Early symptom relief following treatment with the oral bradykinin B2 receptor antagonist deucrictibant immediate-release capsule in patients with hereditary angioedema attacks

Michael E. Manning[1], John Anderson[2], Joshua S. Jacobs[3], H. Henry Li[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[21], Marc A. Riedl[37]

[1]Scottsdale, AZ, United States of America; [2]Birmingham, AL, United States of America; [3]Walnut Creek, CA, United States of America; [4]Chevy Chase, MD, United States of America; [5]Frankfurt, Germany; [6]Madrid, Spain; [7]Grenoble, France; [8]Montréal, QC, Canada; [9]Amsterdam, The Netherlands; [10]Montpellier, France; [11]Paris, France; [12]Budapest, Hungary; [13]Ulm, Germany; [14]Barcelona, Spain; [15]Tel Aviv, Israel; [16]Brno, Czech Republic; [17]Haifa, Israel; [18]London, United Kingdom; [19]Hradec Kralove, Czech Republic; [20]Barcelona, Spain; [21]Berlin, Germany; [22]Ashkelon, Israel; [23]Edmonton, AB, Canada; [24]Napoli, Italy; [25]Sofia, Bulgaria; [26]Mainz, Germany; [27]Krakow, Poland; [28]Toronto, ON, Canada; [29]Brighton, United Kingdom; [30]Ottawa, ON, Canada; [31]Lexington, MA, United States of America (former Pharvaris employees); [32]Bassins, Switzerland; [33]Woerden, The Netherlands; [34]Lexington, MA, United States of America; [35]Frankfurt, Germany; [36]Schilde, Belgium; [37]La Jolla, CA, United States of America

Introduction

- Approved therapies for hereditary angioedema (HAE) attacks are administered parenterally with substantial treatment burden due to administration time and risk of pain or other injection site reactions[1-4], with treatment of many attacks being delayed or forgone.[5-6]
- An unmet need exists for on-demand oral therapies that are effective and well-tolerated and may reduce the treatment burden enabling prompt administration as recommended by international clinical guidelines.[7-9]
- Deucrictibant immediate-release (IR) capsule (PHVS416) is an investigational formulation containing deucrictibant (PHA121), a highly potent, specific, and orally bioavailable competitive antagonist of the bradykinin B2 receptor.[10-11]
- In the Phase 2 RAPIDe-1 trial* (NCT04618211)[12] deucrictibant IR capsule reduced time to onset of symptom relief and to attack resolution measured through the visual analogue scale-3 (VAS-3) and substantially reduced use of rescue medication.[13-14]

Methods

- RAPIDe-1 was a Phase 2, double-blind, placebo-controlled, randomized, crossover, dose-ranging trial of deucrictibant IR capsule for the acute treatment of angioedema attacks in patients with HAE-1/2.
- A primary analysis was performed including 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 analysis, mITT = all randomized participants with ≥1 treated HAE attack and VAS results at both pre-treatment and ≥1 post-treatment time point).
- Mean Symptom Complex Severity (MSCS) score and Treatment Outcome Score (TOS) are validated composite scores based on patient-reported symptoms of attacks at the affected body sites, included in ecallantide clinical trials[15-17]. Changes in MSCS score and in TOS from pre-treatment to 4 hours post-treatment were among the secondary endpoints of RAPIDe-1.
- MSCS is a point-in-time measure of symptom severity:
  - Patient-rated severity of each affected symptom on a categorical scale (0 = normal, 1 = mild, 2 = moderate, 3 = severe)
  - Calculated as average score from all affected body sites (symptom complexes)
  - Decrease in score reflects improvement in symptom severity
- TOS is a measure of symptom response to treatment:
  - Patient assessment of response for each affected body site on categorical scale (significant improvement [100], improvement [50], same [0], worsening [-50], significant worsening [-100])
  - Calculated as weighted average of the response at all body sites using pre-treatment severity as weight
  - Increase in score reflects improvement in symptom from pre-treatment
  - Complex Assessment questions (TOS PRO) evaluate patient-reported changes in attack symptoms from pre-treatment (a lot better or resolved – a little better – same – a little worse – a lot worse)

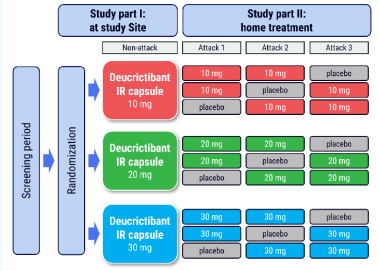

Figure 1. RAPIDe-1 trial design schematic.

Results

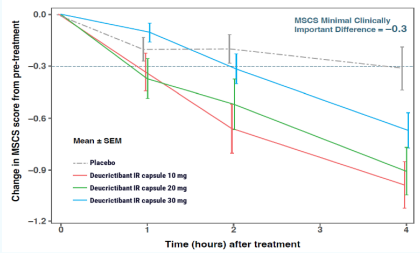

Figure 2. MSCS score measured up to 4 h post-treatment.

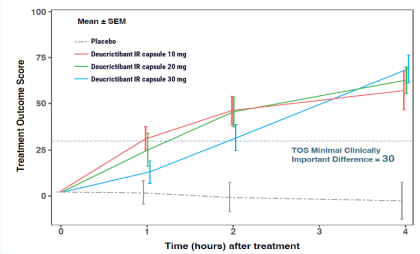

Figure 3. TOS measured up to 4 h post-treatment.

