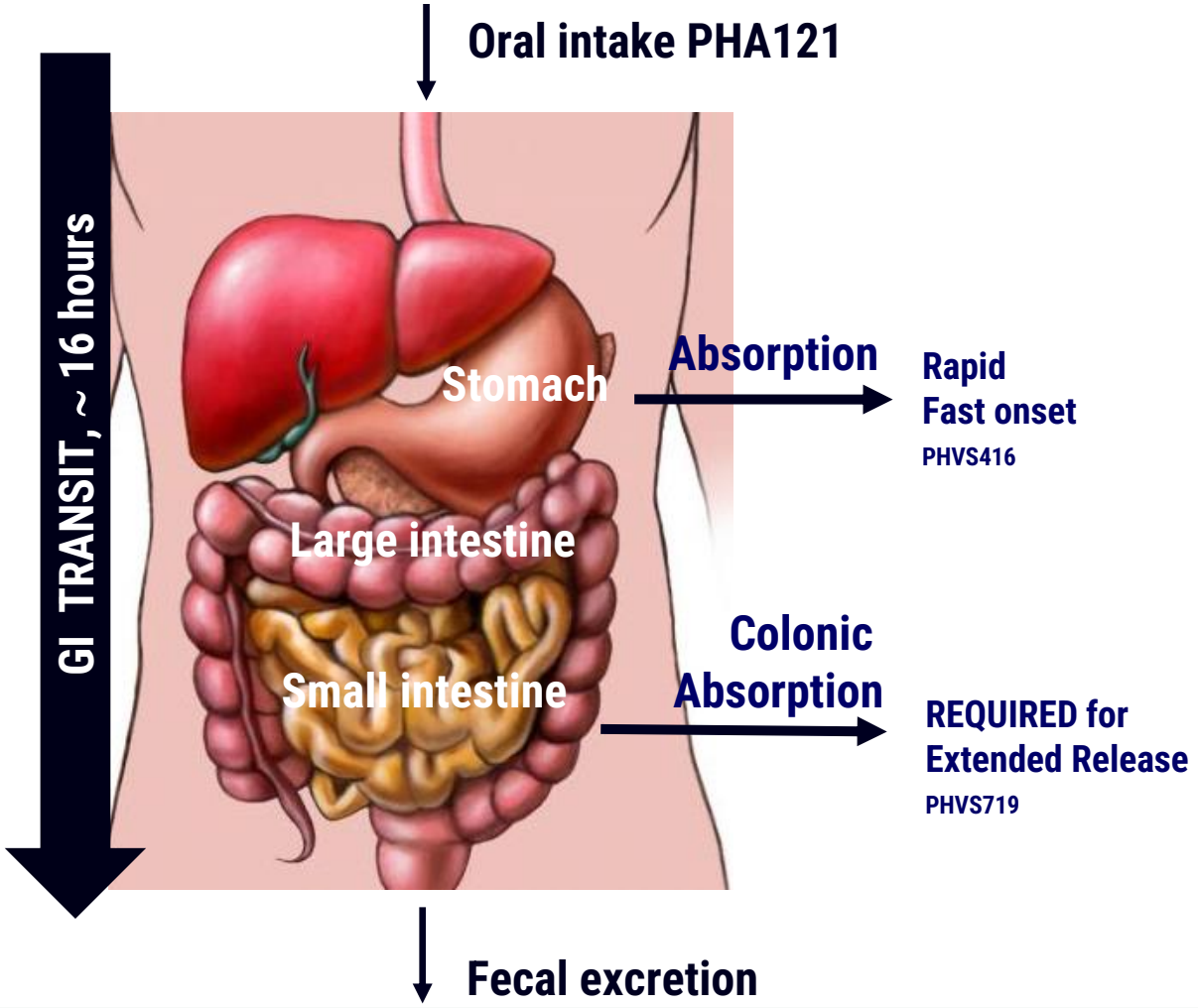
Evidence of PHA121 absorption in the gut

