INTRODUCTION

- In sickle cell disease (SCD), a single point mutation in the beta-globin gene results in haemoglobin S (HbS) production, which can polymerize upon deoxygenation.
- Polymerization distorts the red blood cell (RBC) membrane and generates sickled RBCs, contributing to microvascular occlusions, which may present as acute, painful vaso-occlusive episodes (VOEs).
- Despite existing treatments for VOE prevention, considerable morbidity and mortality remain for patients with SCD. For acute VOEs, treatment is currently limited to pain management and supportive care, representing a significant unmet medical need.
- Accumulating nonclinical data suggest a modulatory role for complement dysregulation in SCD pathophysiology, including in vaso-occlusion, haemolysis, inflammation, thrombogenicity, endothelial inflammation, and end-organ damage.
- Crovalimab is a novel anti-complement C5 monoclonal antibody that allows for small-volume subcutaneous (SC) injection after an initial intravenous (IV) loading dose.
- Across Three Phase 2 trials in patients with paroxysmal nocturnal haemoglobinuria, a complement-mediated disorder, crovalimab was efficacious and well tolerated, and achieved rapid, complete, and sustained complement inhibition.1,2
- Here, we describe two ongoing randomized, double-blind, placebo-controlled trials evaluating crovalimab in patients with SCD: CROSSWALK-a (Phase 1b; NCT0492869) and CROSSWALK-c (Phase 2a; NCT0575824).

CROSSWALK-a

- CROSSWALK-a evaluates the safety, pharmacokinetics, pharmacodynamics, and efficacy of crovalimab in managing acute vaso-occluded complications.
- Patients with a confirmed diagnosis of HbS (homozygous HbS or heterozygous HbS/J0 thalassaemia), presenting with an acute vaso-occluded complication requiring hospitalization, were enrolled in 10 sites in the US, Canada, and Europe.
- In total, 169 patients were randomized, and 106 patients completed the study.
- Patients received a single loading dose of crovalimab or placebo and were followed for an 84-day observation period for the primary endpoint of time to readiness for hospital discharge.

CROSSWALK-c

- CROSSWALK-c evaluates the efficacy, safety, pharmacokinetics, and pharmacodynamics of crovalimab as adjunct therapy in preventing VOEs.
- Patients with a confirmed diagnosis of SCD (homozygous HbS or heterozygous HbS/J0 thalassaemia) and 2–10 VOEs in the 12 months prior to randomization are eligible.
- Eligible patients will be randomized 1:1 to receive weight-based doses of crovalimab or placebo consisting of initial loading doses (IV: Day 1; SC: Day 2 and weekly for Weeks 2–4) and monthly maintenance 50% reduction SC doses Weeks 5–48 for 48 weeks of treatment.

Table 1. Additional key eligibility criteria for CROSSWALK-c

| Patients receiving daily XRT (e.g., hydroxycure, l-glutamine, oxaliplatin, etc.) must be on a stable dose for ≥28 days before study entry.
| Patients should be on a stable dose for ≥28 days prior to VOE presentation.
| Evidence from any reasonable source documenting that the patient is not currently participating in a chronic transfusion protocol.
| Patients may continue to receive ongoing concurrent SCD-directed therapies.

Table 2. Key objectives and endpoints in CROSSWALK-c

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<thead>
<tr>
<th>Objectives</th>
<th>Key endpoints</th>
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<tbody>
<tr>
<td>Safety</td>
<td>Incidence of severe adverse events*</td>
</tr>
<tr>
<td>Effectiveness</td>
<td>Time to first new medical facility VOE from baseline after randomization and time to hospital discharge from index medical facility VOE.</td>
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<tr>
<td>Efficacy</td>
<td>Annualized rate of new home VOE</td>
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*Severe events include life-threatening events, symptomatic acute abdominal pain, acute chest syndrome, unstable angina, heart failure, or death.

Table 3. Additional key eligibility criteria for CROSSWALK-c

| Patients receiving concurrent SCD-directed therapy (e.g., hydroxycure, l-glutamine, oxaliplatin, etc.) must have been on a stable dose, except for weight-based titration, with good adherence by the investigator’s assessment for 3 months prior to study entry.
| Patients receiving erythropoietin must have been prescribed at least 20 units/kg per week for ≥3 months prior to study entry. |
| Adequate hepatic and renal function |

Table 4. Key objectives and endpoints in CROSSWALK-c

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<tr>
<td>Safety</td>
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<tr>
<td>Efficacy</td>
<td>Annualized rate of medical facility VOE*</td>
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*Adverse events include acute abdominal pain, acute chest syndrome, unstable angina, heart failure, or death.

For more information about CROSSWALK-a, please visit: https://clinicaltrials.gov/ct2/show/NCT05075824 or contact: innohe&m@novartis.com

For more information about CROSSWALK-c, please visit: https://clinicaltrials.gov/ct2/show/NCT0492869 or contact: innohe&m@novartis.com

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References