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SCIENCE MEDICINES HEALTH

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EMADOC-1700519818-2894427
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Piasky

Crovalimab

Procedure no: EMA/PAM/0000327351

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Submission deadline	10 February 2026	5 February 2026
☐	Start date	23 February 2026	23 February 2026
☐	CHMP Rapporteur AR	30 March 2026	30 March 2026
☐	CHMP comments	13 April 2026	N/A
☐	Updated CHMP Rapporteur AR	16 April 2026	N/A
☒	CHMP outcome	23 April 2026	23 April 2026

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1. Introduction

On 5 February 2026, the MAH submitted a completed paediatric study for Piasky, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study BO42452 "A Phase IB Randomized, Placebo-Controlled Study Evaluating the Safety, Pharmacokinetics, Pharmacodynamics, and Efficacy of Crovalimab for the Management of Acute Uncomplicated Vaso-Occlusive Episodes (VOE) in Patients with Sickle Cell Disease (SCD)" is a standalone study.

2.2. Information on the pharmaceutical formulation used in the study

Crovalimab was supplied by the Sponsor as a solution for infusion (IV) from a single-use vial, which contains an extractable volume of 2 mL or 340 mg (nominal) crovalimab. For IV infusion, the crovalimab-vial solution should be diluted in 0.9% (w/v) sodium chloride solution prior to administration.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for: Study BO42452 "A Phase IB Randomized, Placebo-Controlled Study Evaluating the Safety, Pharmacokinetics, Pharmacodynamics, and Efficacy of Crovalimab for the Management of Acute Uncomplicated Vaso-Occlusive Episodes (VOE) in Patients with Sickle Cell Disease (SCD).

2.3.2. Clinical study

Study BO42452

A Phase IB Randomized, Placebo-Controlled Study Evaluating the Safety, Pharmacokinetics, Pharmacodynamics, and Efficacy of Crovalimab for the Management of Acute Uncomplicated Vaso-Occlusive Episodes (VOE) in Patients with Sickle Cell Disease (SCD).

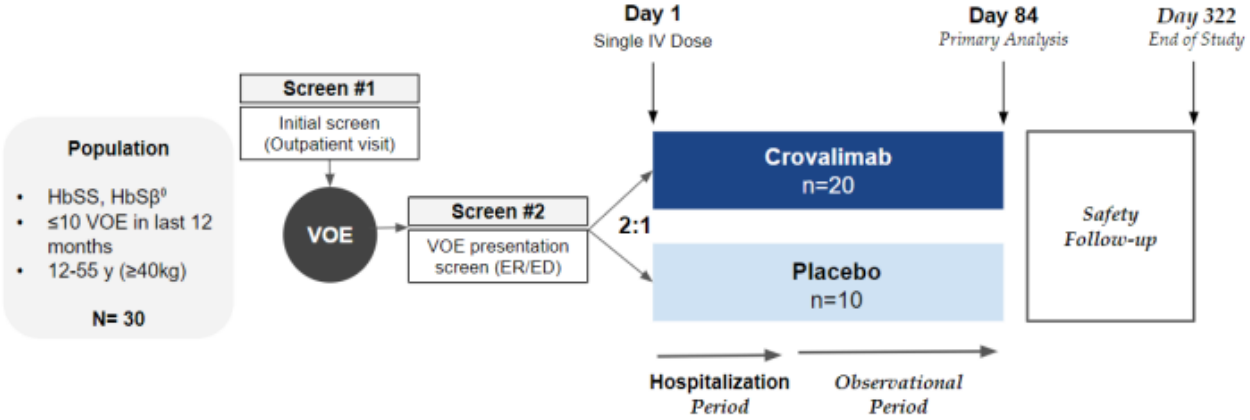
Description

This randomized, multicentre, placebo-controlled, double-blinded, Phase Ib study enrolled participants 12−55 years old, weighing ≥40 kg with a confirmed diagnosis of SCD genotype of sickle cell anaemia (HbSS) or SCD genotype of sickle cell beta zero thalassemia (HbSβ0) who presented with an acute uncomplicated VOE that required admission to a hospital and treatment with parenteral opioid analgesics. Participants were randomly assigned in a 2:1 ratio to crovalimab or placebo, with a planned sample size of 30 participants (20 randomized to crovalimab and 10 randomized to placebo).

After administration of study treatment, participants entered a hospitalization period (Day 1 until discharge). After discharge from the medical facility, participants entered an observational period (Day 14 until Day 84). The hospitalization and observational periods (up until Day 84) were used as reporting periods for the primary analysis. Following the observational period, participants entered safety follow-

up (with safety assessments performed on Day 168 and Day 322). The duration of safety follow-up was determined as 5.5 half-lives from the single dose of crovalimab (approximately 10.5 months). **Figure 1** presents an overview of the study design.

