Efficacy and safety of bradykinin B2 receptor antagonism with deucrictibant immediate-release capsule for treatment of hereditary angioedema attacks: results of RAPIDe-1 phase 2 trial

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Introduction

- Excess bradykinin is the cause of signs and symptoms of swelling during hereditary angioedema (HAE) attacks[1] and efficacy and tolerability of bradykinin B2 receptor antagonism for treatment of HAE attacks has been proven in clinical trials and ~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 approved on-demand medications[8-12] leads to treatment of many HAE attacks being delayed or forgone.[12-15]
- An unmet need exists for on-demand oral therapies that are effective and well-tolerated and may reduce the treatment burden enabling prompt administration.

Methods

- RAPIDe-1* (NCT04618211)[16] was a Phase 2, double-blind, placebo-controlled, randomized, crossover, dose-ranging trial of deucrictibant immediate-release (IR) capsule (PHVS416) for treatment of angioedema attacks in patients with HAE-1/2.
- Key inclusion criteria: diagnosis of HAE-1/2; ≥3 attacks in the last 4 months or ≥2 attacks in the last 2 months prior to screening; access to and experience with use of on-demand medications.
- Key exclusion criteria: pre-enrolment use of: C1-inhibitor (C1-INH) for acute use or short-term prophylaxis (7 days); C1-INH for long-term prophylaxis, oral kallikrein inhibitors, attenuated androgens, anti-fibrinolytics (2 weeks); monoclonal antibodies for HAE (12 weeks); pregnancy or breast-feeding; conditions interfering with participant's safety/ability to participate in the study.
- A primary analysis included 147 qualifying HAE attacks treated by 62 participants with double-blinded placebo or deucrictibant IR capsule 10, 20, or 30 mg [modified intent-to-treat (mITT) analysis = all randomized participants with ≥1 treated HAE attack and non-missing VAS results at both pre-treatment and ≥1 post-treatment time point of that attack].

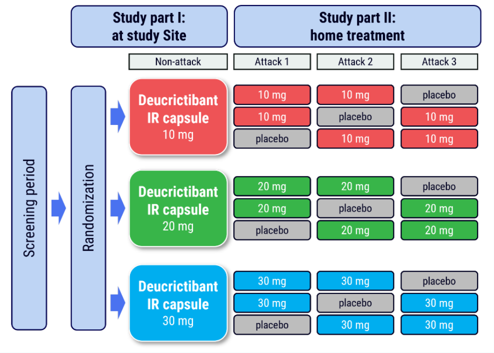


Figure 1. RAPIDe-1 trial design schematic.

Results

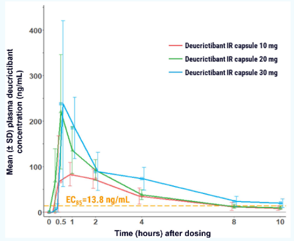
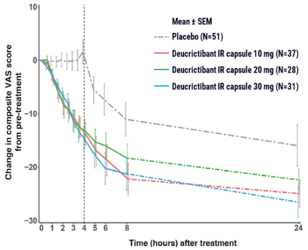


Figure 2. Pharmacokinetic profile of single dose of deucrictibant IR capsule 10, 20 or 30 mg in HAE patients



Difference from placebo in change from pre-treatment to 4 h post-treatment, least-squares mean (95% CIs)		
Deucrictibant IR capsule 10 mg	-16.75 (-21.52, -11.97)	p < 0.0001†
Deucrictibant IR capsule 20 mg	-15.02 (-20.22, -9.81)	p < 0.0001
Deucrictibant IR capsule 30 mg	-16.28 (-21.27, -11.29)	p < 0.0001

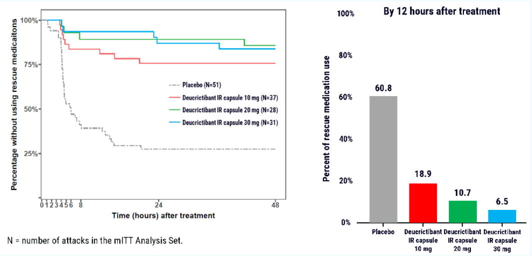
Median VAS-3 at baseline ranged from 24.33 to 27.00 across deucrictibant IR capsule doses (10, 20, and 30 mg). †Nominal p-value; N = number of attacks in the mITT Analysis Set. Figure is based on descriptive summary of mean and SEM (standard error of the mean). Least-squares mean differences, CIs, and p-values come from a mixed-effects model with repeated measures (MMRM). Data after rescue medication use not included.

