# The $EC_{85}$ Derived from the Oral Bradykinin B2 Receptor Antagonist Deucrictibant (PHA121) Against Bradykinin Effects in Healthy Volunteers Predicts the Onset and Duration of Its Clinical Effects in Hereditary Angioedema

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

# Conflicts of interest disclosure

Consultancy fees, research grant support, speaker fees, and/or clinical trial fees

M.M.: Adverum, Attune, BioCryst, CSL Behring, KalVista, Pharming, Pharvaris, Takeda/Shire.

M.A.R.: Astria, BioCryst, Biomarin, CSL Behring, Cycle Pharma, Fresenius-Kabi, Grifols, Ionis, Ipsen, KalVista, Ono Pharma, Pfizer, Pharming, Pharvaris, RegenexBio, Sanofi-Regeneron, Takeda.

A.L.: employee of GrayMattersConsulting and consultant to Pharvaris, holds stocks/stock options in Pharvaris. Advisor to KosaPharma, holds stocks in KosaPharma.

R.C.: employee of CG Consultancy and consultant to Pharvaris, holds stocks in Pharvaris.

P.L.: employee of Pharvaris, holds stocks/stock options in Pharvaris.

K.G.: employee of DGr Pharma and consultant to Pharvaris.

M.R.: employee of Dynakin, S.L.

J.K.: employee of JCK Consult and consultant to Pharvaris, holds stocks/stock options in Pharvaris.

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# Unmet needs for new oral treatments of bradykinin-mediated angioedema

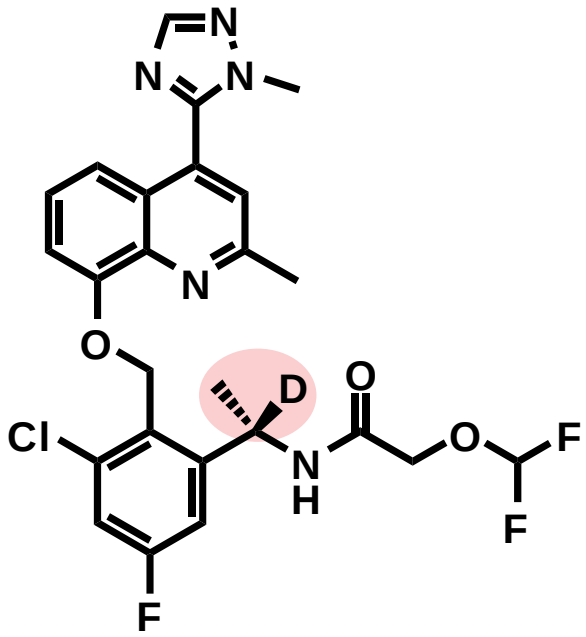
- Excess bradykinin is the cause of signs and symptoms of swelling during HAE attacks[1] and efficacy and tolerability of bradykinin B2 receptor antagonism for treatment of HAE attacks has been proven in clinical trials in ~15 years of post-marketing experience[2-4]

- International guidelines recommend that HAE attacks are treated as early as possible[5-7]
  - Burden associated with parenteral administration of currently approved on-demand medications[8-12] leads to treatment of a number of HAE attacks being delayed or forgone[12-15]

- It is also recommended that patients with HAE are evaluated for long-term prophylaxis taking disease activity, burden, and control as well as patient preference into consideration[7]
  - Oral administration for long-term prophylaxis is favoured by a number of physicians and patients[16-17]

[1]Busse PJ et al. N Engl J Med 2020;382:1136-48; [2]Cicardi M et al. N Engl J Med 2010;363:532-41; [3]Lumry WR et al. Ann Allergy Asthma Immunol 2011;107:529-37; [4]Maurer M et al. Clin Exp Allergy 2022;52:1048-58. [5]Betschel S et al. Allergy Asthma Clin Immunol 2019;15:72; [6]Busse PJ et al. J Allergy Clin Immunol Pract 2021;9:132-50; [7]Maurer M et al. Allergy 2022;77:1961-90; [8]Berinert® [package insert], https://labeling.cslbehring.com/pi/us/berinert/en/berinert-prescribing-information.pdf (accessed 23 April 2023); [9]Firazyr® [package insert], https://www.shirecontent.com/PI/PDFs/Firazyr_USA_ENG.pdf (accessed 23 April 2023); [10]Kalbitor® [package insert], https://www.shirecontent.com/PI/PDFs/Kalbitor_USA_ENG.pdf (accessed 23 April 2023); [11]Ruconest® [package insert], https://www.ruconest.com/wp-content/uploads/Ruconest_PI_Apr2020.pdf (accessed 23 April 2023); [12]Burnette A et al. AAAAI 2023; [13]Tuong LA et al. Allergy Asthma Proc 2014;35:250-4; [14]US Food and Drug Administration, Center for Biologics Evaluation and Research. The voice of the patient–Hereditary angioedema. May 2018. https://www.fda.gov/media/113509/download (accessed 23 April 2023); [15]Radojicic C et al. AAAAI 2023; [16]Geba D et al. J Drug Assess 2021;10:51-6; [17]Bouillet L et al. Allergy Asthma Proc 2022:43:406-12.