Figure 1. Overview of Study Design



ER/ED = Emergency Room/Emergency Department; HbSβ0 = sickle cell disease genotype of sickle cell beta zero thalassemia; HbSS = sickle cell disease genotype of sickle cell anaemia; ICF= Informed Consent Form; VOE= Vaso-Occlusive Episode.

Changes in study conduct

Protocol v2 : Protocol BO42452 was amended based on France Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) feedback to include the following investigational medicinal product (IMP)-related patient enrolment hold criteria: if more than 2 patients on the crovalimab arm had a diagnosis of a serious bacterial infection with confirmation of an encapsulated bacterial organism, then recruitment was to be held.

Protocol v3: Protocol BO42452 was primarily amended to update the terminal half-life of crovalimab from approximately 30 days to approximately 59 days based on primary analysis data from the Phase III Study, YO42311. The population PK model was also updated due to the primary analysis of data from Study YO42311 in patients with paroxysmal nocturnal haemoglobinuria (PNH). Model parameters were re-estimated using pooled PK data from treatment-naive patients with PNH from the Phase I/II Study BP39144 and Study YO42311. As a consequence of the updated half-life and in combination with feedback from the U.K. Medicines and Healthcare products Regulatory Agency, the end of the study was extended from Day 84 to Day 322 to ensure approximately 5.5 half-lives of follow-up. Accordingly, two telephone calls for safety follow-up were added to collect safety information on Days 168 and 322 after study treatment administration. The timeframe in which patients (women of childbearing potential only) must remain abstinent or use contraception was extended from 6 months to approximately 10.5 months (322 days) after the dose of study treatment in the inclusion criteria. The timeframe for the exclusion of patients who are pregnant or breastfeeding, or intending to become pregnant, was updated from 6 months to approximately 10.5 months (322 days) after study drug administration. The reporting period for pregnancies was updated from 6 months to approximately 10.5 months (322 days) after the dose of study drug.

Protocol v4: Protocol BO42452 was primarily amended to align with Clinical Trials Regulation requirements and to comply with requests from the French Ethics Committee. At sites in France, the telephone safety follow-up visit at Day 322 (or 46 weeks) after the study treatment administration was amended to being a study site visit. Subsequently, the final urine pregnancy test that was to be completed by the patient at home was updated to be completed during the study site visit at Day 322.

Protocol v5: Protocol BO42452 was primarily amended to update the inclusion criterion requiring treatment administration within 12 hours from initial evaluation in the emergency room (ER)/emergency

department (ED) or acute medical facility due to operational challenges. The Sponsor extended the timeframe of study treatment administration from within 12 hours to within 24 hours from initial evaluation in the ER/ED or acute medical facility visit for the VOE. In conjunction to this, the exclusion criterion of pain related to the current VOE ongoing for >48 hours prior to VOE presentation was reduced to >36 hours prior to VOE presentation. Additional changes introduced in local Protocol BO42452, Version 3 (Africa), which were made due to the inclusion of sites in African countries with increased risk of malaria infection to support patient safety. The changes related to malaria infection were applicable to patients globally due to international travel.

Methods

Study participants

This study enrols approximately 30 adolescent and adult patients (aged 12-55 years old, ≥ 40 kg) with SCD (HbSS or HbSβ^0), who present to the ER/ED or acute medical facility with an acute uncomplicated VOE. Patients with a history of >10 VOE events within the past 12 months and with a history of hematopoietic stem cell transplant were excluded.

Key Inclusion Criteria

- Age ≥12 to ≤55 years at the time of signing ICF or Assent Form, and VOE presentation
- Body weight ≥40 kg
- Confirmed diagnosis of HbSS or HbSβ0
- Diagnosis of an acute uncomplicated VOE (for definition see Section 3.7.3), that requires admission to a hospital and treatment with parenteral opioid analgesics
- Vaccinations:
  – Vaccination against Neisseria meningitidis serotypes A, C, W, and Y prior to initiation of study treatment
  – Vaccinations against Haemophilus influenzae type B and Streptococcus pneumoniae in accordance with most current SCD specific guidelines or local standard of care, prior to initiation of study treatment
- Pain score ≥2 as measured with the Numerical Rating Scale (NRS) on a 0−10 scale
- Haemoglobin ≥5 g/dL
- Platelet count ≥100,000/µL
- Infection requiring hospitalization or treatment with intravenous (IV) antibiotics within the prior 28 days, or oral antibiotics within the prior 14 days of VOE presentation
- Suspected or active malaria infection within 14 days before drug administration
- All patients living and/or traveling to/from a malaria endemic area within 1 month prior to enrolment must have a negative test (e.g., microscopy or rapid diagnostic test) on Day 1 prior to randomization in order to be eligible
- History of N. meningitidis infection within 6 months prior to VOE presentation
- Transfusion or receipt of blood products within 3 months prior to VOE presentation or as part of best-supportive-care regimen for the current VOE, or current participation in a chronic transfusion protocol