	Placebo	Deucrictibant IR capsule 10 mg	Deucrictibant IR capsule 20 mg	Deucrictibant IR capsule 30 mg
Number of patients with post-treatment TOS PRO	49	21	16	19
Number of attacks with post-treatment TOS PRO	49	36	28	29
Attacks with onset of all symptom complexes "**a little better**" within 48 hours – n (%)	18 (36.7%)	32 (88.9%)	25 (89.3%)	27 (93.1%)
Median (95% CI) time (hours) to **onset of symptom relief** by KM estimate	7.62 (3.95, -)	1.89 (0.97, 3.97)	2.15 (1.75, 4.00)	1.98 (1.80, 3.87)

Onset of symptom relief = the time point when TOS PRO first reaches at least "A little better" for all symptom complexes affected at baseline, and no new symptom in any other symptom complex is reported. Relief is confirmed if the improvement is sustained at 2 consecutive time points.

Table 1. Time to onset of symptom relief measured through TOS PRO.

	Placebo	Deucrictibant IR capsule 10 mg	Deucrictibant IR capsule 20 mg	Deucrictibant IR capsule 30 mg
Number of patients with post-treatment TOS PRO	49	21	16	19
Number of attacks with post-treatment TOS PRO	49	36	28	29
Attacks with onset of all symptom complexes "**a lot better or resolved**" within 48 hours – n (%)	13 (26.5%)	30 (83.3%)	23 (82.1%)	25 (86.2%)
Median (95% CI) time (hours) to **almost complete or complete symptom relief** by KM estimate	23.28 (5.78, 47.17)	4.02 (3.93, 5.77)	5.93 (3.90, 8.58)	4.12 (3.92, 7.22)

Almost complete or complete symptom relief = the time point when TOS PRO first reaches "*A lot better or resolved*" for all symptom complexes affected at baseline, and no new symptom in any other symptom complex is reported.

Table 2. Time to almost complete or complete symptom relief measured through TOS PRO.

Conclusions

- **In the Phase 2 RAPIDe-1 trial deucrictibant IR capsule improved symptoms and reduced time to symptom relief and to resolution of HAE attacks**
- **Clinical meaningful improvement of symptoms was observed during the first hours after treatment with deucrictibant IR capsule**

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]Berinert® [package insert], https://labeling.cslbehring.com/pi/us/berinert/en/berinert-prescribing-information.pdf (accessed 15 August 2023). [2]Firazyr® [package insert], https://www.shirecontent.com/PI/PDFs/Firazyr_USA_ENG.pdf (accessed 15 August 2023). [3]Kalbitor® [package insert], https://www.shirecontent.com/PI/PDFs/Kalbitor_USA_ENG.pdf (accessed 15 August 2023). [4]Ruconest® [package insert], https://www.ruconest.com/wp-content/uploads/Ruconest_PI_Apr2020.pdf (accessed 15 August 2023). [5]Tuong LA et al. Allergy Asthma Proc 2014;35:250-4. [6]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). [7]Betschel S et al. Allergy Asthma Clin Immunol Pract 2021 2021;9:132-50. [8]Busse PJ et al. J Allergy Clin Immunol Pract 2021 2021;9:132-50. [9]Maurer M et al. Allergy 2022;77:1961-90. [10]Lesage A et al. Front Pharmacol 2020;11:916. [11]Lesage A et al. Int Immunopharmacol 2022;105:108523. [12]https://clinicaltrials.gov/ct2/show/NCT04618211 (accessed 15 August 2023). [13]Maurer M et al. AAAAI 2023;411. [14]Farkas H et al. 13th C1-inhibitor Deficiency and Angioedema Workshop 2023;0-19. [15]Vernon MK et al. Qual Life Res 2009;18:929-39. [16]Cicardi M et al. N Engl J Med 2010;363:523-31. [17]Levy RJ et al. Ann Allergy Asthma Immunol 2010;104:523-9.

Research grant support, consultancy fees, speaker fees, and/or clinical trial fees – M.E.M.: Allakos, Amgen, AstraZeneca, BioCryst, Blueprint, CSL Behring, Cycle, Genentech, GSK, KalVista, Merck, Novartis, Pharming, Pharvaris, Sanofi/Regeneron, Takeda. J.A.: BioCryst, BioMarin, CSL Behring, Cycle pharmaceuticals, Pharming, Pharvaris, Takeda. H.H.L.: BioCryst, BioMarin, CSL Behring, Intellia, KalVista, Pharming, Pharvaris, Takeda. E.A.P.: BioCryst, Biomarin, Centogene, CSL Behring, KalVista, Pharming, Pharvaris, Shire/Takeda. M.L.B.: BioCryst, CSL Behring, Shire HGT. L.B.: BioCryst, Blueprint, CSL Behring, Novartis, Shire/Takeda. N.C.: CSL Behring, Dyax, Green Cross, Merck, Novartis, Pharvaris, Sanofi, Sobi, Takeda. D.M.C.: BioCryst, CSL Behring, Pharming, Pharvaris, Shire/Takeda. A.D.T.: BioCryst, Takeda. O.F.: BioCryst, CSL Behring, Takeda. H.F.: BioCryst, CSL Behring, KalVista. OND Pharmaceutical, Pharming, Pharvaris, Takeda. J.G.: CSL Behring, Shire/Takeda. M.C.: CSL Behring, Novartis, Takeda participated in advisory boards organized by BioCryst, CSL Behring, Novartis, Pharming, Pharvaris, Takeda. D.H.: none. B.H.: BioCryst, CSL Behring, KalVista, Pharming Pharvaris, Shire/Takeda. A.K.: CSL Behring, Pharming, Takeda. S.K.-A.: BioCryst, Biotest, CSL Behring, Ionis Pharmaceuticals, KalVista, Pharvaris, Shire/Takeda, X4 Pharmaceuticals. P.K.: none. R.L.: BioCryst, CSL Behring, Takeda. M.Meg.: BioCryst, CSL Behring, KalVista, Novartis, Octapharma, Pharming, Shire/Takeda. A.R.: BioCryst, CSL Behring, Pharming, Pharvaris, Shire/Takeda, Stallergenes, Teva. B.R.: BioCryst, CSL Behring, Ionis, KalVista, Pharvaris, Takeda. G.S.: Pharvaris, Takeda. M.Sta.: Pharming, Pharvaris, Sobi. P.S.: CSL Behring, Novartis, Pfizer, Shire/Takeda. M.Sto.: BioCryst, CSL Behring, KalVista, Pharming, Shire/Takeda. G.L.S.: Aimmune, Amgen, CSL Behring, BMN, Genentech, Green Cross, Kedrion, Leo, Novartis, Novo, Pediapharm, Sanofi. M.D.T.: none. A.V.: Astra Zeneca, Berlin-Chemie/Menarini Group, CSL Behring, Novartis, Pharming, Pharvaris, Shire/Takeda, Sobi, Teva. W.H.Y.: Aimmune, AJK, Aravive/Alx, AstraZeneca, BioCryst, CSL Behring, DBV Technologies, Dermira, Genentech, GlaxoSmithKline, Glenmark, Merck, Novartis, Pharming, Regeneron, Roche, Sanofi, Shire/Takeda. M.-H.J.: employee of Pharvaris at the time the analyses were conducted, holds stocks in Pharvaris. R.C.: employee of CG Consultancy and consultant to Pharvaris, holds stocks in Pharvaris. S.v.L.: employee of SLC Consultancy and consultant to Pharvaris, holds stocks in Pharvaris. H.C.: employee of Pharvaris at the time the analyses were conducted, holds stocks in Pharvaris. L.Z.: employee of Pharvaris, holds stocks in Pharvaris. J.K.: employee of JCK Consult and consultant to Pharvaris, holds stocks/stock options in Pharvaris. A.L.: employee of CrisMatters Consulting and consultant to Pharvaris, holds stocks/stock options in Pharvaris. Advisor to Kosa Pharma, holds stocks in Kosa Pharma. P.L.: employee of Pharvaris, holds stocks/stock options in Pharvaris. M.Mau.: Adverum, Attune, BioCryst, CSL Behring, KalVista, Pharming, Pharvaris, Takeda/Shire. M.A.R.: Aerie, BioCryst, Biomarin, CSL Behring, Cycle Pharma, Fresenius-Kabi, Grifols, Ionis, Ipsen, KalVista, Oxo Pharma, Pfizer, Pharming, Pharvaris, Regeneron, Sanofi Regeneron, Takeda.

