Efficacy and Safety of Oral Deucrictibant 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 deucrictibant for prophylaxis and on-demand treatment of attacks of acquired angioedema due to C1 inhibitor deficiency (AAE-C1INH).

Primary objectives

Deucrictibant		
	Prophylaxis	**On-demand**
Prophylaxis **Deucrictibant extended-release (XR) tablet 40 mg once-daily**	**On-demand** **Deucrictibant immediate-release (IR) capsule 20 mg**	**Part 1:** **Efficacy of deucrictibant XR tablet vs. placebo for prophylaxis against AAE-C1INH attacks**
		Part 2: **Efficacy of deucrictibant IR capsule vs. placebo for on-demand treatment of AAE-C1INH attacks**
		Part 3: **Safety and tolerability of deucrictibant IR capsule for on-demand treatment of repeat AAE-C1INH attacks**

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]
- **Deucrictibant:** a selective, investigational, orally administered antagonist of the bradykinin B2 receptor under investigation for the prevention and treatment of bradykinin-mediated angioedema attacks.[5-14]
- **Prior studies:** POP-AID and ONCE-AID were investigator-initiated proof-of-concept studies.
  - POP-AID, a randomized, double-blind, placebo-controlled, two-part study using the immediate-release (IR) capsule[4]:
    - On-demand treatment of AAE-C1INH attacks with deucrictibant reduced the attack severity compared with placebo.
    - Prophylactic treatment of AAE-C1INH attacks with deucrictibant reduced the occurrence of angioedema attacks and resulted in a mean monthly attack rate of 0.0.
    - Deucrictibant was well tolerated with no serious adverse events reported.
  - ONCE-AID, a long-term open-label prophylaxis study[15]:
    - Four patients (3 rolling over from POP-AID) were treated with deucrictibant extended-release (XR) tablet 40 mg once-daily for an additional 20 months.
    - Deucrictibant was well tolerated with no treatment-related adverse events reported.
    - Deucrictibant resulted in a mean monthly attack rate of 0.1 (one patient reported one mild attack two days after treatment initiation; the other patients remained attack free during the entire duration of treatment).

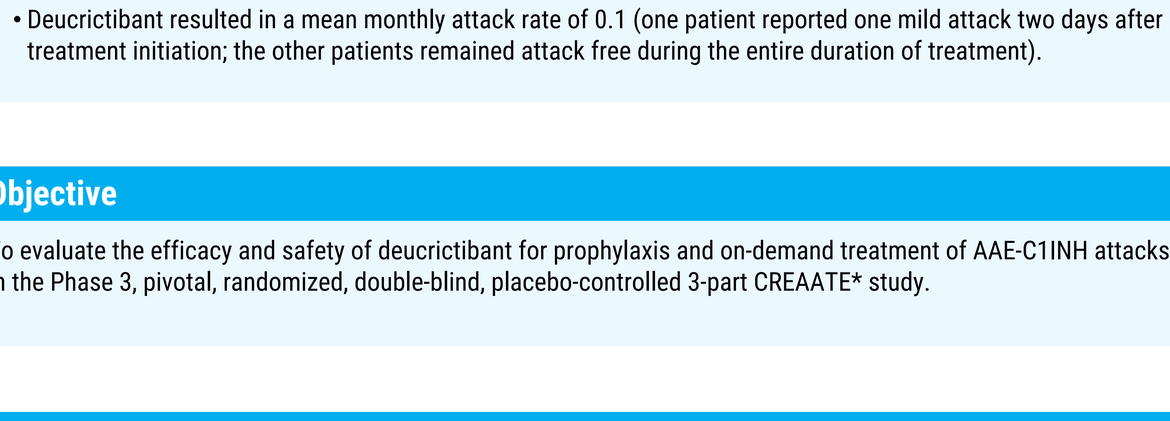
Objective

To evaluate the efficacy and safety of deucrictibant 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 double-blinded deucrictibant XR tablet 40 mg once-daily or matching placebo.
- **Part 2 - On-demand treatment:** participants will be randomized 1:1 to receive double-blinded deucrictibant IR capsule 20 mg or matching placebo to treat 2 separate attacks in a randomized crossover sequence.
  - participants include those rolling over from Part 1 and new participants who are deucrictibant treatment-naïve.
- **Part 3 - On-demand treatment:** participants who complete Part 2 may continue into Part 3. Repeat AAE-C1INH attacks will be treated with open-label deucrictibant IR capsule 20 mg.
- **Pharmacokinetics:** assessments will be conducted for the deucrictibant 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.

CREAATE endpoints

Table 1. CREAATE key inclusion and exclusion criteria

Key inclusion criteria include	Key exclusion criteria include
• Age ≥18 years • Diagnosis of AAE-C1NH, based on the following: – Documented clinical history consistent with AAE-C1INH – C1INH functional level <40% – Absence of family history of angioedema – At least 1 of the following: • C1q below the lower limit of normal • Serological confirmation of anti-C1NH 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	• 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: – 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-C1NH, 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	• 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	• Incidence of TEAEs and SAEs • Change from baseline in clinical laboratory, vital signs, physical examination, and ECG parameters
PK outcomes	• Plasma concentrations of deucrictibant
Patient-reported outcomes	• 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	• 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	• Incidence of TEAEs and SAEs • Change from baseline in clinical laboratory, vital signs, physical examination, and ECG parameters
PK outcomes	• Plasma concentrations of deucrictibant

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

Table 4. Part 3 endpoints

Primary endpoints	• Incidence of TEAEs and SAEs • Change from baseline in clinical laboratory, vital signs, physical examination, and ECG parameters
Secondary endpoints:	
Efficacy	• 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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