

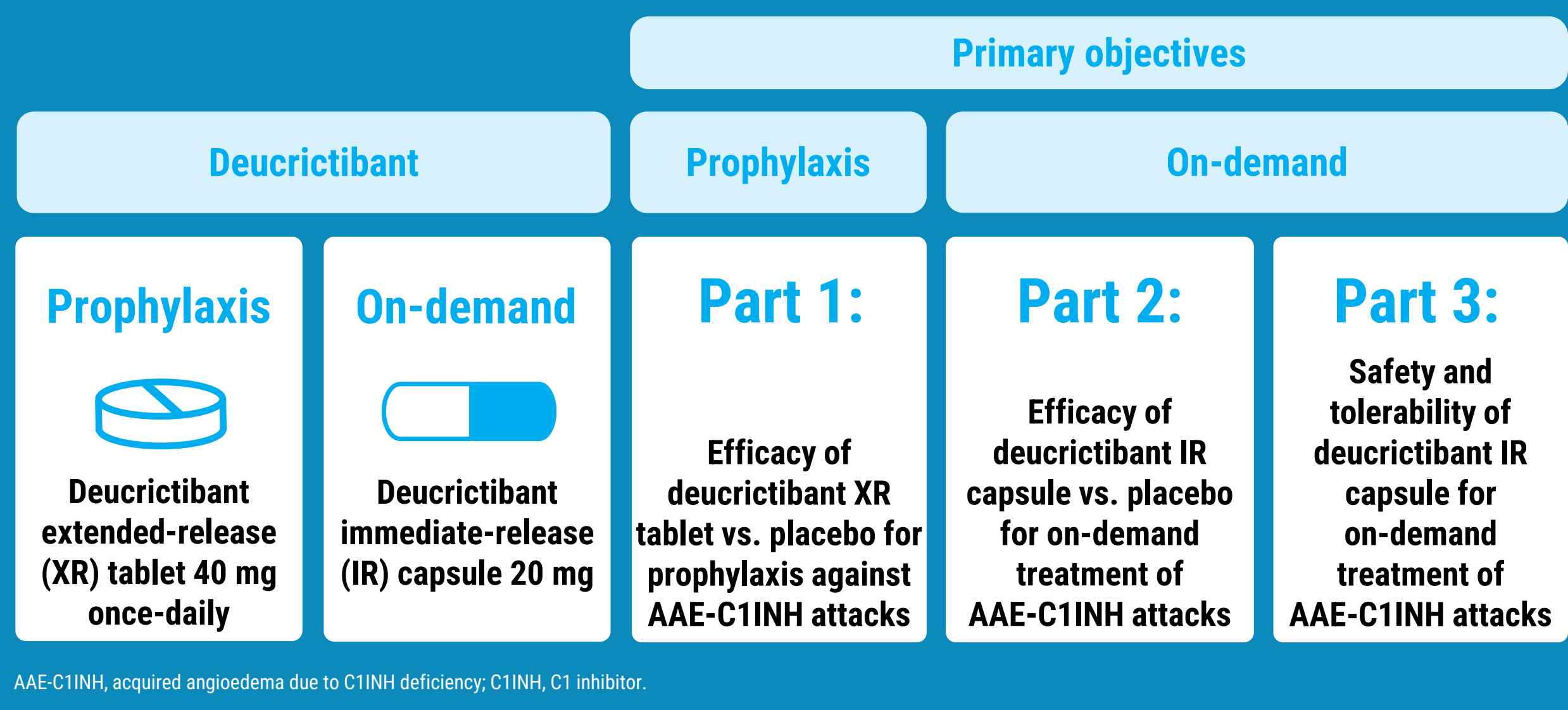
Efficacy and Safety of Oral Deucricitbant for Prophylaxis and On-Demand Treatment of Attacks in Acquired Angioedema with C1 Inhibitor Deficiency: CREAATE Phase 3 Trial Design

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Key takeaways

CREAATE* is a Phase 3, randomized, double-blind, placebo-controlled 3-part study designed to evaluate the efficacy and safety of investigational deucricitbant for prophylaxis and on-demand treatment of attacks of acquired angioedema due to C1 inhibitor deficiency.



AAE-C1INH, acquired angioedema due to C1INH deficiency; C1INH, C1 inhibitor.