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

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.E.M.: Allakos, Amgen, AstraZeneca, BioCryst, Blueprint, CSL Behring, Cycle, Genentech, GSK, KalVista, Merck, Novartis, Pharming, Pharvaris, Sanofi/Regeneron, Takeda.

J.A.: BioCryst, BioMarin, CSL Behring, Cycle Pharmaceuticals, KalVista, Pharming, Pharvaris, Takeda. J.S.J.: BioCryst, CSL Behring, Cycle pharmaceuticals, Oasis pharmaceuticals, Pharming, Pharvaris, Takeda. H.H.L.: BioCryst, BioMarin, CSL Behring, Intellia, KalVista, Pharming, Pharvaris, Takeda. E.A.P.: BioCryst, Biomarin, Centogene, CSL Behring, KalVista; Pharming, Pharvaris, Shire/Takeda. M.L.B.: BioCryst, CSL Behring, Shire HGT. L.B.: BioCryst, Blueprint, CSL Behring, Novartis, Shire/Takeda. H.C.: CSL Behring, Dyax, Green Cross, Merck, Novartis, Pharvaris, Sanofi, Sobi, Takeda. D.M.C.: BioCryst, CSL Behring, Pharming, Pharvaris, Shire/Takeda. A.D-T.: BioCryst, Takeda. O.F.: BioCryst, CSL Behring, Takeda. H.F.: BioCryst, CSL Behring, KalVista, ONO Pharmaceutical, Pharming, Pharvaris, Takeda. J.G.: CSL Behring, Shire/Takeda. M.G.: CSL Behring, Novartis, Takeda; participated in advisory boards organized by BioCryst, CSL Behring, Novartis, Pharming, Pharvaris, Takeda. D.H.: none. R.H.: BioCryst, CSL Behring, KalVista, Pharming Pharvaris, Shire/Takeda. A.K.: CSL Behring, Pharming, Takeda. S.K.-A.: BioCryst, Biotest, CSL Behring, Ionis Pharmaceuticals, KalVista, Pharvaris, Shire/Takeda, X4 Pharmaceuticals. P.K.: none. R.L.: BioCryst, CSL Behring, Takeda. M.Mag.: BioCryst, CSL Behring, KalVista, Novartis, Octapharma, Pharming, Shire/Takeda. A.R.: BioCryst, CSL Behring, Pharming, Pharvaris, Shire/Takeda, Stallergens, Teva. B.R.: BioCryst, CSL-Behring, Ionis, KalVista, Pharvaris, Takeda. G.S.: Pharvaris, Takeda. M.Sta.: Pharming, Pharvaris, Sobi. P.S.: CSL Behring, Novartis, Pfleger, Shire/Takeda. M.Sto.: BioCryst, CSL Behring, KalVista, Pharming, Shire/Takeda. G.L.S.: Aimmune, Amgen, CSL Behring, DBV, Genentech, Green Cross, Kedrion, Leo, Novartis, Novo, Pediapharm, Sanofi. M.D.T.: none. A.V.: Astra Zeneca, Berlin-Chemie/MenariniGroup, CSL Behring, Novartis, Pharming, Pharvaris, Shire/Takeda, Sobi, Teva. W.H.Y.: Aimmune, ALK, AnaptysBio, AstraZeneca, BioCryst, CSL Behring, DBV Technologies, Dermira, Genentech, GlaxoSmithKline, Glenmark, Merck, Novartis, Pharming, Regeneron, Roche, Sanofi, Shire/Takeda. M.Mau.: 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.