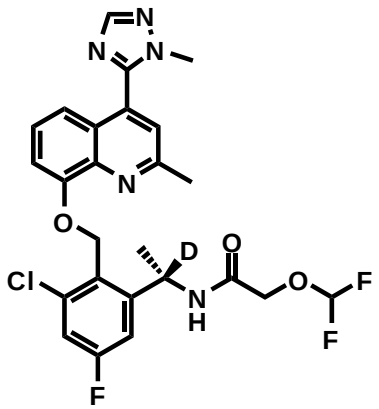
# Deucrictibant (formerly PHA121, PHA-022121) is an orally bioavailable, selective, highly potent, competitive antagonist of bradykinin B2 receptor




- Antagonist of bradykinin B2 receptor (-*tibant* stem[1])
- 2.4-fold lower molecular weight than icatibant
- Metabolic soft spot stabilized by introduction of a *deu*terium atom
  - Optimized for metabolic stability and exposure in humans
- Pure antagonistic activity at bradykinin B2 receptor (no partial agonistic activity as icatibant was found to exert at high concentrations, as reached locally at site of injection[2])

Lesage A et al. Front Pharmacol 2020;11:916. Lesage A et al. Int Immunopharmacol 2022;105:108523.
[1]https://cdn.who.int/media/docs/default-source/international-nonproprietary-names-(inn)/who-pharm-s-nom-1570.pdf (accessed 23 April 2023); [2]https://www.ema.europa.eu/en/documents/assessment-report/firazyr-epar-public-assessment-report_en.pdf (accessed 23 April 2023).

# Two formulations of deucrictibant are currently under development for hereditary angioedema




## Deucrictibant immediate-release (IR) capsule

- softgel capsule formulation
- rapid absorption in stomach and gut upon oral administration
- being developed for treatment of HAE attacks (RAPIDe-1 Phase 2 trial[1-2], RAPIDe-2 extension study[3*])
- bid dosing in proof-of-concept CHAPTER-1 Phase 2 trial[4*] for prophylaxis of HAE attacks

## Deucrictibant extended-release (XR) tablet

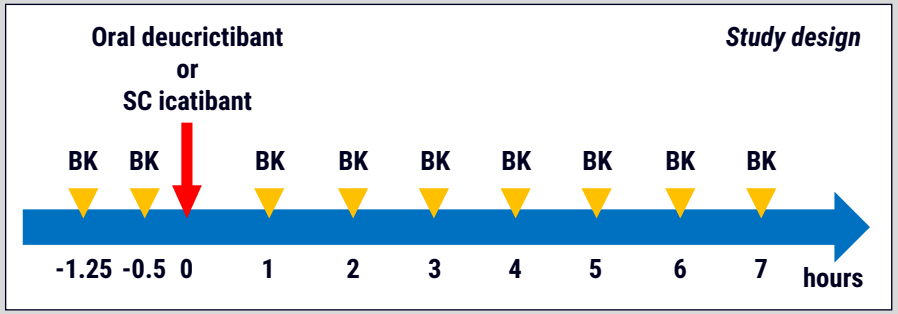
- tablet formulation
- prolonged colonic absorption upon oral administration[5]
- completed Phase 1 studies[6]
- being developed for prophylaxis of HAE attacks[6]

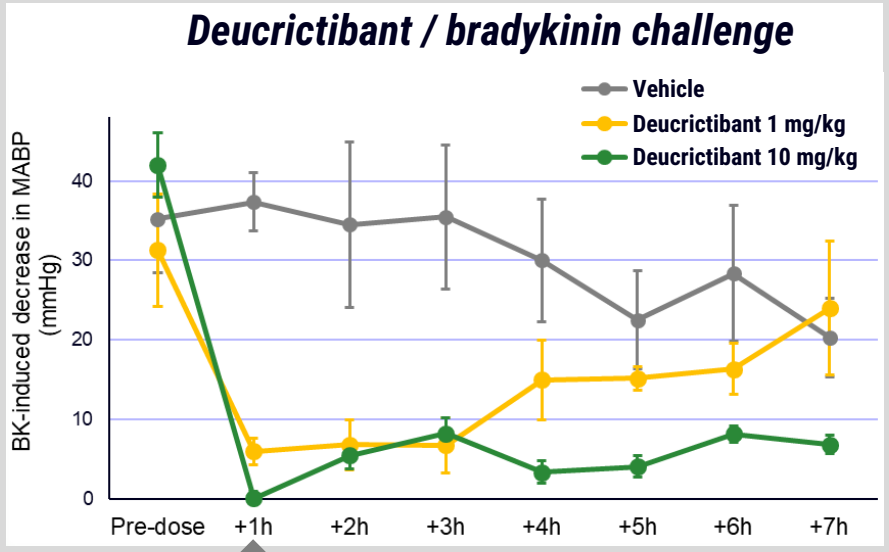
HAE: hereditary angioedema.