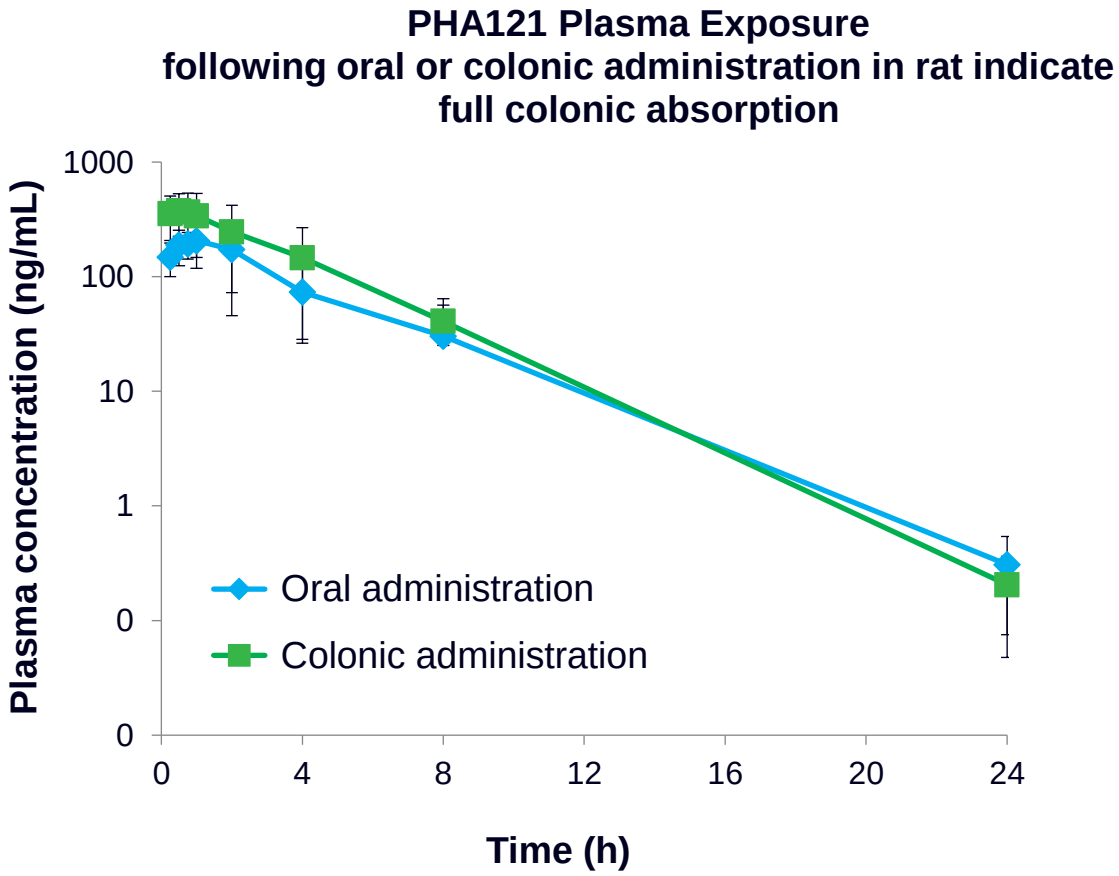
Fecal excretion in rat & monkey

	Excretion of PHA121, 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 PHA121 excretion, suggesting full absorption in the GI tract