M.-H.J.: employee of Pharvaris at the time the analyses were conducted, holds stocks in Pharvaris. R.C.: employee of CG Consultancy and consultant to Pharvaris, holds stocks in Pharvaris. S.v.L.: employee of SLC Consultancy and consultant to Pharvaris, holds stocks in Pharvaris. H.C.: employee of Pharvaris at the time the analyses were conducted, holds stocks in Pharvaris. L.Z.: employee of Pharvaris, holds stocks in Pharvaris. J.K.: employee of JCK Consult and consultant to Pharvaris, holds stocks/stock options in Pharvaris. A.L.: employee of GrayMattersConsulting and consultant to Pharvaris, holds stocks/stock options in Pharvaris. Advisor to KosaPharma, holds stocks in KosaPharma. P.L.: employee of Pharvaris, holds stocks/stock options in Pharvaris.

RAPIDe-1 was a Pharvaris-sponsored clinical trial. ClinicalTrials.gov Identifier: NCT04618211. EudraCT Number: 2020-003445-11.

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

Introduction

- Approved therapies for hereditary angioedema (HAE) attacks are administered parenterally with substantial treatment burden due to administration time and risk of pain or other injection site reactions[1-4], with treatment of many attacks being delayed or forgone.[5-6]
- An unmet need exists for on-demand oral therapies that are effective and well-tolerated and may reduce the treatment burden enabling prompt administration as recommended by international clinical guidelines.[7-9]
- Deucrictibant immediate-release (IR) capsule (PHVS416) is an investigational formulation containing deucrictibant (PHA121), a highly potent, specific, and orally bioavailable competitive antagonist of the bradykinin B2 receptor.[10-11]

[1]Berinert® [package insert], https://labeling.cslbehring.com/pi/us/berinert/en/berinert-prescribing-information.pdf (accessed 15 August 2023). [2]Firazyr® [package insert], https://www.shirecontent.com/PI/PDFs/Firazyr_USA_ENG.pdf (accessed 15 August 2023). [3]Kalbitor® [package insert], https://www.shirecontent.com/PI/PDFs/Kalbitor_USA_ENG.pdf (accessed 15 August 2023). [4]Ruconest® [package insert], https://www.ruconest.com/wp-content/uploads/Ruconest_PI_Apr2020.pdf (accessed 15 August 2023). [5]Tuong LA et al. Allergy Asthma Proc 2014;35:250-4. [6]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). [7]Betschel S et al. Allergy Asthma Clin Immunol 2019;15:72. [8]Busse PJ et al. J Allergy Clin Immunol Pract 2021 2021;9:132-50. [9]Maurer M et al. Allergy 2022;77:1961-90. [10]Lesage A et al. Front Pharmacol 2020;11:916. [11]Lesage A et al. Int Immunopharmacol 2022;105:108523.

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

Methods

- RAPIDe-1 was a Phase 2, double-blind, placebo-controlled, randomized, crossover, dose-ranging trial of deucrictibant IR capsule for the acute treatment of angioedema attacks in patients with HAE-1/2[12].

- A primary analysis was performed including 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 analysis, mITT = all randomized participants with ≥1 treated HAE attack and VAS results at both pre-treatment and ≥1 post-treatment time point).