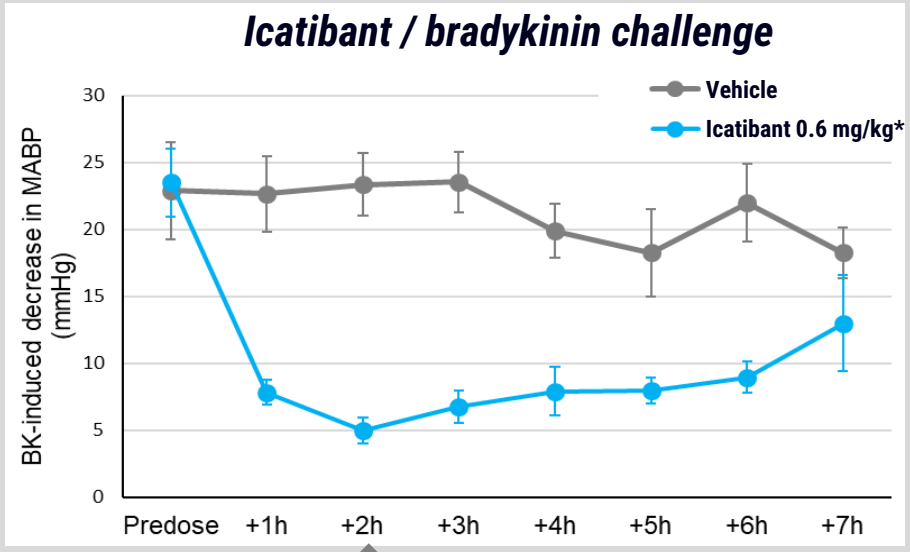
[1]Maurer M et al. AAAAI 2023; [2]https://clinicaltrials.gov/ct2/show/NCT04618211; [3]https://clinicaltrials.gov/ct2/show/NCT05396105; [4]https://clinicaltrials.gov/ct2/show/NCT05047185; [5]Lesage A et al. ACAAI 2022; [6]Groen K et al. ACAAI 2022.

*In August 2022, the U.S. Food & Drug Administration (FDA) placed a hold on the clinical trials of deucrictibant in the U.S. based on its review of non clinical data. FDA has subsequently agreed to partially lift the clinical hold on RAPIDe-1 trial and allow 2 remaining U.S. participants in RAPIDe-1 to complete treatment of a final HAE attack per protocol. All other clinical studies of deucrictibant are currently on hold in the U.S.. Regulators in ex U.S. countries have been notified of the U.S. clinical hold. For the latest information and updates visit: https://ir.Pharvaris.com/.