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





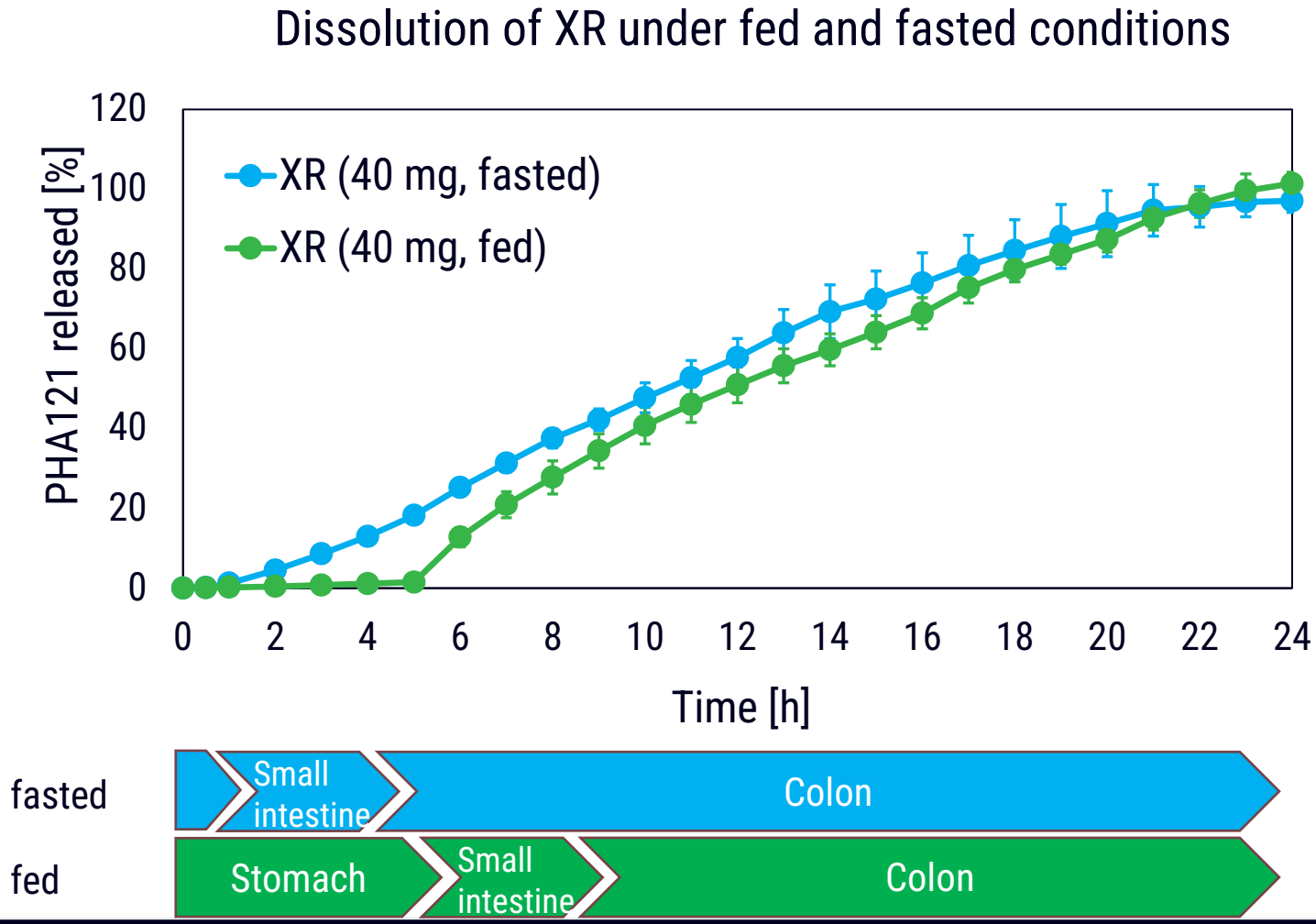
Low/absent excretion of unchanged PHA121 confirms high extent of absorption in human gastrointestinal tract