Key Exclusion Criteria

- More than 10 VOEs within the last 12 months prior to presentation, that have required a medical facility visit (e.g., ER/ED, hospital, clinic, infusion centre, day hospital, etc.), as determined by medical history or by patient recall
- Pain related to the current VOE ongoing for >36 hours prior to VOE presentation
- Current or previous treatment with complement inhibitor therapy (e.g., crovalimab, eculizumab, or ravulizumab)

- Acute pain related to avascular necrosis (where the presenting pain is limited to the affected joint), hepatic or splenic sequestration, or priapism per investigator assessment
- Pain atypical of an acute uncomplicated VOE that is the primary cause for presentation to the ER/ED or acute medical facility (e.g., chronic pain, abdominal pain, headache), or other alternative cause or explanation for pain presentation (e.g., infection, surgical pain) per investigator assessment
- Evidence of or suspicion of ACS, defined as: the presence of new segmental radiographic pulmonary infiltrate involving at least one complete lung segment that is consistent with alveolar consolidation but excluding atelectasis, and at least one of the following additional signs or symptoms: chest pain, temperature ≥38.5°C (101.3°F), respiratory symptoms, or exam findings consistent with ACS
- Evidence or high suspicion of a severe systemic infection (e.g., osteomyelitis, pneumonia, meningitis, or sepsis) per investigator assessment
- Presence of fever ≥38°C (100.4°F)

Treatments

The investigational medicinal products (IMPs) for this study are crovalimab and placebo.

Patients in this study were planned to receive a single IV dose of crovalimab according to a weight-based dosing approach **(Table 1).**

Table 1. Crovalimab dosing

Body Weight	Single Crovalimab Dose	Infusion Duration
≥40 kg to <100 kg	1000 mg IV	60 ± 10 min
≥100 kg	1500 mg IV	90 ± 10 min

The placebo is administered by IV infusion with equal volume and over the same duration as weight-based crovalimab.

Objective(s)

Outcomes/endpoints

Primary Objective	**Corresponding Endpoints**
To evaluate the safety of crovalimab compared with placebo	• Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0 • Change from baseline in targeted vital signs and clinical laboratory test results • Incidence and severity of infusion-related reactions and hypersensitivity
PK Objective	**Corresponding Endpoints**
To characterize the crovalimab PK profile	• Serum concentrations of crovalimab over time • Relationship between crovalimab drug exposure and PD endpoints (this exploratory endpoint will be discussed in a separate PK/PD Report)
PD Objective	**Corresponding Endpoints**
To evaluate PD biomarkers that can provide evidence of crovalimab activity	• Change over time in PD biomarkers, including CH50 measured by a liposome immunoassay, and total and free complement component 5 concentration, and soluble complement 5b-9 concentrations (sC5b-9; exploratory)
Exploratory Efficacy Objective	**Corresponding Endpoints**
	• Time to improvement of the primary acute uncomplicated VOE from baseline, defined as the first achieved from the following events:

	- Confirmed decrease in pain score of at least 2 points from the maximal predose pain score, that is sustained in at least two pain assessments conducted a minimum of 6 hours apart from each other (as measured with the NRS on a 0−10 scale [Mathias et al. 2011]) AND transition to oral pain medications for a minimum of 6 hours after the last dose of parenteral opioids, OR - Readiness for hospital discharge (as defined by the patient's assessment that pain can be managed at home AND agreement from investigator), OR - Hospital discharge • Total cumulative opioid dose (parenteral and oral) in morphine-equivalent units per kilograms (MEU/kg) from baseline to the time of acute uncomplicated VOE improvement • Time to discontinuation of all parenteral opioids from baseline (defined as time from baseline to the completion of the last dose of parenteral opioids) • Time to readiness for hospital discharge from baseline • Time to hospital discharge from baseline • Time to a confirmed decrease in pain score of at least 2 points from the maximal predose pain score, that is sustained in at least two assessments conducted a minimum of 6 hours apart from each other, as measured with the NRS on a 0−10 scale • Change in pain score from the maximal pre-dose pain score to the score at hospital discharge, as measured with the NRS on a 0−10 scale • Proportion of patients who develop ACS from baseline to Day 28 • Proportion of patients requiring intensive care unit or critical care admission for SCD-related complications from baseline to time of hospital discharge • Proportion of patients requiring blood transfusion for SCD-related complications from baseline to the time of hospital discharge • Readmission rate for a VOE or VOE-related event within 28 days of discharge of the primary acute uncomplicated VOE

Sample size

The primary purpose of this study was to assess the safety of crovalimab in participants with SCD with an acute uncomplicated VOE. The planned sample size of approximately 30 randomized participants (20 to crovalimab and 10 to placebo) was based on clinical considerations and taking into account the recruitment challenges in the acute medical setting.