# In non-human primates, oral deucrictibant inhibited bradykinin effects with rapid achievement of maximal activity



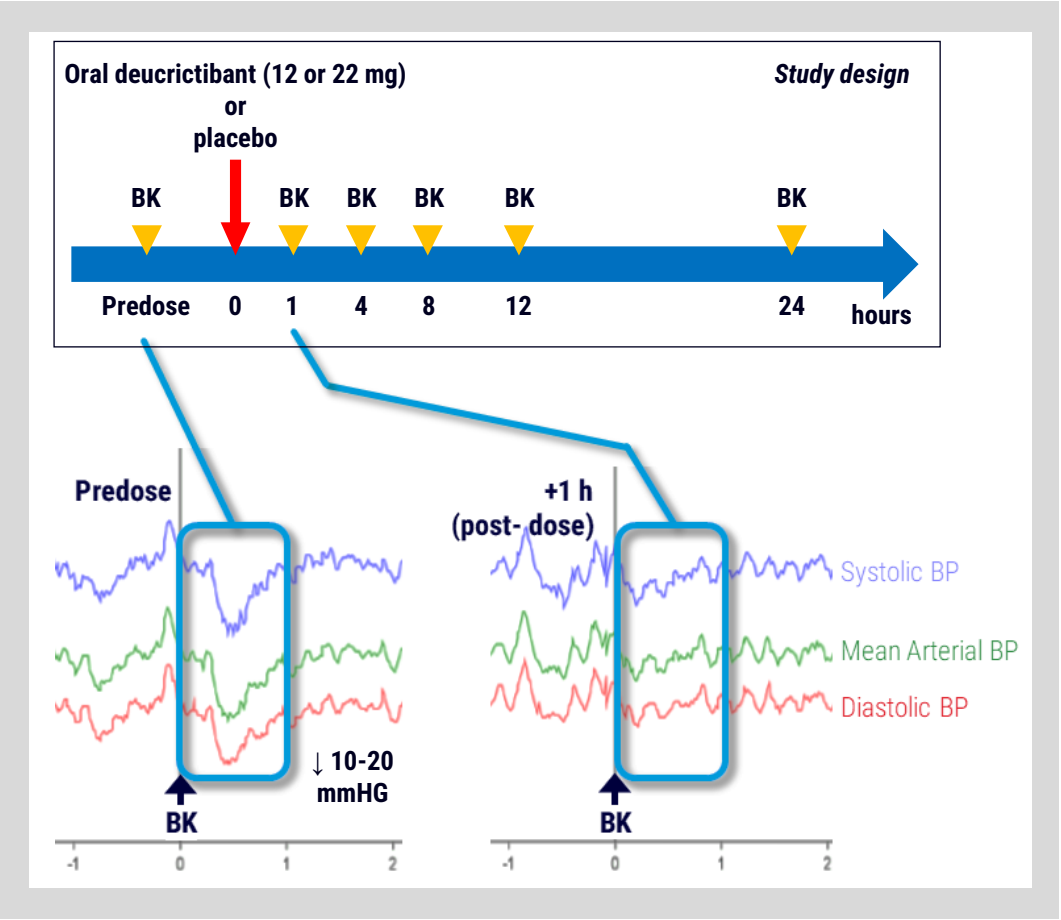




Maximal activity at 1 hour

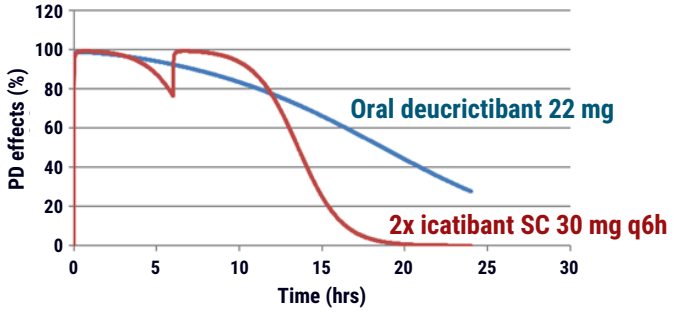
Maximal activity at 2 hours

BK: bradykinin; MABP: mean arterial blood pressure; SC: subcutaneous.
Adapted from Lesage A et al. AAAAI 2020. *The monkey dose of icatibant used was equivalent to the human therapeutic dose of 30 mg.

# In healthy volunteers, oral deucrictibant inhibited bradykinin-mediated hemodynamic changes




- Serial bradykinin challenges allowed to:
  - assess duration of deucrictibant *in vivo* PD effects




***1 dose of deucrictibant 22 mg predicted to exert PD effects with duration similar to that of 2 sequential doses of icatibant 30 mg***

  - derive deucrictibant potency: composite $EC_{50}$ and $EC_{85}$ (concentrations achieving 50% and 85% of the maximum observable effect)

| | Deucrictibant | Icatibant[1] |
|---|---|---|
| $EC_{50}$ | 2.4 ng/mL | 9.5 ng/mL |
| $EC_{85}$ | 13.8 ng/mL | 53.8 ng/mL |

***Deucrictibant ~4x higher potent vs. icatibant (published data[1])***

BK: bradykinin; BP: blood pressure; PD: pharmacodynamic; q6h, every 6 hours; SC, subcutaneous.
Adapted from Derendorf H et al. ACAAI 2020. [1]https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022150Orig1s000ClinPharmR.pdf (accessed 23 April 2023).

# *In vivo* bradykinin-challenge studies: summary of findings

- **Study in non-human primates**:
  - bradykinin-antagonistic properties confirmed in a pharmacologically active species *in vivo*
  - rapid achievement of maximal bradykinin-antagonistic effects
- **Study in humans**:
  - bradykinin-antagonistic properties confirmed in humans *in vivo*
  - duration of pharmacodynamic effects longer vs. a dose of icatibant
  - composite $EC_{85}$ derived as surrogate for therapeutic levels
  - therapeutically relevant target concentrations estimated (dose selection for Phase 2 trials)