Background

- Acquired angioedema due to C1 inhibitor deficiency (AAE-C1INH):** a bradykinin-mediated condition characterized by painful subcutaneous and/or submucosal swelling attacks and estimated to be 10-times rarer than hereditary angioedema (HAE), another bradykinin-mediated angioedema.¹⁻⁴
- Unmet need:** currently no approved therapies to prevent or treat AAE-C1INH attacks.¹⁻⁴
- Deucricitbant:** a selective, investigational, orally administered antagonist of the bradykinin B2 receptor under investigation for the prevention and treatment of bradykinin-mediated angioedema attacks.⁵⁻¹⁵
- Prior studies:** POP-AID and ONCE-AID were investigator-initiated proof-of-concept studies.
 - POP-AID, a randomized, double-blind, placebo-controlled, two-part study⁴:
 - On-demand treatment of AAE-C1INH attacks with deucricitbant reduced the attack severity compared with placebo.
 - Prophylactic treatment of AAE-C1INH attacks with deucricitbant reduced the occurrence of angioedema attacks and resulted in a mean monthly attack rate of 0.0.
 - Deucricitbant was well tolerated with no serious adverse events reported.
 - ONCE-AID, a long-term open-label prophylaxis study¹⁶:
 - Four patients (3 rolling over from POP-AID) were treated with deucricitbant XR tablet 40 mg once-daily for up to 20 months.
 - Deucricitbant was well tolerated with no treatment-related adverse events reported.
 - Deucricitbant resulted in a mean monthly attack rate of 0.1 (one patient reported one mild attack two days after treatment initiation; the remaining patients were attack free).

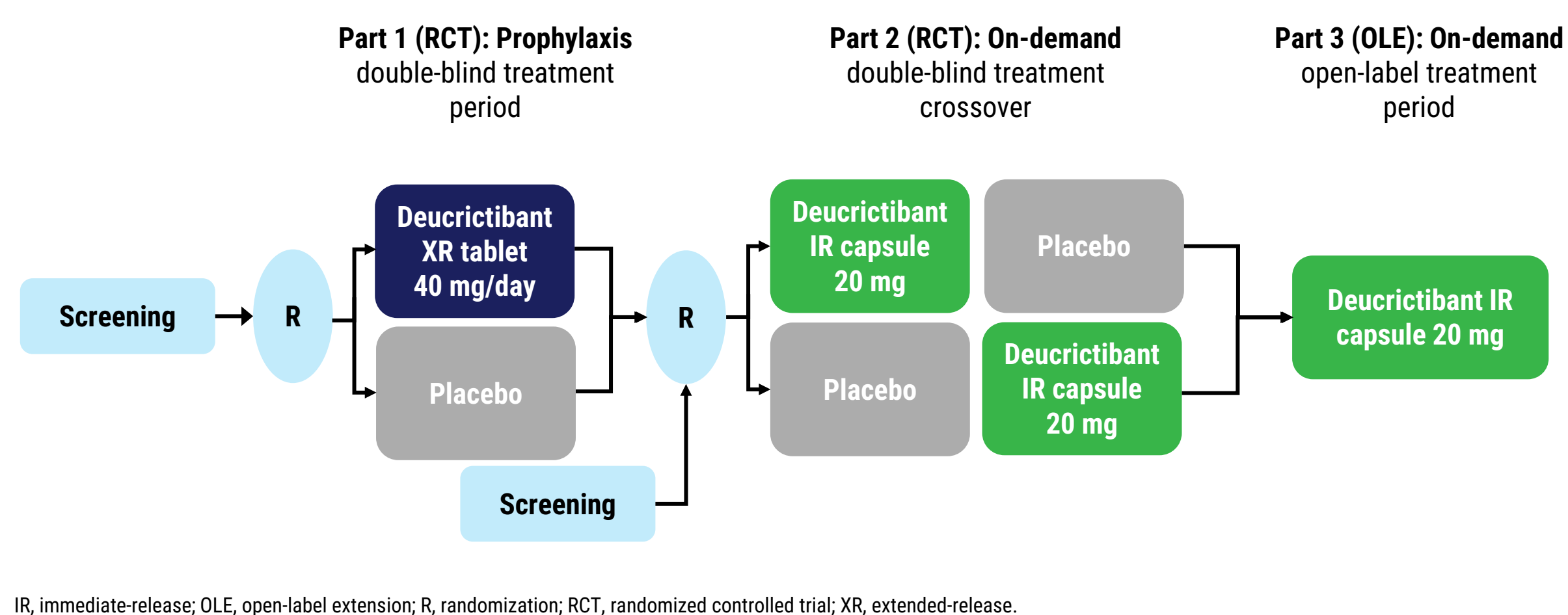
Objective

To evaluate the efficacy and safety of deucricitbant for prophylaxis and on-demand treatment of AAE-C1INH attacks in the Phase 3, pivotal, randomized, double-blind, placebo-controlled 3-part CREAATE* study.