Randomisation and blinding (masking)

This is a randomized, placebo-controlled, double-blind study. Patients were randomly assigned in a 2:1 ratio through use of a block-based randomization method to one of two treatment arms: crovalimab or placebo.

Study site personnel and patients were blinded to treatment assignment during the study. The Sponsor and its agents were also blinded to treatment assignment, with the exception of individuals who require access to patient treatment assignments to fulfil their job roles during a clinical trial. These roles include the unblinding group responsible, clinical supply chain managers, sample handling staff, operational assay group personnel, IxRS service provider, and IMC members.

If unblinding was necessary for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator was able to break the treatment code by contacting the IxRS. The investigator was not required to

contact the Medical Monitor prior to breaking the treatment code; however, the treatment code was not to be broken except in emergency situations.

If the investigator wished to know the patient's treatment assignment for any reason other than a medical emergency, he or she was to contact the Medical Monitor directly. The investigator was to document and provide an explanation for any non-emergency unblinding. If the Medical Monitor agreed to patient unblinding, the investigator was able to break the treatment code by contacting the IxRS.

As per health authority reporting requirements, the Sponsor's Drug Safety representative was to break the treatment code for all serious, unexpected suspected adverse reactions that are considered by the investigator or Sponsor to be related to study drug. The investigator, patient, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who were required to have access to patient treatment assignments to fulfil their roles (as defined above), were to remain blinded to treatment assignment.

Statistical Methods

The primary purpose of this study is to assess the safety of crovalimab in patients with SCD with an acute uncomplicated VOE.

The sample size of approximately 30 patients (20 on crovalimab and 10 on placebo) is based on clinical considerations and taking into account the recruitment challenges in the acute medical setting. There will not be any formal hypothesis testing of the efficacy endpoints. The preliminary efficacy and safety analyses will be descriptive and used to support the development of subsequent studies.

The primary analysis will be conducted on the safety analysis population. The safety analysis population consists of all randomized patients who received the single dose of study treatment, with patients grouped according to treatment received. All efficacy endpoints are exploratory.

Given the hypothesis-generating nature of this study, the Sponsor could choose to conduct exploratory interim efficacy analyses.

Results

Participant flow

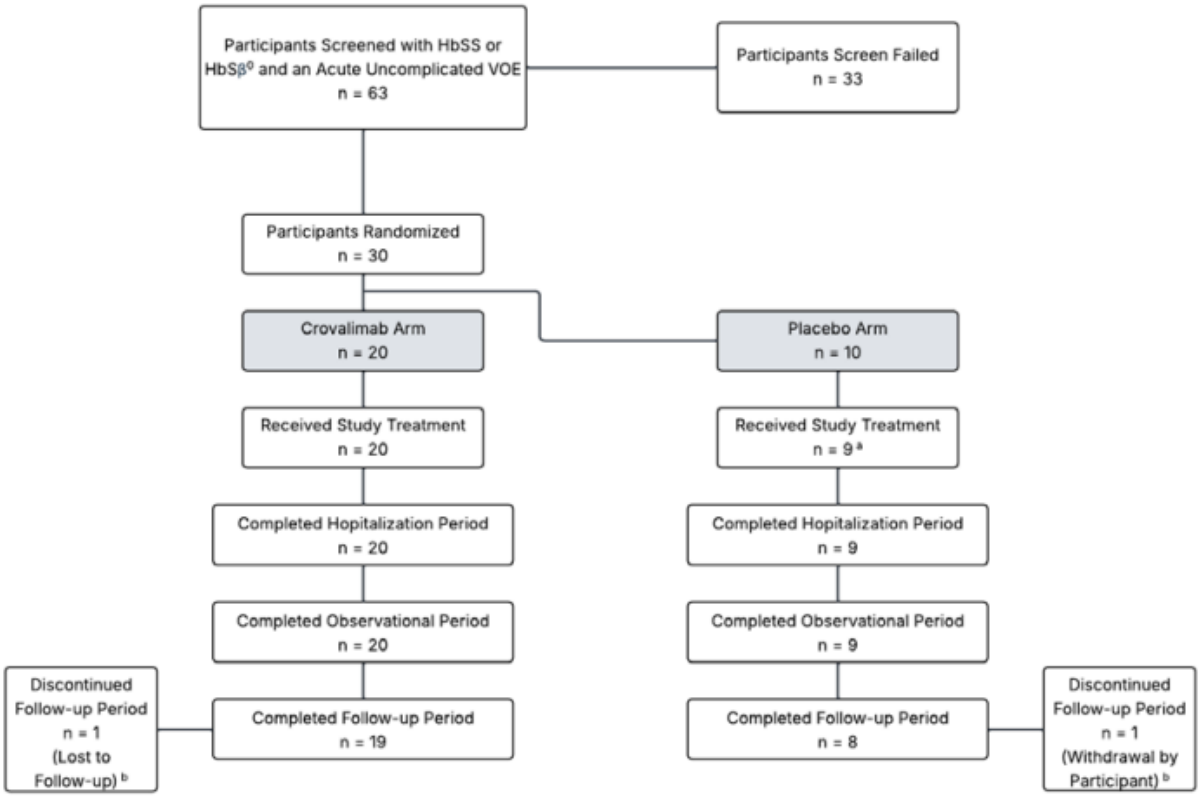
Study BO42452 was conducted at 13 investigational sites in 10 countries in adult and adolescent participants with SCD. Countries with the highest number of sites were Spain, Kenya, and the United States (2 sites each). Of the 63 participants screened, 33 were screen failures, leading to randomization of 30 participants in total.