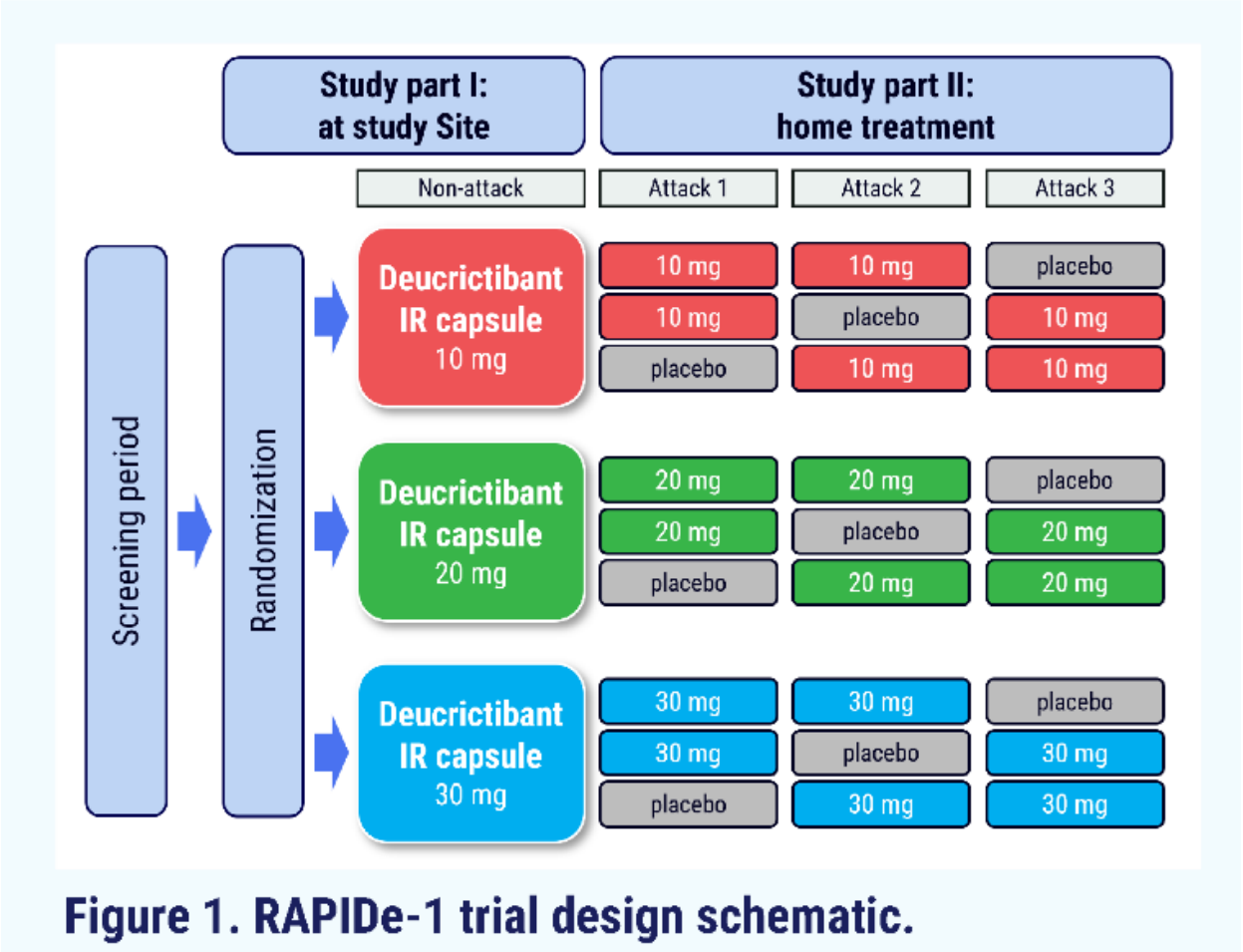

Figure 1. RAPIDe-1 trial design schematic.

[12]https://clinicaltrials.gov/ct2/show/NCT04618211 (accessed 15 August 2023).

Results – MSCS

- MSCS is a point-in-time measure of symptom severity:
  - Patient-rated severity of each affected symptom on a categorical scale
    (0 = normal, 1 = mild, 2 = moderate, 3 = severe)
  - Calculated as average score from all affected body sites (symptom complexes)
  - Decrease in score reflects improvement in symptom severity

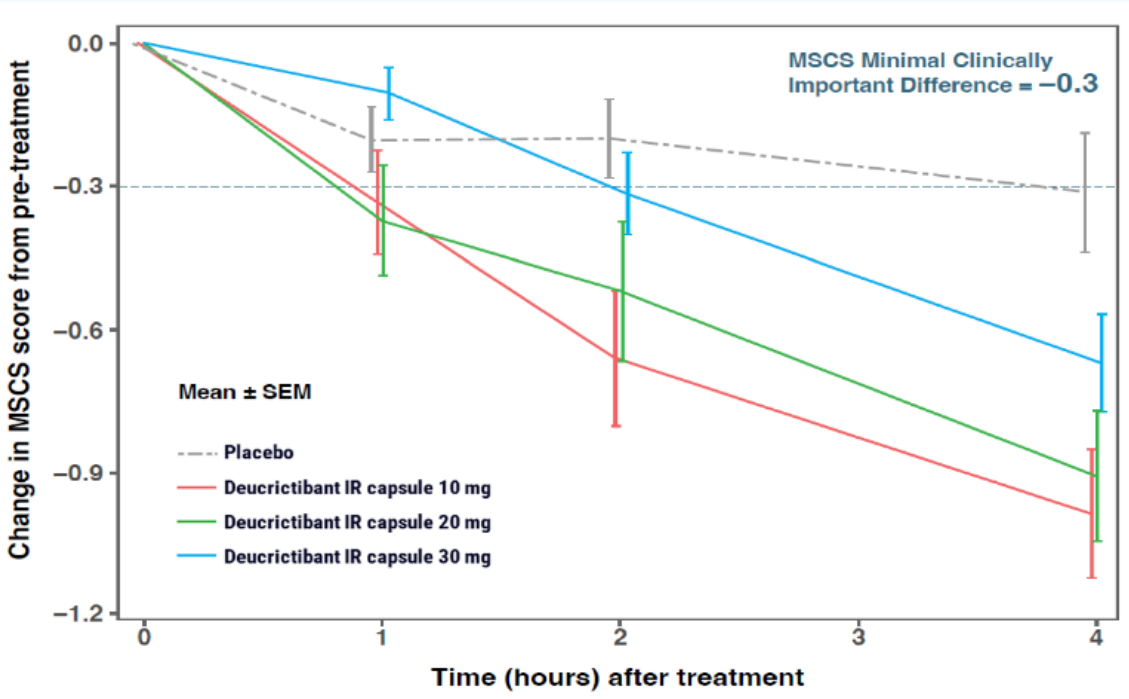

Figure 2. MSCS score measured up to 4 h post-treatment.

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

Results – TOS

- TOS is a measure of symptom response to treatment:
  - Patient assessment of response for each affected body site on categorical scale
  - (significant improvement [100], improvement [50], same [0], worsening [-50], significant worsening [-100])
  - Calculated as weighted average of the response at all body sites using pre-treatment severity as weight
  - Increase in score reflects improvement in symptom from pre-treatment