Figure 3 and Table 1. Results of primary endpoint: reduction of attack symptoms by VAS-3.

	Placebo N=51	Deucrictibant IR capsule 10 mg N=37	Deucrictibant IR capsule 20 mg N=28	Deucrictibant IR capsule 30 mg N=31
Time to onset of symptom relief by VAS-3 ≥30% reduction[a]				
Median time in hours (95% CI)	8.0 (7.6, 46.9)	2.1 (1.5, 2.9)	2.7 (1.9, 3.5)	2.5 (1.9, 3.8)
Hazard ratio		3.81	3.08	3.61
p-value		<0.0001	0.0021	<0.0001
Time to VAS-3 ≥50% reduction[a]				
Median time in hours (95% CI)	22.8 (20.0, 24.1)	3.3 (2.4, 3.9)	4.0 (2.9, 6.0)	4.0 (3.3, 5.8)
Hazard ratio		4.55	3.65	3.87
p-value		<0.0001	0.0003	<0.0001
Time to almost complete or complete symptom relief by VAS-3[a]				
Median time in hours (95% CI)	42.0 (22.0, 48.1)	5.8 (3.6, 7.5)	20.0 (4.5, 20.0)	20.0 (6.0, 20.1)
Hazard ratio		5.09	2.25	2.65
p-value		<0.0001	0.0127	0.0001
Change in MSCS[b] score at 4 hours[c]				
Least-squares mean difference: Deucrictibant IR capsule – placebo		-0.79	-0.61	-0.39
p-value		<0.0001	0.0008	0.0291
TOS[d] at 4 hours[c]				
Least-squares mean difference: Deucrictibant IR capsule – placebo		64.13	62.69	71.06
p-value		<0.0001	<0.0001	<0.0001

N = Number of attacks included in the mITT Analysis Set. p-values for deucrictibant IR capsule 20mg and 30mg are based on statistical tests in the pre-specified multiple comparison procedure, other p-values are nominal. [a]Hazard ratios and p-values are based on marginal Cox proportional hazards models. [b]Minimal clinically important difference for MSCS = -0.30. [c]p-values are based on mixed-effects models for repeated measures. [d]Minimal clinically important difference for TOS = 30.

Table 2. Results of key secondary efficacy endpoints.



N = number of attacks in the mITT Analysis Set.

Figure 4. Additional secondary endpoint: use of rescue medication.

	Study part I (non-attack)			Study part II (attacks 1, 2, 3)			
	Deucrictibant IR capsule				Deucrictibant IR capsule		
	10 mg N=23	20 mg N=24	30 mg N=25	Placebo N=53	10 mg N=38	20 mg N=29	30 mg N=36
Subjects (study part I) or attacks (study part II) with any treatment-related AEs	1 (4.3%)	1 (4.2%)	-	1 (1.9%)	-	-	1 (2.8%)
Headache	-	1 (4.2%)	-	-	-	-	-
Nausea	1 (4.3%)	-	-	-	-	-	1 (2.8%)
Vomiting	-	-	-	-	-	-	1 (2.8%)
Fatigue	-	-	-	-	-	-	1 (2.8%)
Blister	-	-	-	1 (1.9%)	-	-	-

N = Number of participants (Part I) and number of attacks (Part II) in the Safety Analysis Set. The Safety Analysis Set includes all randomized participants who received ≥1 dose of study drug between Part I and Part II.

Table 3. Treatment-related adverse events within 48 hours after administration of study drug.

Conclusions

The Phase 2 RAPIDe-1 trial for treatment of attacks in patients with HAE-1/2 met primary and all key secondary endpoints, providing evidence on the efficacy and safety of deucrictibant IR capsule in treating HAE attacks and supporting its further development as a potential on-demand therapy for HAE.

The FDA has placed a hold on clinical trials of deucrictibant for long-term prophylaxis in the U.S. For the latest information and updates visit: https://ir.Pharvaris.com/.