Twenty participants were randomized to the crovalimab arm, and 10 participants were randomized to the placebo arm.

Of the 30 participants randomized, 29 received a single dose of study treatment. One participant in the placebo arm was discontinued before dosing due to meeting an exclusion criterion (fever) after screening.

Participant disposition is presented in **Figure 2**.

Figure 2. Participant Disposition (All Screened Participants)



CCOD = Clinical CutOff Date; HbSβ0 = sickle cell disease genotype of sickle cell beta zero thalassemia; HbSS= sickle cell disease genotype of sickle cell anaemia; VOE= Vaso-Occlusive Episode.
[a] One participant in the placebo arm was discontinued before dosing due to meeting an exclusion criterion (fever) after screening.
[b] Both participants who discontinued the study during the follow-up period discontinued prior to the primary analysis CCOD.

Protocol deviations

Up to the time of the final analysis, 118 major protocol deviations were observed in 29 participants (96.7%) in the study. Twenty participants (100.0%) in the crovalimab arm and 9 participants (90.0%) in the placebo arm, respectively, had at least one major protocol deviation (**Table 2**). The proportion of participants with at least one major protocol deviation was generally balanced between the crovalimab and placebo arms. Most major protocol deviations in both arms were procedural in nature, and none of the major protocol deviations posed an increased safety risk to any participant continuing study treatment or were considered to have affected the integrity of the study and data interpretability. Three participants (1 participant [5.0%] in crovalimab arm and 2 participants [20.0%] in placebo arm) did not require hospitalization or parenteral opioids for VOE management; thus, they did not meet the protocol definition of an acute uncomplicated VOE. There were no protocol deviations related to COVID-19.

Table 2. Summary of Major Protocol Deviations, Intent-to-Treat Population

Category Description	Placebo (n=10)	Crova (n=20)	All patients (n=30)
Total number of patients with at least one major protocol deviation	9 (90.0%)	20 (100%)	29 (96.7%)
Total number of major protocol deviations	26	92	118
Exclusion			
• Concurrent diagnosis of hepatic or splenic sequestration, priapism, or acute chest syndrome.	0	1 (5.0%)	1 (3.3%)
• Major surgery or hospital admission within the prior 30 days.	0	1 (5.0%)	1 (3.3%)
• Transfusion within the prior 3 months or ongoing chronic transfusions.	0	1 (5.0%)	1 (3.3%)
Inclusion			
• Vaccination criteria not met	1 (10.0%)	3 (15.0%)	4 (13.3%)
• Hospitalization or parenteral opioids not required for VOE management	2 (20.0%)	1 (5.0%)	3 (10.0%)
• Informed Consent or Assent not signed		1 (5.0%)	3 (10.0%)
• Laboratory criteria not met		1 (5.0%)	2 (6.7%)
• Ongoing SCD therapy not at stable dose	2 (20.0%)	1 (5.0%)	1 (3.3%)
• SCD genotype requirement not met	1 (10.0%)	1 (5.0%)	1 (3.3%)
Procedural			
• Failure to adhere to antibiotic prophylaxis (where indicated).	0	9 (45.0%)	14 (46.7%)
• Failure to report SAE, AESI and pregnancy per protocol.	0	9 (45.0%)	12 (40.0%)
• Missed or out of window observational visits.	5 (50.0%)	8 (40.0%)	12 (40.0%)
• Other significant procedural deviation.		9 (45.0%)	12 (40.0%)
• Other missed assessments during hospitalization (e.g. readiness for discharge etc).	3 (30.0%)	9 (45.0%)	12 (40.0%)
• Missing baseline assessments (including laboratory assessments)		5 (25.0%)	12 (40.0%)
• Missing PK, PD, ADA, or Biomarker samples	4 (40.0%)	3 (15.0%)	10 (33.3%)
• Missing NRS assessment(s)		2 (10.0%)	
• Failure to obtain signature of updated ICF	3 (30.0%)	1 (5.0%)	
• GCP non-compliance that compromises patient safety or the integrity of the study	1 (10.0%)	0	6 (20.0%)
• Vitals not obtained before first infusion or missed vitals for two consecutive assessments		1 (5.0%)	3 (10.0%)
			2 (6.7%)
	1 (10.0%)		1 (3.3%)
			1 (3.3%)
	0		1 (3.3%)
	0		
	0		
	1 (10.0%)		
	0		