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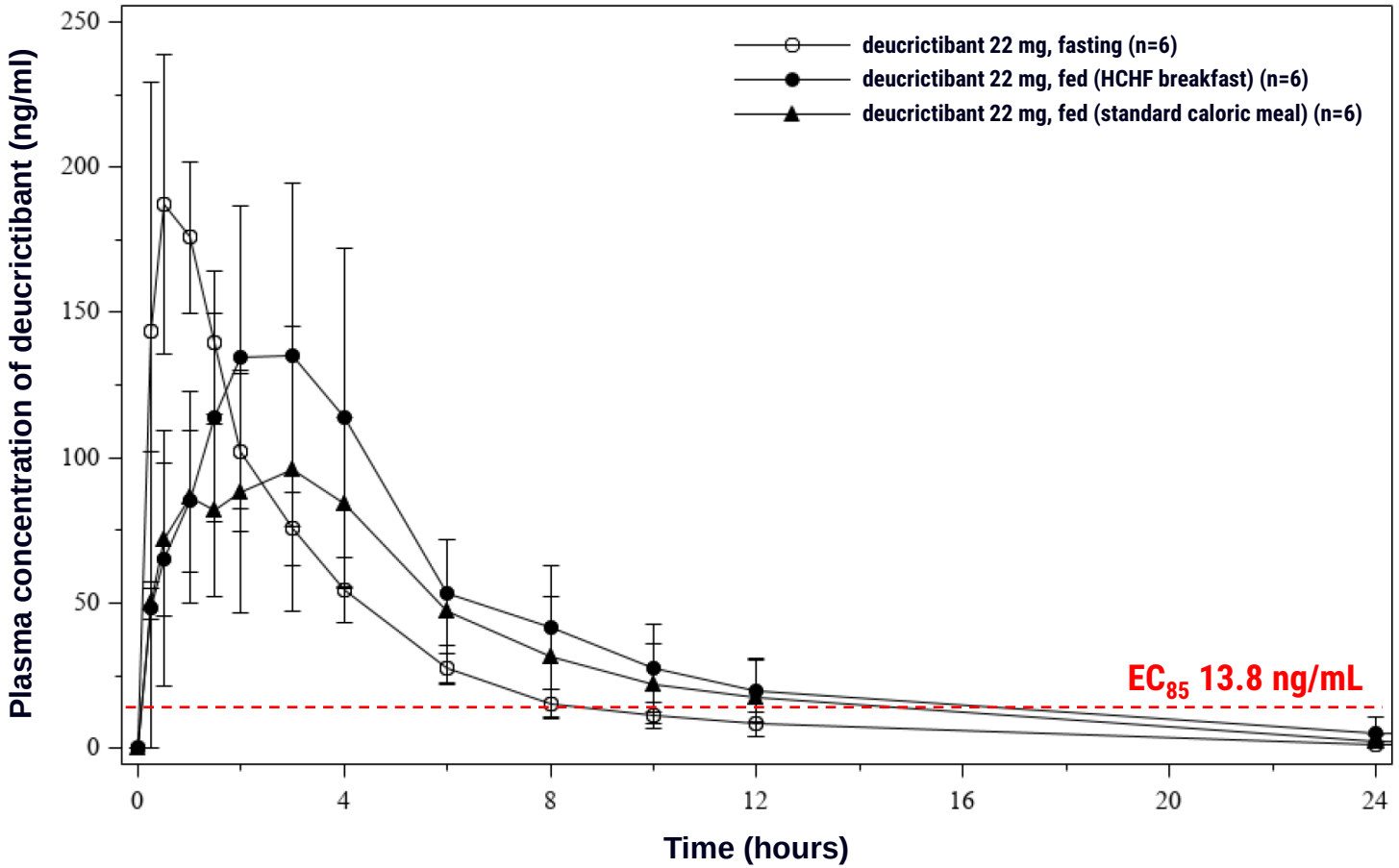
# $EC_{85}$ as surrogate marker of threshold of therapeutic levels

- For bradykinin B2 receptor antagonism (icatibant), concentrations predicted to be above $EC_{85}$ were shown to correlate with therapeutic efficacy and its duration

- Achievement and persistence of plasma concentrations $\geq EC_{85}$ are considered to be therapeutically relevant for deucrictibant as surrogate markers of its onset and duration of clinical effects, respectively

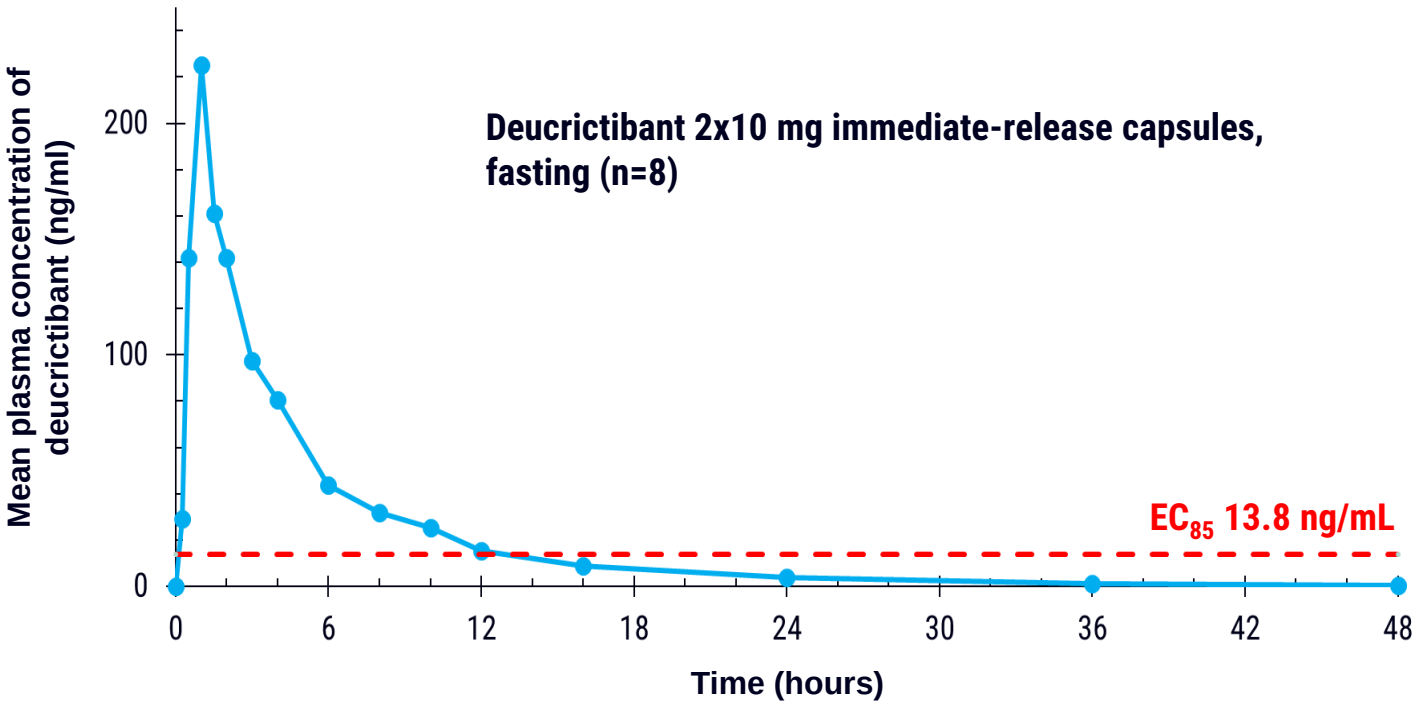
# Therapeutic levels are rapidly achieved following oral administration of deucrictibant solution in Phase 1 study