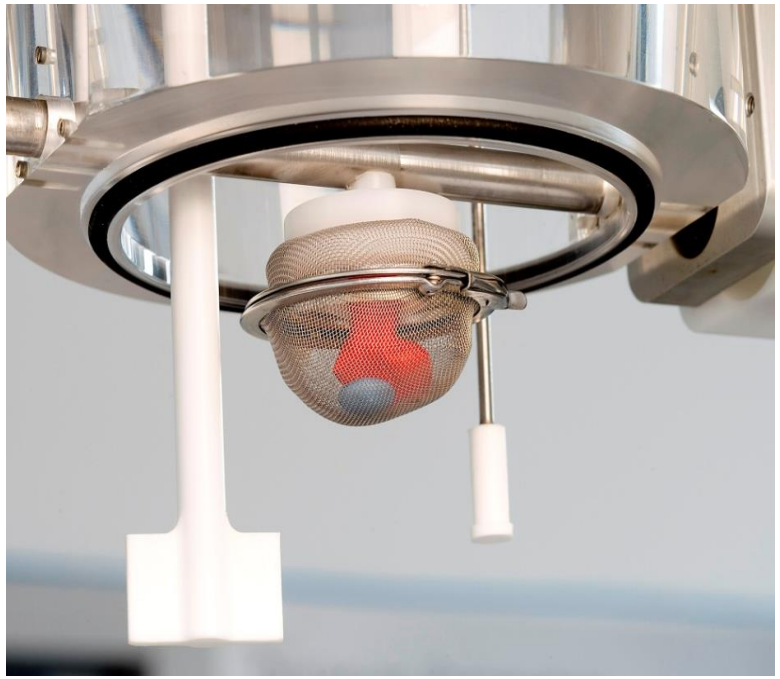
Single dose mass balance study with PHA121 in human *	Excretion of PHA121, recovery over 72 h in %		Oral bioavailability, Fpo
	Urine	Feces	
	0.09	3.2	57%

**Single-dose mass balance and absolute bioavailability study with an oral 20 mg dose of PHA121 and an oral and intravenous microtracer dose of ^{14}C-PHA-022121 in healthy male subjects*

- High oral bioavailability together with low fecal excretion of PHA121 confirmed the assumption of high absorption throughout the gastrointestinal tract

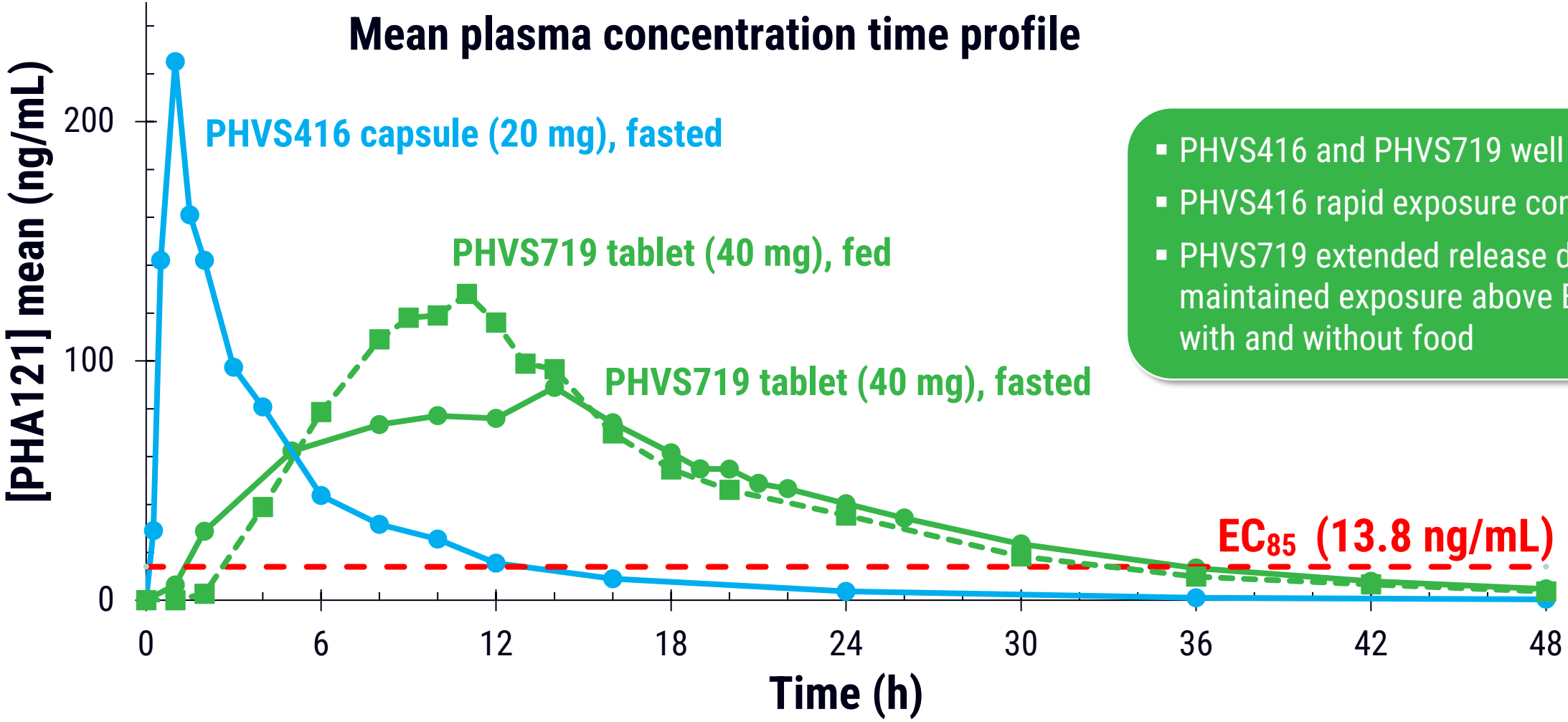
In vitro, gradual, near linear dissolution of PHA121 from XR tablet