Percentages are based on N in the column header. For frequency counts by deviation, multiple occurrences of the same deviation in an individual are counted only once. For frequency counts of "Total number of major protocol deviations", multiple occurrences of the same deviation in an individual are counted separately. CCOD: 18AUG2025 Data Extract Date: 18SEPT2025.

Number analysed

The number of participants in each of the 5 analysis populations defined for this study is provided in **Table 3**.

Table 3. Summary of Analysis Populations, All Patients

Analysis population	Placebo (n=10)	Crova (n=20)	All patients (n=30)
Intent-to-treat	10	20	30
Safety Analysis Set	9	20	29
Biomarker Analysis Set	7	19	26
Pharmacokinetic Analysis Set	0	20	20
Immunogenicity Analysis Set	0	20	20

One participant (10.0%) in the placebo arm was randomized but discontinued prior to dosing (the patient met an exclusion criterion [fever] after screening). This patient was included in the ITT Population but was excluded from the Safety Analysis Set.

Baseline data

Demographic characteristics were generally balanced between the crovalimab and placebo arms (**Table 4**).

There was a higher proportion of participants in the placebo arm treated within 24 hours of VOE onset compared with the crovalimab arm. In the crovalimab arm, 8 participants (40.0%) received treatment within 24 hours of VOE onset. In the placebo arm, 7 participants (77.8%) received treatment within 24 hours of VOE onset.

Table 4. Summary of Demographics and Baseline Characteristics, Intent-to-Treat Population

	Placebo (n=10)	Crova (n=20)
Age (yr) • n • Mean • Median • Min-Max	 10 20.2 (6.0) 20.5 13-29	 20 22.5 (5.8) 21.0 14-33
Age group • n • 12-17 • ≥ 18	 10 4 (40.0%) 6 (60.0%)	 20 3 (15.0%) 17 (85.0%)
Sex • n • Male • Female	 10 7 (70.0%) 3 (30.0%)	 20 11 (55.0%) 9 (45.0%)
Ethnicity • n • Hispanic or Latino • Not Hispanic or Latino • Not Stated • Unknown	 10 1 (10.0%) 6 (60.0%) 2 (20.0%) 1 (10.0%)	 20 2 (10.0%) 10 (50.0%) 8 (40.0%) 0
Race • n • Black or African American • White • Not reported	 10 8 (80.0%) 0 2(20.0%)	 20 9 (45.0%) 3 (15.0%) 8 (40.0%)

Weight • n • Mean • Median • Min-Max	 10 63.21 (17.96) 60.85 40.2 - 94.5	 20 63.97 (12.10) 62.70 42.0 - 84.0
Confirmed Diagnosis of SCD • n • HBSS • HBS Beta 0-Thalassemia	 10 9 (90.0%) 1 (10.0%)	 20 18 (90.0%) 2 (10.0%)
Number of Prior VOEs • n • Mean (SD) • Median • Min-Max	 10 4.20 (2.39) 4.00 1.0 - 8.0	 20 4.95 (3.07) 4.50 1.0 - 10.0
Number of Prior VOEs Category • n • < 4 • ≥ 4	 10 3 (30.0%) 7 (70.0%)	 20 8 (40.0%) 12 (60.0%)
SCD Related Complications • n • ACS • Stroke • Sequestration (hepatic or splenic) • Priapism • Avascular Necrosis • Pulmonary Hypertension • Renal complications • Other	 6 3 (30.0%) 0 2 (20.0%) 1 (10.0%) 1 (10.0%) 0 0 5 (50.0%)	 15 9 (45.0%) 1 (5.0%) 2 (10.0%) 1 (5.0%) 5 (25.0%) 0 3 (15.0%) 10 (50.0%)
SCD directed therapy • n • No • Hydroxyurea/Hydroxycarbamide • L-glutamine • Voxelotor • Crizanlizumab • Other	 10 0 10 (100%) 0 0 0 0	 20 1 (5.0%) 19 (95.0%) 1 1 0 0
RBC Transfusions in the Last 12 months • n • No • Yes	 10 6 (60.0%) 4 (40.0%)	 20 13 (65.0%) 7 (35.0%)
Duration of VOE Prior to Presentation Category (hours) • n • 0 – 24 • 24 - 36	 10 10 (100%) 0	 20 19 (95.0%) 1 (5.0%)
Duration of VOE Prior to Presentation (hours) • n • Mean (SD) • Median • Min - Max	 10 9.40 (5.15) 9.00 2.0 - 18.0	 20 14.35 (9.57) 16.50 2.0 - 34.0
Duration of VOE prior to treatment administration group (hours) • N • 0 – 24 • ≥ 24	 9 7 (77.8%) 2 (22.2%)	 20 8 (40.0%) 12 (60.0%)
Duration of VOE prior to treatment administration (hours) • n • Mean (SD) • Median • Min - Max	 9 17.37 (7.00) 17.83 7.9 - 30.2	 20 24.79 (12.54) 26.97 4.0 - 46.4
Baseline NRS Score		