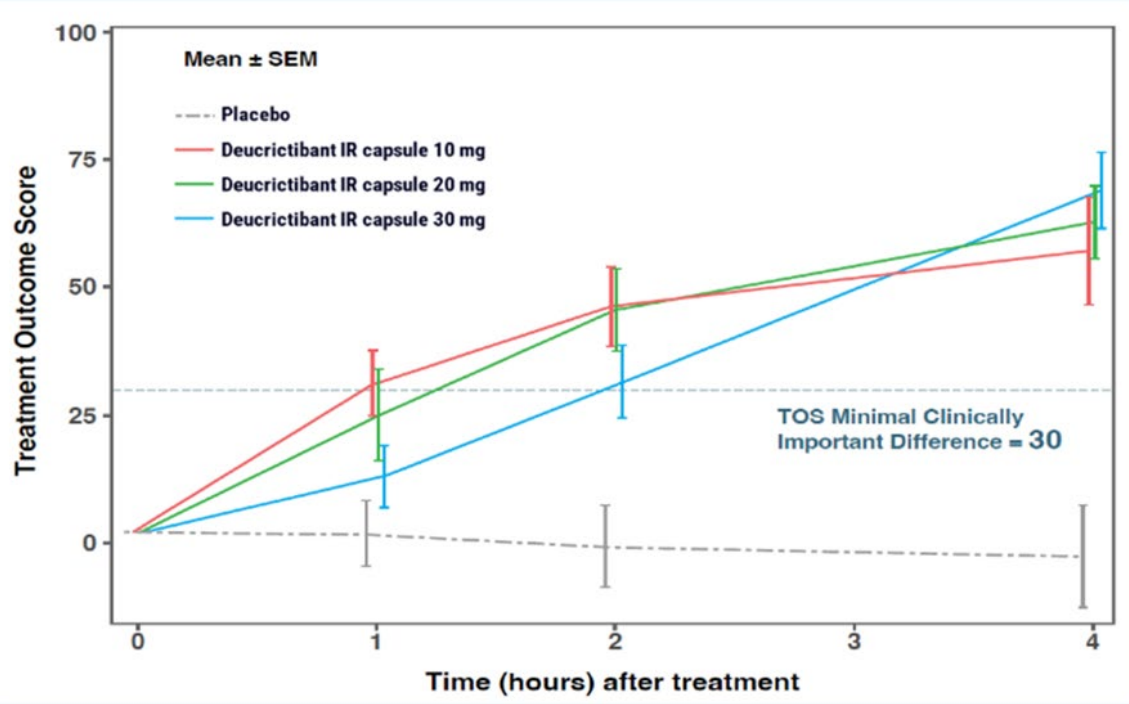

Figure 3. TOS measured up to 4 h post-treatment.

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

Results – TOS PRO

- Complex Assessment questions (TOS PRO) evaluate patient-reported changes in attack symptoms from pre-treatment
  - a lot better or resolved
  - a little better
  - same
  - a little worse
  - a lot worse

	Placebo	Deucrictibant IR capsule 10 mg	Deucrictibant IR capsule 20 mg	Deucrictibant IR capsule 30 mg
Number of patients with post-treatment TOS PRO	49	21	16	19
Number of attacks with post-treatment TOS PRO	49	36	28	29
Attacks with onset of all symptom complexes **"a little better"** within 48 hours – n (%)	18 (36.7%)	32 (88.9%)	25 (89.3%)	27 (93.1%)
Median (95% CI) time (hours) to **onset of symptom relief** by KM estimate	7.62 (3.95, -)	1.89 (0.97, 3.97)	2.15 (1.75, 4.00)	1.98 (1.80, 3.87)

Onset of symptom relief = the time point when TOS PRO first reaches at least "A little better" for all symptom complexes affected at baseline, and no new symptom in any other symptom complex is reported. Relief is confirmed if the improvement is sustained at 2 consecutive time points.

Table 1. Time to onset of symptom relief measured through TOS PRO.

	Placebo	Deucrictibant IR capsule 10 mg	Deucrictibant IR capsule 20 mg	Deucrictibant IR capsule 30 mg
Number of patients with post-treatment TOS PRO	49	21	16	19
Number of attacks with post-treatment TOS PRO	49	36	28	29
Attacks with onset of all symptom complexes **"a lot better or resolved"** within 48 hours – n (%)	13 (26.5%)	30 (83.3%)	23 (82.1%)	25 (86.2%)
Median (95% CI) time (hours) to **almost complete or complete symptom relief** by KM estimate	23.28 (5.78, 47.17)	4.02 (3.93, 5.77)	5.93 (3.90, 8.58)	4.12 (3.92, 7.22)

Almost complete or complete symptom relief = the time point when TOS PRO first reaches *"A lot better or resolved"* for all symptom complexes affected at baseline, and no new symptom in any other symptom complex is reported.

Table 2. Time to almost complete or complete symptom relief measured through TOS PRO.

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

Conclusions

- In the Phase 2 RAPIDe-1 trial deucrictibant IR capsule improved symptoms and reduced time to symptom relief and to resolution of HAE attacks
- Clinical meaningful improvement of symptoms was observed during the first hours after treatment with deucrictibant IR capsule

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

Early symptom relief following treatment with the oral bradykinin B2 receptor antagonist deucrictibant immediate-release capsule in patients with hereditary angioedema attacks

Michael E. Manning[1], John Anderson[2], Joshua S. Jacobs[3], H. Henry Li[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[21], Marc A. Riedl[37]

[1]Scottsdale, AZ, United States of America; [2]Birmingham, AL, United States of America; [3]Walnut Creek, CA, United States of America; [4]Chevy Chase, MD, United States of America; [5]Frankfurt, Germany; [6]Madrid, Spain; [7]Grenoble, France; [8]Montréal, QC, Canada; [9]Amsterdam, The Netherlands; [10]Montpellier, France; [11]Paris, France; [12]Budapest, Hungary; [13]Ulm, Germany; [14]Barcelona, Spain; [15]Tel Aviv, Israel; [16]Brno, Czech Republic; [17]Haifa, Israel; [18]London, United Kingdom; [19]Hradec Kralove, Czech Republic; [20]Barcelona, Spain; [21]Berlin, Germany; [22]Ashkelon, Israel; [23]Edmonton, AB, Canada; [24]Napoli, Italy; [25]Sofia, Bulgaria; [26]Mainz, Germany; [27]Krakow, Poland; [28]Toronto, ON, Canada; [29]Brighton, United Kingdom; [30]Ottawa, ON, Canada; [31]Lexington, MA, United States of America (former Pharvaris employees); [32]Bassins, Switzerland; [33]Woerden, The Netherlands; [34]Lexington, MA, United States of America; [35]Frankfurt, Germany; [36]Schilde, Belgium; [37]La Jolla, CA, United States of America