- Mean plasma levels >$EC_{85}$ reached in 15 minutes in almost all subjects and in 30 minutes in all subjects after single dose of deucrictibant solution 22 mg
- Mean plasma levels >$EC_{85}$ maintained for approx. 8-12 hours after single dose of deucrictibant solution 22 mg
- No significant impact of food intake on achievement of therapeutic levels

HCHF: high-calorie high-fat.
Adapted from Crabbé R et al. AAAAI 2021.

# Therapeutic levels are rapidly achieved following oral administration of deucrictibant immediate-release capsule in Phase 1 study




- Mean plasma levels >$EC_{85}$ reached in 15 minutes after single dose of deucrictibant immediate-release capsule (2x10 mg)
- Mean plasma levels >$EC_{85}$ maintained for ~12 hours after single dose of deucrictibant immediate-release capsule (2x10 mg)

Adapted from Groen K et al. ACAAI 2022.

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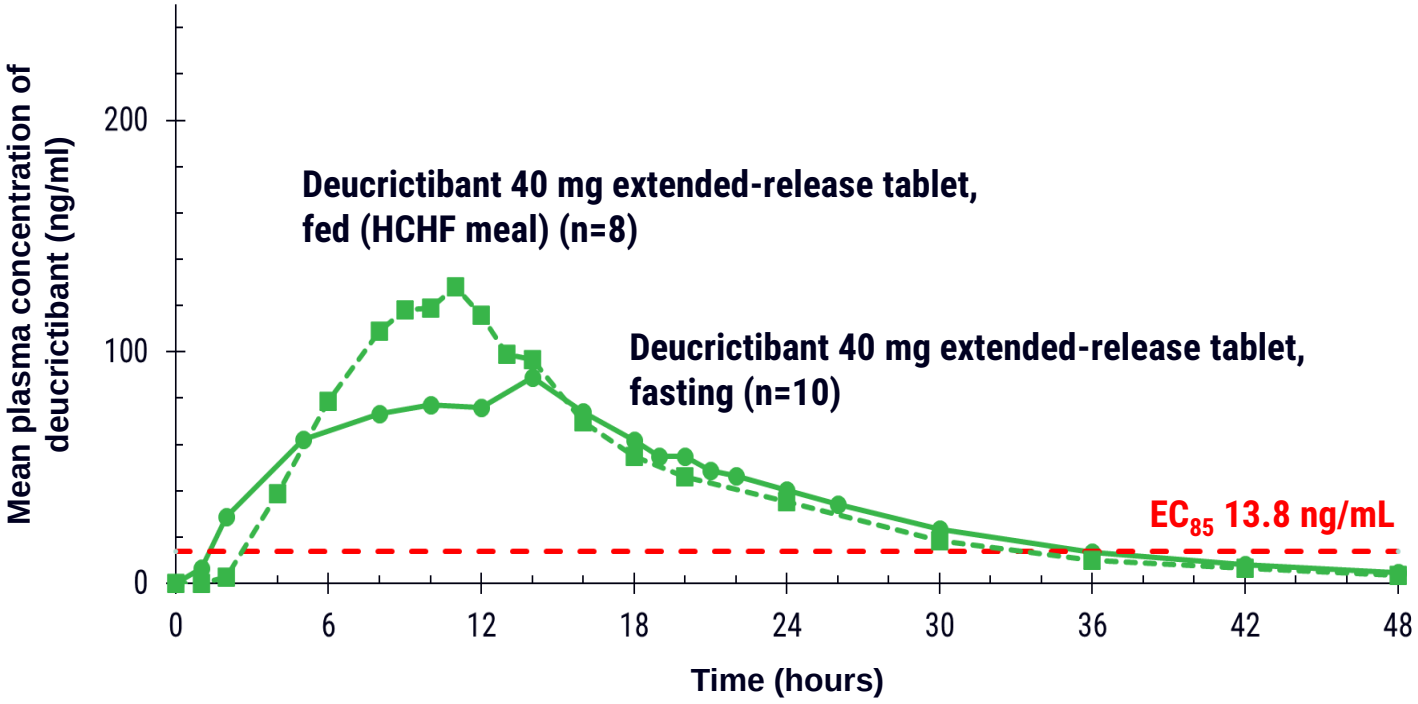
# Therapeutic levels are maintained for >24 hours following oral administration of deucrictibant extended-release tablet in Phase 1 study