• n • Mean (SD) • Median • Min - Max	9 5.00 (1.58) 5.00 3.0 - 7.0	20 5.70 (2.03) 6.00 2.0 - 10.0
Baseline Haemoglobin (g/L) • n • Mean (SD) • Median • Min - Max	 8 89.00 (6.74) 87.00 80.0-101.0	 20 83.16 (11.09) 82.00 67.0-103.0

***CHMP comment*:**

Major protocol deviations were reported in most participants, however the clinical impact appears limited and mainly reflected by operational challenges in the context of acute VOEs. Many of these deviations relate to administrative or procedural aspects (vaccination documentation, consent procedures...), while the small sample size likely inflated the reported percentages. Eligibility-related deviations were infrequent and occurred only in a small number of participants.

Antibiotic prophylaxis non-adherence (45%) may be the most clinically relevant deviation since prophylactic antibiotics are often recommended in SCD to reduce infection risk. However, the study safety data did not identify a clear infection signal attributable to this deviation.

Regarding baseline characteristics, only a small proportion of the randomized population was paediatric, with only 3 participants in the crovalimab arm (15.0%). The very limited number of participants in this subgroup does not allow for any meaningful conclusions to be drawn for paediatric subjects.

A majority of participants had a history of frequent VOEs, with 60% (12/20) in the treatment arm and 70% (7/10) in the placebo arm reporting ≥4 prior VOEs, suggesting a severe disease burden. Baseline SCD-related complications were also common. Acute chest syndrome (ACS) was reported in 45% of participants in the crovalimab arm and 30% in the placebo arm, while avascular necrosis was observed in 25% and 10% of participants, respectively. Almost all participants were receiving hydroxyurea/hydroxycarbamide (95% in the crovalimab arm and 100% in the placebo arm). Recent transfusion history was relatively balanced between arms, with approximately 35–40% of participants having received RBC transfusions within the previous 12 months.

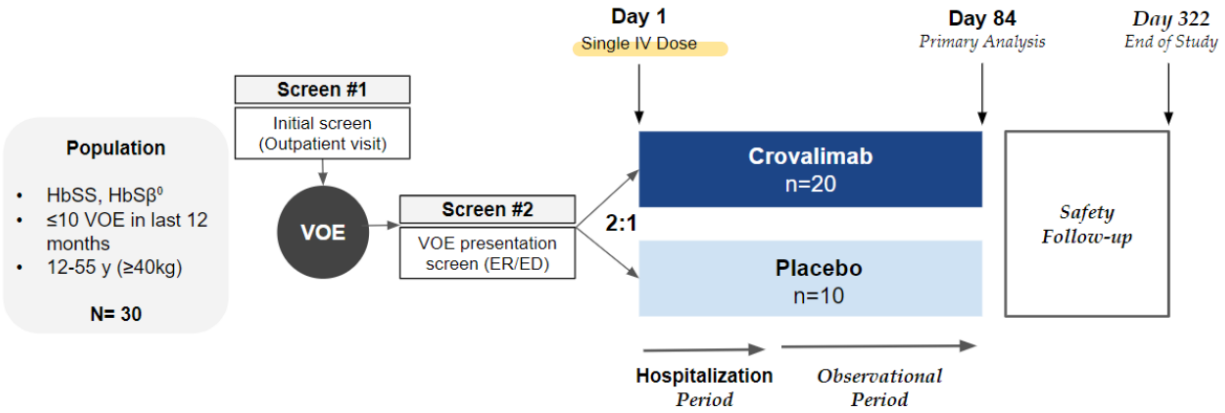
PK results

Crovalimab (medicinal product: PIASKY) is an immunosuppressant and works as a terminal complement activity inhibitor (inhibits cleavage of component 5 of the complement system).

Crovalimab is indicated for the treatment of adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH). An initial Marketing Authorisation Application (MAA) for crovalimab in the treatment of patients with PNH was granted by the EMA on August 2024 (EMEA/H/C/06061).