References

[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 15 August 2023). [9]Firazyr® [package insert], https://www.shirecontent.com/PI/PDFs/Firazyr_USA_ENG.pdf (accessed 15 August 2023). [10]Kalbitor® [package insert], https://www.shirecontent.com/PI/PDFs/Kalbitor_USA_ENG.pdf (accessed 15 August 2023). [11]Ruconest® [package insert], https://www.ruconest.com/wp-content/uploads/Ruconest_PI_Apr2020.pdf (accessed 15 August 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 15 August 2023). [15]Radojicic C et al. AAAAI 2023. [16]https://clinicaltrials.gov/ct2/show/NCT04618211 (accessed 15 August 2023).

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Conflicts of interest disclosure

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

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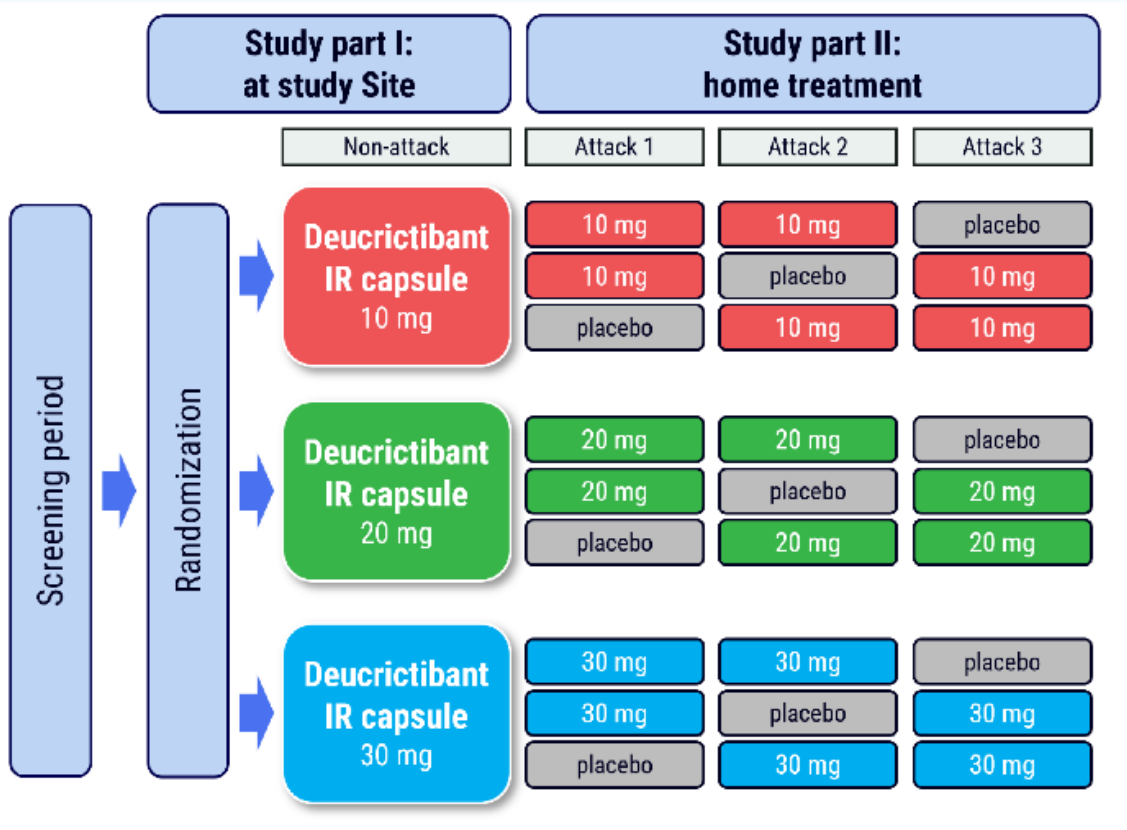

Figure 1. RAPIDe-1 trial design schematic.