Introduction

- Approved therapies for hereditary angioedema (HAE) attacks are administered parenterally with substantial treatment burden due to administration time and risk of pain or other injection site reactions[1-4], with treatment of many attacks being delayed or forgone.[5-6]
- An unmet need exists for on-demand oral therapies that are effective and well-tolerated and may reduce the treatment burden enabling prompt administration as recommended by international clinical guidelines.[7-9]
- Deucrictibant immediate-release (IR) capsule (PHVS416) is an investigational formulation containing deucrictibant (PHA121), a highly potent, specific, and orally bioavailable competitive antagonist of the bradykinin B2 receptor.[10-11]
- In the Phase 2 RAPIDe-1 trial* (NCT04618211)[12] deucrictibant IR capsule reduced time to onset of symptom relief and to attack resolution measured through the visual analogue scale-3 (VAS-3) and substantially reduced use of rescue medication.[13-14]

Methods

- RAPIDe-1 was a Phase 2, double-blind, placebo-controlled, randomized, crossover, dose-ranging trial of deucrictibant IR capsule for the acute treatment of angioedema attacks in patients with HAE-1/2.
- A primary analysis was performed including 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 analysis, mITT = all randomized participants with ≥1 treated HAE attack and VAS results at both pre-treatment and ≥1 post-treatment time point).
- Mean Symptom Complex Severity (MSCS) score and Treatment Outcome Score (TOS) are validated composite scores based on patient-reported symptoms of attacks at the affected body sites, included in ecallantide clinical trials[15-17]. Changes in MSCS score and in TOS from pre-treatment to 4 hours post-treatment were among the secondary endpoints of RAPIDe-1.
- MSCS is a point-in-time measure of symptom severity:
  - Patient-rated severity of each affected symptom on a categorical scale (0 = normal, 1 = mild, 2 = moderate, 3 = severe)
  - Calculated as average score from all affected body sites (symptom complexes)
  - Decrease in score reflects improvement in symptom severity
- TOS is a measure of symptom response to treatment:
  - Patient assessment of response for each affected body site on categorical scale (significant improvement [100], improvement [50], same [0], worsening [-50], significant worsening [-100])
  - Calculated as weighted average of the response at all body sites using pre-treatment severity as weight
  - Increase in score reflects improvement in symptom from pre-treatment
  - Complex Assessment questions (TOS PRO) evaluate patient-reported changes in attack symptoms from pre-treatment (a lot better or resolved – a little better – same – a little worse – a lot worse)

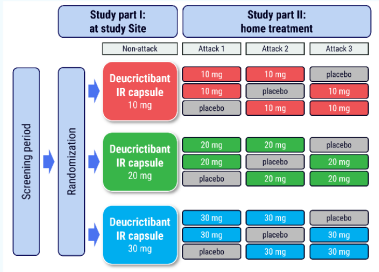

Figure 1. RAPIDe-1 trial design schematic.

Results

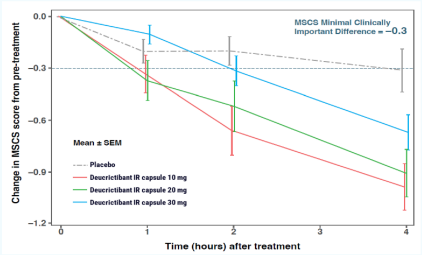

Figure 2. MSCS score measured up to 4 h post-treatment.

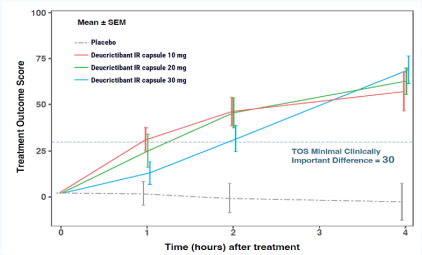

Figure 3. TOS measured up to 4 h post-treatment.

	Placebo	Deucrictibant IR capsule 10 mg	Deucrictibant IR capsule 20 mg	Deucrictibant IR capsule 30 mg
Number of patients with post-treatment TOS PRO	49	21	16	19
Number of attacks with post-treatment TOS PRO	49	36	28	29
Attacks with onset of all symptom complexes "**a little better**" within 48 hours – n (%)	18 (36.7%)	32 (88.9%)	25 (89.3%)	27 (93.1%)
Median (95% CI) time (hours) to **onset of symptom relief** by KM estimate	7.62 (3.95, -)	1.89 (0.97, 3.97)	2.15 (1.75, 4.00)	1.98 (1.80, 3.87)

Onset of symptom relief = the time point when TOS PRO first reaches at least "A little better" for all symptom complexes affected at baseline, and no new symptom in any other symptom complex is reported. Relief is confirmed if the improvement is sustained at 2 consecutive time points.

Table 1. Time to onset of symptom relief measured through TOS PRO.

	Placebo	Deucrictibant IR capsule 10 mg	Deucrictibant IR capsule 20 mg	Deucrictibant IR capsule 30 mg
Number of patients with post-treatment TOS PRO	49	21	16	19
Number of attacks with post-treatment TOS PRO	49	36	28	29
Attacks with onset of all symptom complexes "**a lot better or resolved**" within 48 hours – n (%)	13 (26.5%)	30 (83.3%)	23 (82.1%)	25 (86.2%)
Median (95% CI) time (hours) to **almost complete or complete symptom relief** by KM estimate	23.28 (5.78, 47.17)	4.02 (3.93, 5.77)	5.93 (3.90, 8.58)	4.12 (3.92, 7.22)

Almost complete or complete symptom relief = the time point when TOS PRO first reaches "*A lot better or resolved*" for all symptom complexes affected at baseline, and no new symptom in any other symptom complex is reported.

Table 2. Time to almost complete or complete symptom relief measured through TOS PRO.