CREAATE study

- Part 1 - Prophylaxis:** participants will be randomized 1:1 to receive placebo or deucricitbant extended-release (XR) tablet 40 mg/day.
- Part 2 - On-demand treatment:** participants will be randomized 1:1 to receive double-blinded placebo or deucricitbant immediate-release (IR) capsule 20 mg to treat 2 separate attacks in a randomized crossover sequence.
 - participants include those rolling over from Part 1 and new participants who are deucricitbant treatment-naïve.
- Part 3 - On-demand treatment:** participants who complete Part 2 may continue into Part 3. AAE-C1INH attacks will be treated with open-label deucricitbant IR capsule 20 mg.
- Pharmacokinetics:** assessments will be conducted for the deucricitbant XR tablet and IR capsule (non-attack state).

Figure 1. CREAATE study design



IR, immediate-release; OLE, open-label extension; R, randomization; RCT, randomized controlled trial; XR, extended-release.

COIs: M.C.: BioCryst, CSL Behring, KalVista, Menarini, MSD, Novartis, Otsuka, Pharming, Pharvaris, Sobi, Takeda, UCB; A.A.: Astra, BioCryst, CSL Behring, Intellia, Ionis, KalVista, Octapharma, Pharvaris, Takeda; E.A.-P.: Astra, BioCryst, BioMarin, CSL Behring, Intellia, KalVista, Otsuka, Pharming, Pharvaris, Takeda; A.B.: Astra, CSL Behring, Ionis, Intellia, KalVista, Pharvaris, Takeda; L.Bo.: BioCryst, Blueprint, CSL Behring, GSK, KalVista, Novartis, Pharvaris, Takeda; L.Br.: none; T.Ca.: Astra, BioCryst, CSL Behring, KalVista, Novartis, Pharming, Pharvaris, Takeda, IdiPAZ program for promoting research activities; T.Cr.: ADARX, Astra, BioCryst, GlaxoSmithKline, Grifols, Ionis, Intellia, KalVista, Pharvaris, Takeda, Director of ACARE International Hereditary Angioedema Center, member of the Medical Advisory Board for the HAE-A; A.D.D.: BioCryst, CSL Behring, Ionis, KalVista, Otsuka, Pharming, Pharvaris, Takeda; H.F.: BioCryst, CSL Behring, Intellia, KalVista, ONO Pharmaceutical, Pharming, Pharvaris, Takeda; J.S.F.: CSL Behring, Menarini, Novartis, Pharvaris, Takeda, Viatri; A.G.: BioCryst, CSL Behring, Shire-Takeda; D.G.: BioCryst, CSL Behring, Pharming, Takeda; M.G.: BioCryst, CSL Behring, Novartis, member of the immunology clinical reference group; P.G.: BioCryst, CSL Behring, KalVista, Pharming, Takeda; J.S.J.: BioCryst, CSL Behring, Cycle Pharma, Intellia, Ionis, KalVista, Pharming, Pharvaris, Takeda; S.K.-A.: BioCryst, Biotest, CSL Behring, Ionis, KalVista, Otsuka, Pharvaris, Takeda; L.L.: BioCryst, CSL Behring, Novartis, Takeda; H.J.L.: Astra, CSL Behring, Intellia, KalVista, Pharvaris, Takeda; M.M.: Astra, BioCryst, CSL Behring, Intellia, KalVista, Novartis, Octapharma, Otsuka, Pharvaris, Takeda; M.E.M.: AstraZeneca, Astra, BioCryst, Blueprint, Celldex, Cogent, CSL Behring, GSK, Ionis, Intellia, KalVista, Merck, Novartis, Pharming, Pharvaris, Regeneron, Takeda, Teva; F.P.: BioCryst, CSL Behring, Otsuka, Pharvaris, Takeda; M.A.R.: Astra, BioCryst, BioMarin, Celldex, CSL Behring, Cycle Pharma, Grifols, Intellia, Ionis, KalVista, Novartis, Pharming, Pharvaris, Sanofi-Regeneron, Takeda; M.S.: BioCryst, CSL Behring, KalVista, Pharming, Pharvaris, Takeda; C.S.: none; P.T.: CSL Behring, Takeda; A.V.: AstraZeneca, Berlin-Chemie/Menarini Group, CSL Behring, KalVista, Novartis, Pharming, Pharvaris, Sobi, Takeda; H.J.W.: BioCryst, BioMarin, CSL Behring, Genentech, GSK, Takeda; P.F.K.Y.: Astra, BioCryst, CSL Behring, KalVista, Pharming, Pharvaris, Takeda; A.Z.: BioCryst, CSL Behring, KalVista, Pharming, Pharvaris, Takeda; C.C., J.M., L.Z.: employees of Pharvaris, holds stock in Pharvaris; R.C.: employee of RC Consultancy and consultant to Pharvaris, holds stocks in Pharvaris; P.Lu: employee of Pharvaris, holds stocks in Pharvaris; D.M.C.: Astra, BioCryst, CSL Behring, Ionis, Intellia, KalVista, Otsuka, Pharvaris, Takeda.