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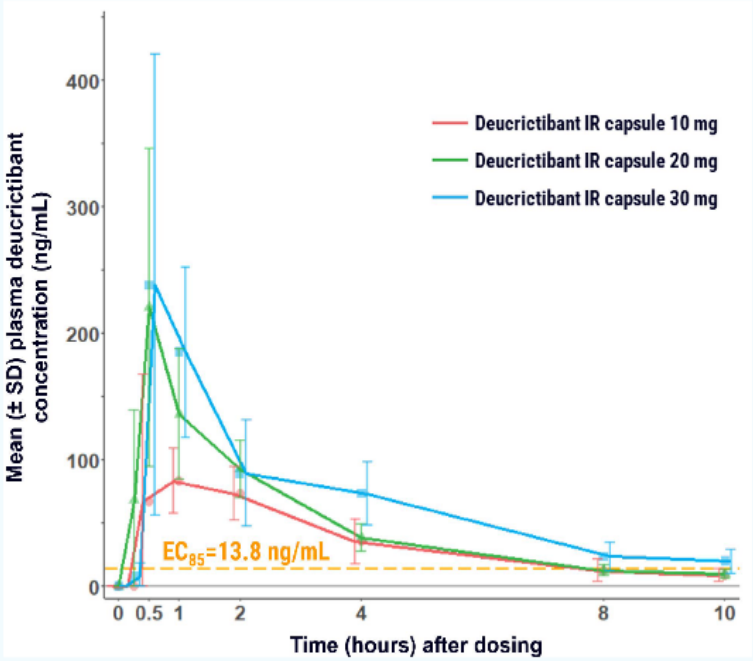

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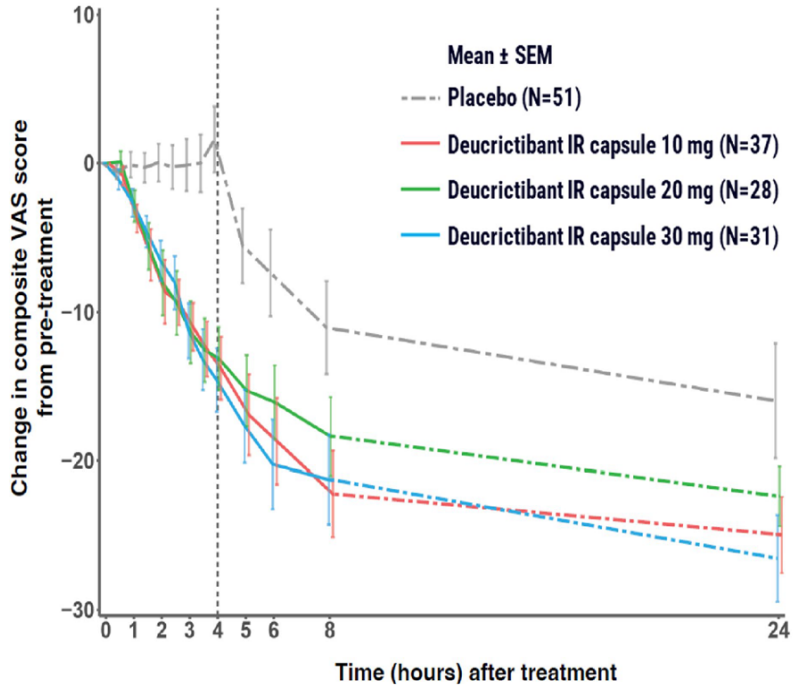