Simulated GI matrix and mechanical stress

The extended release formulation (PHVS719) compared to PHVS416
Single-dose PK study demonstrates QD potential for PHVS719



- PHVS416 and PHVS719 well tolerated
- PHVS416 rapid exposure confirmed
- PHVS719 extended release demonstrated: maintained exposure above EC85 for >24h with and without food

PHVS719: Film-coated extended-release tablet containing PHA121

(samples, not the actual product)

- PHVS719 meets target product profile for oral prophylactic treatment of HAE
  - 24 hours coverage of anticipated therapeutic exposure
  - PHVS719 will be used for Chapter-2, our Phase 3 trial for prophylactic treatment of HAE

First-in-human, orally available B2 antagonist with two innovative formulations to optimize the treatment experience for all types of HAE patients

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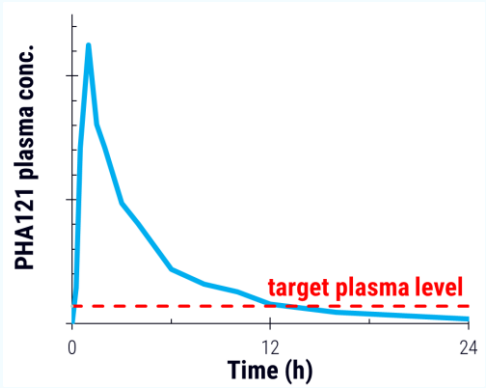

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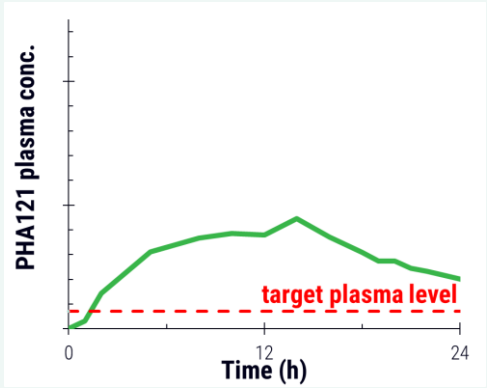

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