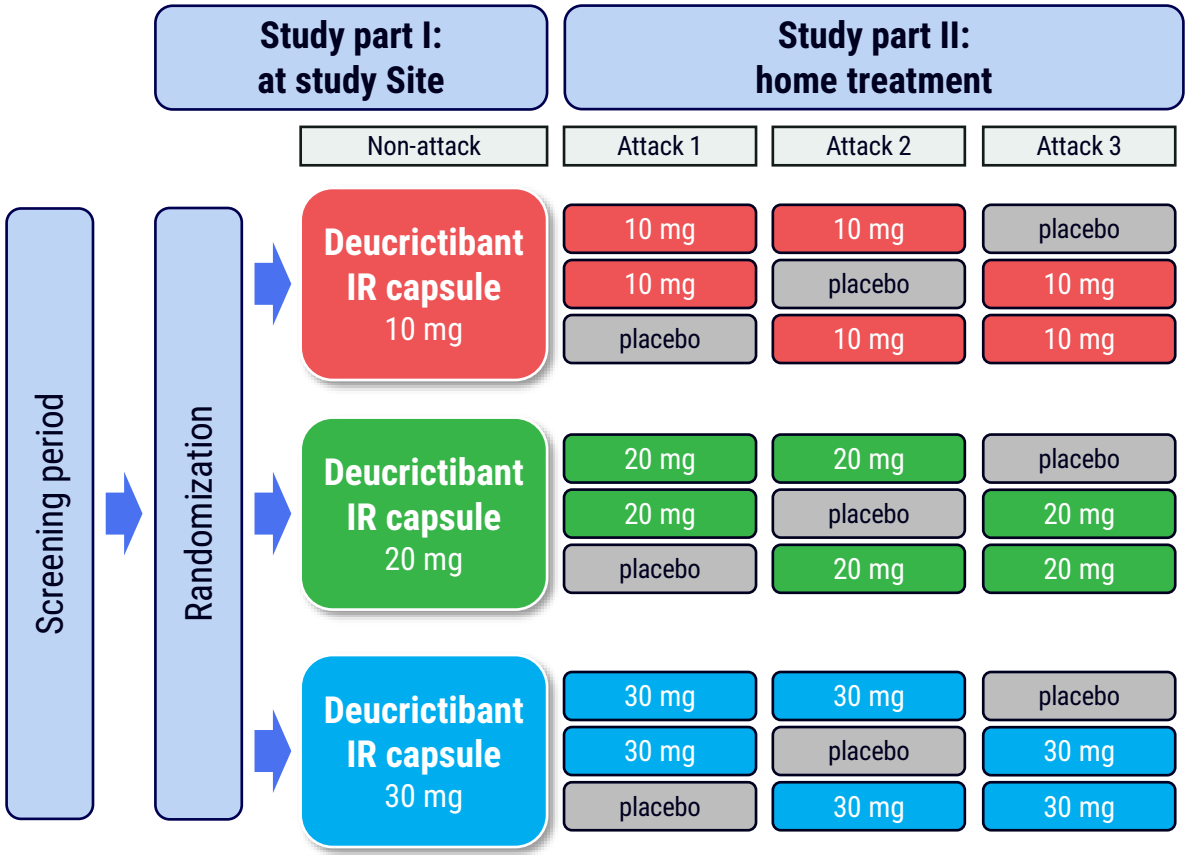



- Mean plasma levels >$EC_{85}$ reached in ~3 hours after single dose of deucrictibant extended-release tablet 40 mg
- Mean plasma levels >$EC_{85}$ maintained for >24 hours after single dose of deucrictibant extended-release tablet 40 mg
- Pharmacokinetic steady state anticipated to be achieved in ~3 days
- No significant impact of food intake on achievement of therapeutic levels
- Potential for once-daily oral administration for long-term prophylaxis

HCHF: high-calorie high-fat.
Adapted from Groen K et al. ACAAI 2022.