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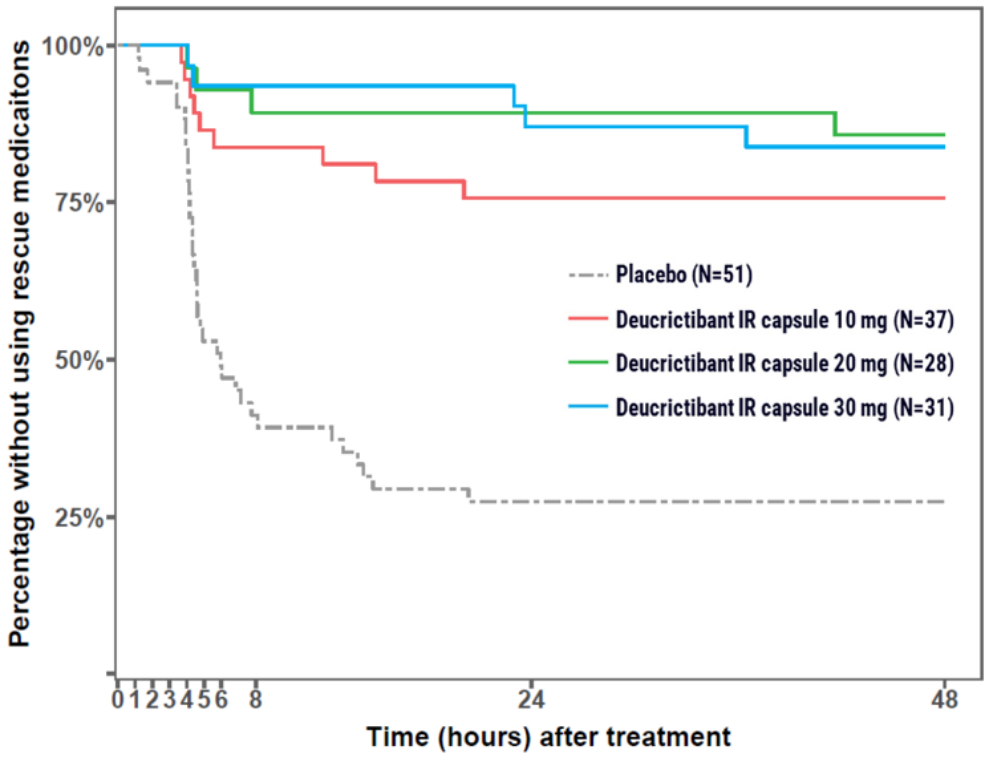
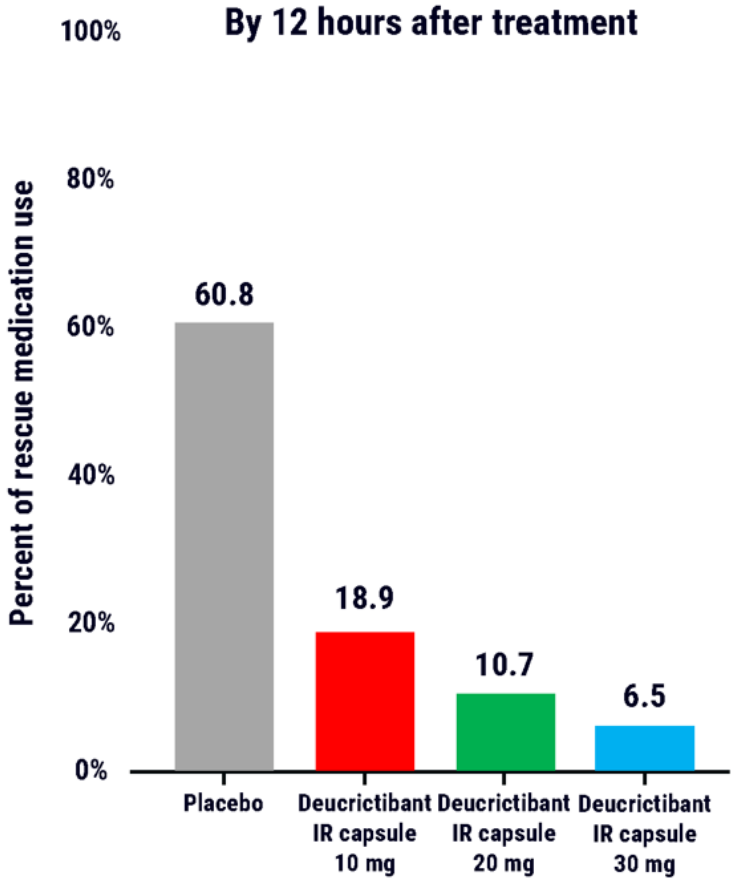
p-value		<0.0001	0.0021	<0.0001
Time to VAS-3 ≥50% reduction[a]				
Median time in hours (95% CI)	22.8 (20.0, 24.1)	3.3 (2.4, 3.9)	4.0 (2.9, 6.0)	4.0 (3.3, 5.8)
Hazard ratio		4.55	3.65	3.87
p-value		<0.0001	0.0003	<0.0001
Time to almost complete or complete symptom relief by VAS-3[a]				
Median time in hours (95% CI)	42.0 (22.0, 48.1)	5.8 (3.6, 7.5)	20.0 (4.5, 20.0)	20.0 (6.0, 20.1)
Hazard ratio		5.09	2.25	2.65
p-value		<0.0001	0.0127	0.0001
Change in MSCS[b] score at 4 hours[c]				
Least-squares mean difference: Deucrictibant IR capsule – placebo		-0.79	-0.61	-0.39
p-value		<0.0001	0.0008	0.0291
TOS[d] at 4 hours[c]				
Least-squares mean difference: Deucrictibant IR capsule – placebo		64.13	62.69	71.06
p-value		<0.0001	<0.0001	<0.0001

N = Number of attacks included in the mITT Analysis Set. p-values for deucrictibant IR capsule 20mg and 30mg are based on statistical tests in the pre-specified multiple comparison procedure, other p-values are nominal. [a]Hazard ratios and p-values are based on marginal Cox proportional hazards models. [b]Minimal clinically important difference for MSCS = -0.30. [c]p-values are based on mixed-effects models for repeated measures. [d]Minimal clinically important difference for TOS = 30.

