Efficacy and safety of bradykinin B2 receptor antagonism with oral deucrictibant in prophylaxis of hereditary angioedema attacks: CHAPTER-1 phase 2 trial design

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Rationale

- 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]

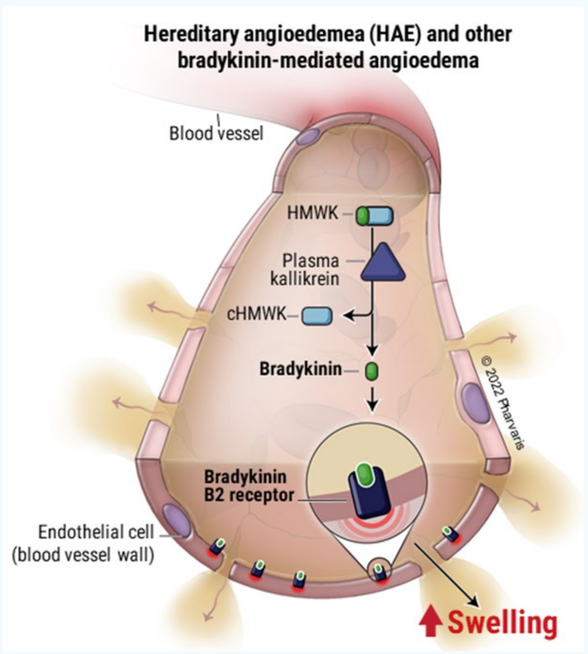

Figure 1. Bradykinin-forming cascade in bradykinin-mediated angioedema.

- International guidelines recommend that patients are evaluated for long-term prophylaxis at every visit, taking disease activity, burden, and control as well as patient preference into consideration.[5]
- An unmet need exists for oral HAE long-term prophylaxis therapies that are efficacious and well- tolerated.[6-7]
- Deucrictibant is a potent, selective, orally administered antagonist of bradykinin B2 receptor under development for on-demand and prophylactic treatment of HAE attacks.[8-14]

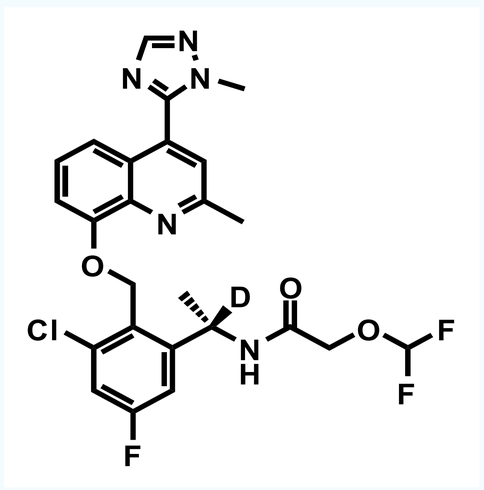

Figure 2. Structure of deucrictibant.

Methods

- CHAPTER-1* (NCT05047185) is a double-blind, placebo-controlled, dose-ranging, parallel-group, 2-part proof-of-concept phase 2 trial of deucrictibant for long-term prophylaxis against angioedema attacks in HAE-1/2.

Key inclusion criteria	Key exclusion criteria
• Aged ≥18 and ≤75 years • Diagnosis of HAE-1/2 • Documented history of ≥3 HAE attacks within the last 3 consecutive months prior to screening, or ≥2 HAE attacks during the screening period (up to 8 weeks) • Reliable access and experience to use standard of care acute attack medications	• Use of C1-inhibitor, oral kallikrein inhibitors, attenuated androgens, anti-fibrinolytics, or monoclonal HAE therapy within a defined period prior to enrollment • Pregnancy or breast-feeding • Clinically significant abnormal electrocardiogram • Any other systemic disease or significant disease or disorder interfering with the patient's safety or ability to participate in the study • Abnormal hepatic or renal function • Participation in any other investigational drug study within defined period

Table 1. CHAPTER-1 eligibility criteria.[12]

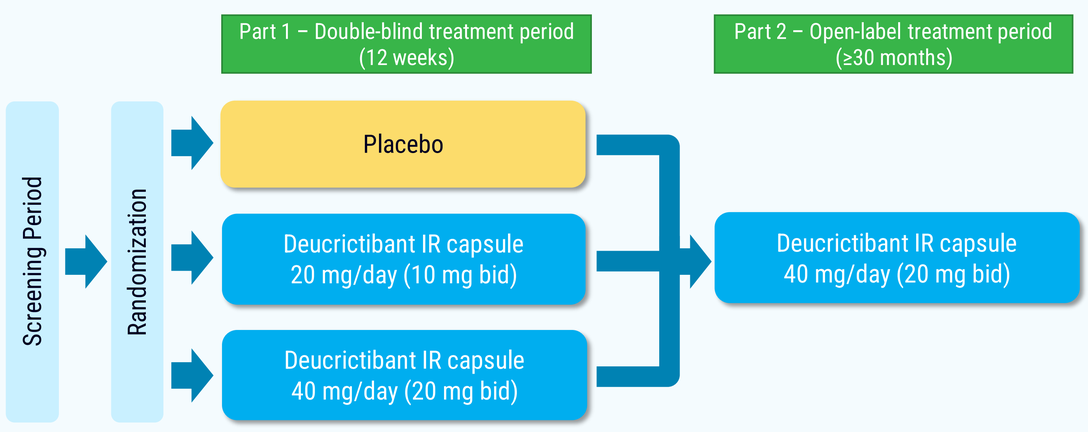

Figure 3. CHAPTER-1 trial design schematic.

Results

Primary endpoint	Time-normalized number of Investigator-confirmed HAE attacks
Secondary endpoints	Include: • Number of Investigator-confirmed moderate/severe HAE attacks • Number of Investigator-confirmed attacks requiring on-demand treatment • Proportion of participants achieving reduction in the attack rate during treatment • Number of participants as well as of days that are free from attacks • Time to first Investigator-confirmed HAE attack in the treatment period • Number of Investigator-confirmed HAE attacks resulting in a visit to the emergency department or an admission to hospital
Safety endpoints	Include: • Occurrence of treatment-emergent adverse events • Clinical laboratory tests • Vital signs

Table 2. Key study endpoints.[12]

- The study involved 29 participating sites across Canada, Europe, Israel, the United Kingdom and the United States. Enrollment of target population of participants is complete (n=34).[12]
- During the double-blind, placebo-controlled, 12-week Part 1 of the trial, participants receive daily treatment with either placebo or one of two dose regimens of deucrictibant [10 mg twice a day (bid) or 20 mg bid, immediate-release (IR) capsule (PHVS416) formulation].
- The primary objectives of CHAPTER-1 Part 1 are to evaluate the efficacy as well as the safety and tolerability of deucrictibant for prophylaxis against HAE attacks. The primary analysis will be conducted after all patients have completed Part 1 of the study or have been discontinued from the study.
- After completing Part 1, participants have the opportunity to continue treatment with open-label deucrictibant 20 mg bid in Part 2, with the objective to evaluate long-term outcomes of treatment.

Conclusions

- **The CHAPTER-1 trial is the first trial designed to evaluate the efficacy and safety of bradykinin B2 receptor antagonism by deucrictibant in long-term prophylaxis of HAE attacks.**
- **Enrollment of target population was met with 34 patients enrolled. Top-line results are expected by end of 2023.**
- **Data from this proof-of-concept study is expected to inform the design of an anticipated Phase 3 study utilizing a once-daily extended-release (XR) formulation of deucrictibant (PHVS719).**

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