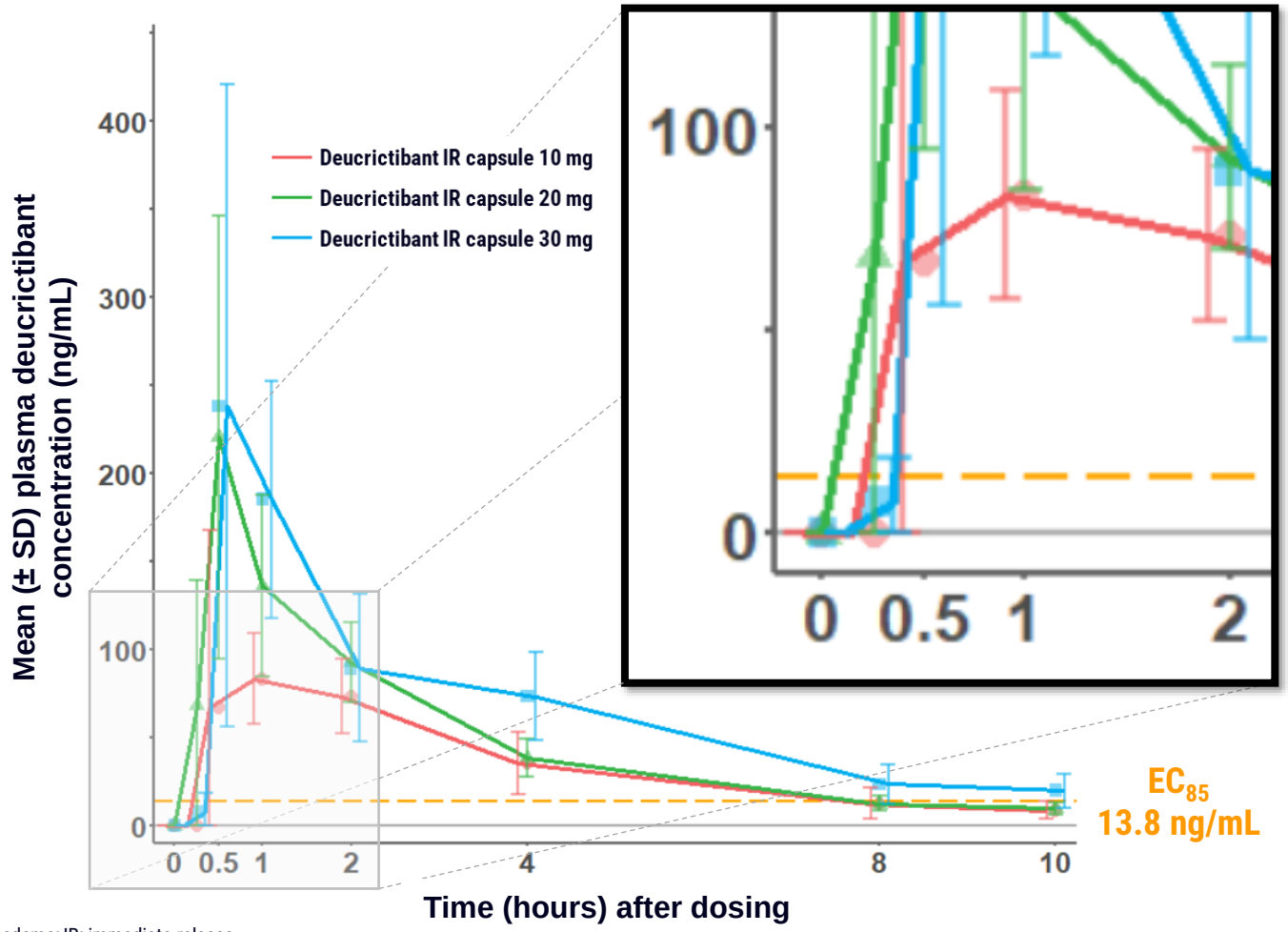
# RAPIDe-1: phase 2 trial of deucrictibant immediate-release (IR) capsule as on-demand treatment for HAE-1/2 attacks

- **Double-blind, placebo-controlled, cross-over trial with 3-dose levels**
  - **Study part I** – randomized patients received a single dose of deucrictibant IR capsule at study Site for PK and safety assessment
  - **Study part II** – randomized patients treated up to 3 qualifying HAE attacks: 2 attack with deucrictibant IR capsule and 1 attack with placebo
- **74 HAE patients enrolled from 31 Sites**


HAE: hereditary angioedema; IR: immediate-release; PK: pharmacokinetic; VAS: visual analogue score.
ClinicalTrials.gov Identifier: NCT04618211, https://clinicaltrials.gov/ct2/show/NCT04618211; EudraCT Number: 2020-003445-11 (both accessed 27 April 2023).

# Pharmacokinetics of deucrictibant IR capsule in RAPIDe-1 confirmed rapid achievement of therapeutic levels for all doses assessed




- Rapid absorption with mean plasma levels >$EC_{85}$ reached within 15-30 minutes for all doses of deucrictibant IR capsule
- Mean plasma levels of deucrictibant maintained >$EC_{85}$ for approx. 8 to >10 hours (10 to 30 mg deucrictibant IR capsule doses)

HAE: hereditary angioedema; IR: immediate-release.
Maurer M et al. AAAAI 2023.

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# Conclusions

- Deucrictibant is an orally bioavailable antagonist of bradykinin B2 receptor under development in 2 formulations: immediate-release capsule and extended-release tablet

- Bradykinin-challenge studies of deucrictibant allowed to:
  - confirm the bradykinin-antagonistic properties of deucrictibant *in vivo*
  - determine the $EC_{85}$ (13.8 ng/mL) as surrogate threshold for therapeutic levels

- Following oral administration, therapeutic levels of deucrictibant were shown to be achieved within 15-30 minutes and to be maintained longer vs. icatibant

- In a Phase 2 trial of deucrictibant immediate-release capsule for treatment of HAE attacks, clinical effects were observed within the first hours after oral administration of single dose (10-30 mg)

- Deucrictibant extended-release tablet has the potential of a once-daily oral administration for long-term prophylaxis of HAE attacks

HAE: hereditary angioedema.