Table 2. Results of key secondary efficacy endpoints.

Results – Use of rescue medication





N = number of attacks in the mITT Analysis Set.

Figure 4. Additional secondary endpoint: use of rescue medication.

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Results – Safety

	Study part I (non-attack)			Study part II (attacks 1, 2, 3)			
	Deucrictibant IR capsule				Deucrictibant IR capsule		
	10 mg N=23	20 mg N=24	30 mg N=25	Placebo N=53	10 mg N=38	20 mg N=29	30 mg N=36
Subjects (study part I) or attacks (study part II) with any treatment-related AEs	**1 (4.3%)**	**1 (4.2%)**	**-**	**1 (1.9%)**	**-**	**-**	**1 (2.8%)**
Headache	-	1 (4.2%)	-	-	-	-	-
Nausea	1 (4.3%)	-	-	-	-	-	1 (2.8%)
Vomiting	-	-	-	-	-	-	1 (2.8%)
Fatigue	-	-	-	-	-	-	1 (2.8%)
Blister	-	-	-	1 (1.9%)	-	-	-

N = Number of participants (Part I) and number of attacks (Part II) in the Safety Analysis Set. The Safety Analysis Set includes all randomized participants who received ≥1 dose of study drug between Part I and Part II.

Table 3. Treatment-related adverse events within 48 hours after administration of study drug.

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Conclusions

- The Phase 2 RAPIDe-1 trial for treatment of attacks in patients with HAE-1/2 met primary and all key secondary endpoints, providing evidence on the efficacy and safety of deucrictibant IR capsule in treating HAE attacks and supporting its further development as a potential on-demand therapy for HAE.

The FDA has placed a hold on clinical trials of deucrictibant for long-term prophylaxis in the U.S. For the latest information and updates visit: https://ir.Pharvaris.com/.

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

Efficacy and safety of bradykinin B2 receptor antagonism with deucrictibant immediate-release capsule for treatment of hereditary angioedema attacks: results of RAPIDe-1 phase 2 trial

Joshua S. Jacobs[1], John Anderson[2], H. Henry Li[3], Michael E. Manning[4], Emel Aygören-Pürsün[5], Maria Luisa Baeza[6], Laurence Bouillet[7], Hugo Chapdelaine[8], Danny M. Cohn[9], Aurélie Du-Thanh[10], Olivier Fain[11], Henriette Farkas[12], Jens Greve[13], Mar Guilarte[14], David Hagin[15], Roman Hakl[16], Aharon Kessel[17], Sorena Kiani-Alikhan[18], Pavlina Králícková[19], Ramon Lleonart[20], Markus Magerl[21], Avner Reshef[22], Bruce Ritchie[23], Giuseppe Spadaro[24], Maria Staevska[25], Petra Staubach[26], Marcin Stobiecki[27], Gordon L. Sussman[28], Michael D. Tarzi[29], Anna Valerieva[25], William H. Yang[30], Marie-Helene Jouvin[31], Rafael Crabbé[32], Simone van Leeuwen[33], Huaihou Chen[31], Li Zhu[34], Jochen Knolle[35], Anne Lesage[36], Peng Lu[34], Marcus Maurer[22], Marc A. Riedl[37]

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Introduction

- Excess bradykinin is the cause of signs and symptoms of swelling during hereditary angioedema (HAE) attacks[1] and efficacy and tolerability of bradykinin B2 receptor antagonism for treatment of HAE attacks has been proven in clinical trials and ~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 approved on-demand medications[8-12] leads to treatment of many HAE attacks being delayed or forgone.[12-15]
- An unmet need exists for on-demand oral therapies that are effective and well-tolerated and may reduce the treatment burden enabling prompt administration.