Conclusions

- **In the Phase 2 RAPIDe-1 trial deucrictibant IR capsule improved symptoms and reduced time to symptom relief and to resolution of HAE attacks**
- **Clinical meaningful improvement of symptoms was observed during the first hours after treatment with deucrictibant IR capsule**

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]Berinert® [package insert], https://labeling.cslbehring.com/pi/us/berinert/en/berinert-prescribing-information.pdf (accessed 15 August 2023). [2]Firazyr® [package insert], https://www.shirecontent.com/PI/PDFs/Firazyr_USA_ENG.pdf (accessed 15 August 2023). [3]Kalbitor® [package insert], https://www.shirecontent.com/PI/PDFs/Kalbitor_USA_ENG.pdf (accessed 15 August 2023). [4]Ruconest® [package insert], https://www.ruconest.com/wp-content/uploads/Ruconest_PI_Apr2020.pdf (accessed 15 August 2023). [5]Tuong LA et al. Allergy Asthma Proc 2014;35:250-4. [6]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). [7]Betschel S et al. Allergy Asthma Clin Immunol Pract 2021 2021;9:132-50. [8]Busse PJ et al. J Allergy Clin Immunol Pract 2021 2021;9:132-50. [9]Maurer M et al. Allergy 2022;77:1961-90. [10]Lesage A et al. Front Pharmacol 2020;11:916. [11]Lesage A et al. Int Immunopharmacol 2022;105:108523. [12]https://clinicaltrials.gov/ct2/show/NCT04618211 (accessed 15 August 2023). [13]Maurer M et al. AAAAI 2023;411. [14]Farkas H et al. 13th C1-inhibitor Deficiency and Angioedema Workshop 2023;0-19. [15]Vernon MK et al. Qual Life Res 2009;18:929-39. [16]Cicardi M et al. N Engl J Med 2010;363:523-31. [17]Levy RJ et al. Ann Allergy Asthma Immunol 2010;104:523-9.

Research grant support, consultancy fees, speaker fees, and/or clinical trial fees – M.E.M.: Allakos, Amgen, AstraZeneca, BioCryst, Blueprint, CSL Behring, Cycle, Genentech, GSK, KalVista, Merck, Novartis, Pharming, Pharvaris, Sanofi/Regeneron, Takeda. J.A.: BioCryst, BioMarin, CSL Behring, Cycle pharmaceuticals, Pharming, Pharvaris, Takeda. H.H.L.: BioCryst, BioMarin, CSL Behring, Intellia, KalVista, Pharming, Pharvaris, Takeda. K.A.P.: BioCryst, Biomarin, Centogene, CSL Behring, KalVista, Pharming, Pharvaris, Shire/Takeda. M.L.B.: BioCryst, CSL Behring, Shire HGT. L.B.: BioCryst, Blueprint, CSL Behring, Novartis, Shire/Takeda. N.C.: CSL Behring, Dyax, Green Cross, Merck, Novartis, Pharvaris, Sanofi, Sobi, Takeda. D.M.C.: BioCryst, CSL Behring, Pharming, Pharvaris, Shire/Takeda. A.D.T.: BioCryst, Takeda. O.F.: BioCryst, CSL Behring, Takeda. H.F.: BioCryst, CSL Behring, KalVista, OND Pharmaceutical, Pharming, Pharvaris, Takeda. J.G.: CSL Behring, Shire/Takeda. M.C.: CSL Behring, Novartis, Takeda participated in advisory boards organized by BioCryst, CSL Behring, Novartis, Pharming, Pharvaris, Takeda. D.H.: none. B.H.: BioCryst, CSL Behring, KalVista, Pharming Pharvaris, Shire/Takeda. A.K.: CSL Behring, Pharming, Takeda. S.K.-A.: BioCryst, Biotest, CSL Behring, Ionis Pharmaceuticals, KalVista, Pharvaris, Shire/Takeda, X4 Pharmaceuticals. P.K.: none. R.L.: BioCryst, CSL Behring, Takeda. M.Meg.: BioCryst, CSL Behring, KalVista, Novartis, Octapharma, Pharming, Shire/Takeda. A.R.: BioCryst, CSL Behring, Pharming, Pharvaris, Shire/Takeda, Stallergenes, Teva. B.R.: BioCryst, CSL Behring, Ionis, KalVista, Pharvaris, Takeda. G.S.: Pharvaris, Takeda. M.Sta.: Pharming, Pharvaris, Sobi. P.S.: CSL Behring, Novartis, Pfizer, Shire/Takeda. M.Sto.: BioCryst, CSL Behring, KalVista, Pharming, Shire/Takeda. G.L.S.: Aimmune, Amgen, CSL Behring, BMN, Genentech, Green Cross, Kedrion, Leo, Novartis, Novo, Pedianet, Sanofi. M.D.T.: none. A.V.: Astra Zeneca, Berlin-Chemie/Menarini Group, CSL Behring, Novartis, Pharming, Pharvaris, Shire/Takeda, Sobi, Teva. W.H.Y.: Aimmune, AJK, Aravive/Alx, AstraZeneca, BioCryst, CSL Behring, DBV Technologies, Dermira, Genentech, GlaxoSmithKline, Glenmark, Merck, Novartis, Pharming, Regeneron, Roche, Sanofi, Shire/Takeda. M.-H.J.: employee of Pharvaris at the time the analyses were conducted, holds stocks in Pharvaris. R.C.: employee of CG Consultancy and consultant to Pharvaris, holds stocks in Pharvaris. S.v.L.: employee of SLC Consultancy and consultant to Pharvaris, holds stocks in Pharvaris. H.C.: employee of Pharvaris at the time the analyses were conducted, holds stocks in Pharvaris. L.Z.: employee of Pharvaris, holds stocks in Pharvaris. J.K.: employee of JCK Consult and consultant to Pharvaris, holds stocks/stock options in Pharvaris. A.L.: employee of CrageMatters Consulting and consultant to Pharvaris, holds stocks/stock options in Pharvaris. Advisor to Kosa Pharma, holds stocks in Kosa Pharma. P.L.: employee of Pharvaris, holds stocks/stock options in Pharvaris. M.Mau.: 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, Oxo Pharma, Pfizer, Pharming, Pharvaris, Regeneron, Sanofi Regeneron, Takeda.

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

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