Acknowledgments: Medical writing services were provided by Jonny Turner, PhD, of Envision Pharma Group, and was funded by Pharvaris.

*CREAATE is a Pharvaris-sponsored clinical trial.

CREAATE endpoints

Table 1. CREAATE key inclusion and exclusion criteria

Key inclusion criteria	Key exclusion criteria
<ul style="list-style-type: none"> Age ≥18 years Diagnosis of AAE-C1INH, based on the following: <ul style="list-style-type: none"> Documented clinical history consistent with AAE-C1INH C1INH functional level <40% Absence of family history of angioedema At least 1 of the following: <ul style="list-style-type: none"> C1q below the lower limit of normal Serological confirmation of anti-C1INH autoantibodies Stable underlying disease with history of recent attacks Access and ability to use standard-of-care on-demand treatment to manage AAE-C1INH attacks 	<ul style="list-style-type: none"> Any concomitant diagnosis of recurrent angioedema other than AAE-C1INH Participation in any other investigational drug study Participants who received any of the following prophylaxis medications prior to screening: <ul style="list-style-type: none"> C1INH, oral kallikrein inhibitors, or anti-fibrinolytics within 2 weeks Attenuated androgens within 4 weeks Monoclonal antibody therapy within 10 weeks Pregnant or breastfeeding

AAE-C1INH, acquired angioedema due to C1 inhibitor deficiency; C1INH, C1 inhibitor; C1q, complement component 1q.

Table 2. Part 1 endpoints

Primary endpoint	Time-normalized (per 4 weeks) number of investigator-confirmed AAE-C1INH attacks
Secondary endpoints:	
Efficacy	<ul style="list-style-type: none"> Proportion of participants who are AAE-C1INH attack free Time-normalized number of investigator-confirmed AAE-C1INH attacks treated with on-demand medication Time normalized number of investigator-confirmed moderate and severe AAE-C1INH attacks Time-normalized number of investigator-confirmed severe AAE-C1INH attacks Proportion of participants achieving ≥50%, ≥70%, and ≥90% reduction in AAE-C1INH attack rate compared with baseline
Safety	<ul style="list-style-type: none"> Incidence of TEAEs and SAEs Change from baseline in clinical laboratory, vital signs, physical examination, and ECG parameters
PK outcomes	Plasma concentrations of deucricitbant
Patient-reported outcomes	<ul style="list-style-type: none"> Angioedema Quality of Life (AE-QoL) Questionnaire Angioedema Control Test 4-week version (AECT-4wk) Patient Global Assessment of Change (PGA-C) compared with Patient Global Assessment of Status (PGA-S) at baseline EuroQoL 5 Dimension 5 Level (EQ-5D-5L)

AAE-C1INH, acquired angioedema due to C1INH deficiency; C1INH, C1 inhibitor; ECG, electrocardiogram; PK, pharmacokinetic; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Table 3. Part 2 endpoints

Primary endpoint	Time to symptom relief measured using Patient Global Impression of Change (PGI-C) within 12 hours post treatment
Secondary endpoints:	
Efficacy	<ul style="list-style-type: none"> Time to complete symptom resolution measured using Patient Global Impression of Severity (PGI-S) within 48 hours post-treatment Time to symptom relief measured using PGI-S within 12 hours post-treatment Proportion of study drug-treated attacks achieving complete symptom resolution measured using PGI-S at 24 hours post-treatment Time to end of progression in attack symptoms within 12 hours
Safety	<ul style="list-style-type: none"> Incidence of TEAEs and SAEs Change from baseline in clinical laboratory, vital signs, physical examination, and ECG parameters
PK outcomes	Plasma concentrations of deucricitbant

ECG, electrocardiogram; PK, pharmacokinetic; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Table 4. Part 3 endpoints

Primary endpoints	<ul style="list-style-type: none"> Incidence of TEAEs and SAEs Change from baseline in clinical laboratory, vital signs, physical examination, and ECG parameters
Secondary endpoints:	
Efficacy	<ul style="list-style-type: none"> Time to symptom relief measured using PGI-C within 12 hours post-treatment Time to symptom relief measured using PGI-S within 12 hours post-treatment Proportion of study drug-treated attacks achieving complete symptom resolution measured using PGI-S at 24 hours post-treatment

ECG, electrocardiogram; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

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

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