Methods

- RAPIDe-1* (NCT04618211)[16] was a Phase 2, double-blind, placebo-controlled, randomized, crossover, dose-ranging trial of deucrictibant immediate-release (IR) capsule (PHVS416) for treatment of angioedema attacks in patients with HAE-1/2.
- Key inclusion criteria: diagnosis of HAE-1/2; ≥3 attacks in the last 4 months or ≥2 attacks in the last 2 months prior to screening; access to and experience with use of on-demand medications.
- Key exclusion criteria: pre-enrolment use of: C1-inhibitor (C1-INH) for acute use or short-term prophylaxis (7 days); C1-INH for long-term prophylaxis, oral kallikrein inhibitors, attenuated androgens, anti-fibrinolytics (2 weeks); monoclonal antibodies for HAE (12 weeks); pregnancy or breast-feeding; conditions interfering with participant's safety/ability to participate in the study.
- A primary analysis included 147 qualifying HAE attacks treated by 62 participants with double-blinded placebo or deucrictibant IR capsule 10, 20, or 30 mg [modified intent-to-treat (mITT) analysis = all randomized participants with ≥1 treated HAE attack and non-missing VAS results at both pre-treatment and ≥1 post-treatment time point of that attack].

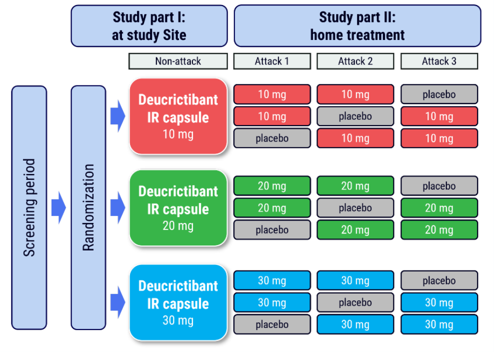
Study part I:
at study Site
Study part II:
home treatment
Non-attack
Attack 1
Attack 2
Attack 3
Screening period
Randomization
Deucrictibant
IR capsule
10 mg
10 mg
10 mg
placebo
10 mg
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Figure 1. RAPIDe-1 trial design schematic.

Results

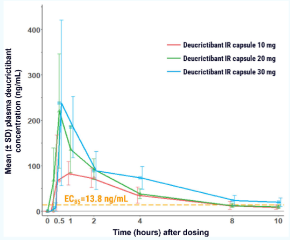
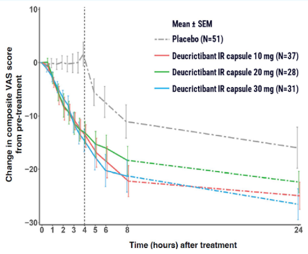


Figure 2. Pharmacokinetic profile of single dose of deucrictibant IR capsule 10, 20 or 30 mg in HAE patients



Difference from placebo in change from pre-treatment to 4 h post-treatment, least-squares mean (95% CIs)		
Deucrictibant IR capsule 10 mg	-16.75 (-21.52, -11.97)	p < 0.0001†
Deucrictibant IR capsule 20 mg	-15.02 (-20.22, -9.81)	p < 0.0001
Deucrictibant IR capsule 30 mg	-16.28 (-21.27, -11.29)	p < 0.0001

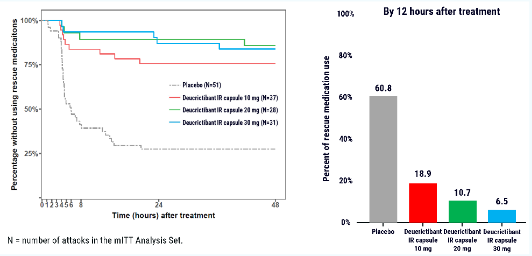
Median VAS-3 at baseline ranged from 24.33 to 27.00 across deucrictibant IR capsule doses (10, 20, and 30 mg). †Nominal p-value; N = number of attacks in the mITT Analysis Set. Figure is based on descriptive summary of mean and SEM (standard error of the mean). Least-squares mean differences, CIs, and p-values come from a mixed-effects model with repeated measures (MMRM). Data after rescue medication use not included.

Figure 3 and Table 1. Results of primary endpoint: reduction of attack symptoms by VAS-3.

	Placebo N=51	Deucrictibant IR capsule 10 mg N=37	Deucrictibant IR capsule 20 mg N=28	Deucrictibant IR capsule 30 mg N=31
Time to onset of symptom relief by VAS-3 ≥30% reduction[a]				
Median time in hours (95% CI)	8.0 (7.6, 46.9)	2.1 (1.5, 2.9)	2.7 (1.9, 3.5)	2.5 (1.9, 3.8)
Hazard ratio		3.81	3.08	3.61
p-value		<0.0001	0.0021	<0.0001
Time to VAS-3 ≥50% reduction[a]				
Median time in hours (95% CI)	22.8 (20.0, 24.1)	3.3 (2.4, 3.9)	4.0 (2.9, 6.0)	4.0 (3.3, 5.8)
Hazard ratio		4.55	3.65	3.87
p-value		<0.0001	0.0003	<0.0001
Time to almost complete or complete symptom relief by VAS-3[a]				
Median time in hours (95% CI)	42.0 (22.0, 48.1)	5.8 (3.6, 7.5)	20.0 (4.5, 20.0)	20.0 (6.0, 20.1)
Hazard ratio		5.09	2.25	2.65
p-value		<0.0001	0.0127	0.0001
Change in MSCS[b] score at 4 hours[c]				
Least-squares mean difference: Deucrictibant IR capsule – placebo		-0.79	-0.61	-0.39
p-value		<0.0001	0.0008	0.0291
TOS[d] at 4 hours[c]				
Least-squares mean difference: Deucrictibant IR capsule – placebo		64.13	62.69	71.06
p-value		<0.0001	<0.0001	<0.0001

N = Number of attacks included in the mITT Analysis Set. p-values for deucrictibant IR capsule 20mg and 30mg are based on statistical tests in the pre-specified multiple comparison procedure, other p-values are nominal. [a]Hazard ratios and p-values are based on marginal Cox proportional hazards models. [b]Minimal clinically important difference for MSCS = -0.30. [c]p-values are based on mixed-effects models for repeated measures. [d]Minimal clinically important difference for TOS = 30.

Table 2. Results of key secondary efficacy endpoints.


Percentage without using rescue medications
Placebo (N=51)
Deucrictibant IR capsule 10 mg (N=37)
Deucrictibant IR capsule 20 mg (N=28)
Deucrictibant IR capsule 30 mg (N=31)
Time (hours) after treatment
By 12 hours after treatment
Percent of rescue medication use
60.8
18.9
10.7
6.5
Placebo
Deucrictibant IR capsule 10 mg
Deucrictibant IR capsule 20 mg
Deucrictibant IR capsule 30 mg

N = number of attacks in the mITT Analysis Set.

Figure 4. Additional secondary endpoint: use of rescue medication.

	Study part I (non-attack)			Study part II (attacks 1, 2, 3)			
	Deucrictibant IR capsule				Deucrictibant IR capsule		
	10 mg N=23	20 mg N=24	30 mg N=25	Placebo N=53	10 mg N=38	20 mg N=29	30 mg N=36
Subjects (study part I) or attacks (study part II) with any treatment-related AEs	1 (4.3%)	1 (4.2%)	-	1 (1.9%)	-	-	1 (2.8%)
Headache	-	1 (4.2%)	-	-	-	-	-
Nausea	1 (4.3%)	-	-	-	-	-	1 (2.8%)
Vomiting	-	-	-	-	-	-	1 (2.8%)
Fatigue	-	-	-	-	-	-	1 (2.8%)
Blister	-	-	-	1 (1.9%)	-	-	-

N = Number of participants (Part I) and number of attacks (Part II) in the Safety Analysis Set. The Safety Analysis Set includes all randomized participants who received ≥1 dose of study drug between Part I and Part II.

Table 3. Treatment-related adverse events within 48 hours after administration of study drug.

Conclusions

The Phase 2 RAPIDe-1 trial for treatment of attacks in patients with HAE-1/2 met primary and all key secondary endpoints, providing evidence on the efficacy and safety of deucrictibant IR capsule in treating HAE attacks and supporting its further development as a potential on-demand therapy for HAE.

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[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 15 August 2023). [9]Firazyr® [package insert], https://www.shirecontent.com/PI/PDFs/Firazyr_USA_ENG.pdf (accessed 15 August 2023). [10]Kalbitor® [package insert], https://www.shirecontent.com/PI/PDFs/Kalbitor_USA_ENG.pdf (accessed 15 August 2023). [11]Ruconest® [package insert], https://www.ruconest.com/wp-content/uploads/Ruconest_PI_Apr2020.pdf (accessed 15 August 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 15 August 2023). [15]Radojicic C et al. AAAAI 2023. [16]https://clinicaltrials.gov/ct2/show/NCT04618211 (accessed 15 August 2023).

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*RAPIDe-1 was a Pharvaris-sponsored clinical trial. ClinicalTrials.gov Identifier: NCT04618211.

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