In the current submission, crovalimab was evaluated in patients with sickle cell disease (SCD) aged 12-55 years old (with a weight of 40 kg and above). Study BO42452 was provided as a standalone post-authorisation measure (PAM) in respect of Article 46 of Regulation (EC) No 1901/2006. As the efficacy data was inconclusive for this study (cf. clinical assessment), no changes to SmPC were claimed, including PK properties.

The study design was summed up as follows:



The study design comprised placebo and crovalimab arms with intent-to-treat N=10 and N=20 participants in the placebo and crovalimab arms, respectively. One participant discontinued prior to dose administration due to fever. One additional placebo arm subject withdrew from study during the follow up period (prior to the primary analysis clinical cut-off date). As for the crovalimab arm, one participant was lost to follow up period (prior to the primary analysis clinical cut-off date). Ultimately, N=8 and N=19 participants completed the study in the placebo and crovalimab arms, respectively.

A weight-based approach was used for crovalimab dose administration, in accordance with SmPC:

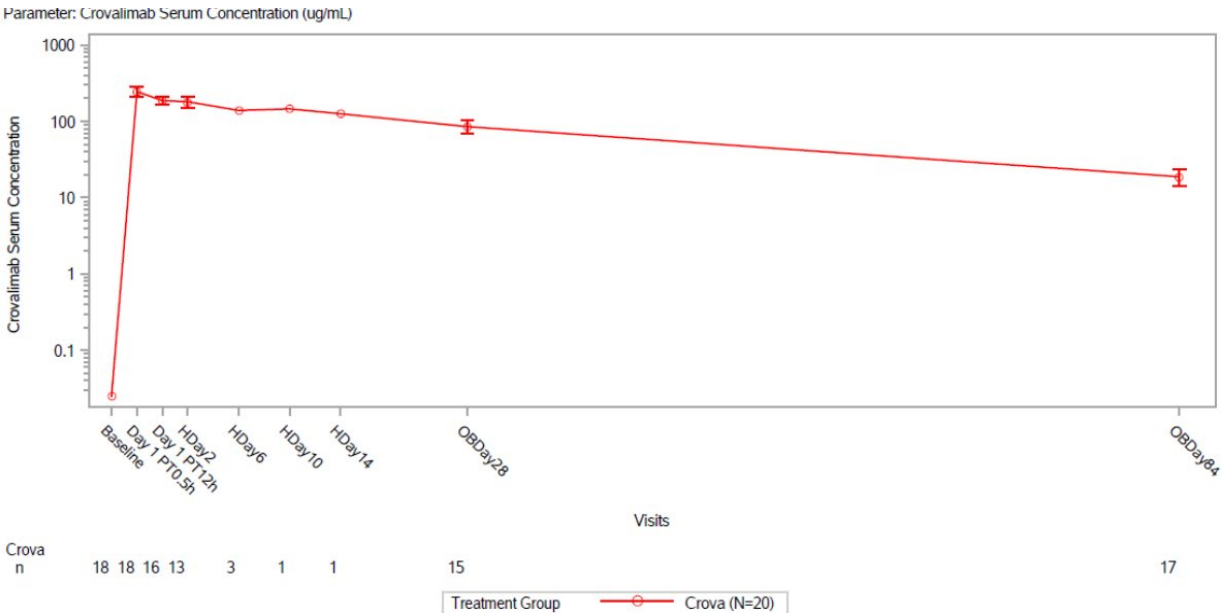
Body weight	Single crovalimab dose	Infusion duration
≥40 kg to <100 kg	1000 mg IV	60 ±10min
≥100 kg	1500 mg IV	90 ±10min

Study samples were collected according to the following schedule:

	Predose baseline[a]	Day 1[b]	Days 2, 6, 10 and 14	Hospital discharge	Observation period: days 28 and 84
Serum PK	X	X	X	X	X
Plasma and serum PD	X	X	X	X	X
Serum ADA	X	_	X[c]	X	X
[a] = within 24 hours prior to study treatment administration [b] = within30min of EOI, 12 hours (±6 hours) post EOI [c] = day 14 only EOI = end of infusion					

A validated analytical method was used for serum quantification of crovalimab (ELISA, calibration range from 50.0 ng/mL (LLOQ) to 3200 ng/mL (ULOQ)) in line with the previously validated method during MAA application (Method ID: M08.RO7112689.huse.1). A validated method was used for detection of anti-RO7112689 antibodies in human serum by ELISA assay.

Serum concentrations of crovalimab were quantified in adult and adolescent participants with SCD. Crovalimab serum concentrations were 187.31 µg/mL [95% CI: 167.24 to 207.38] and 85.33 µg/mL [95% CI: 68.45 to 102.21] on Days 1 and 28, respectively. At Day 84, the mean serum crovalimab concentration of 18.82 µg/mL [95% CI: 14.39 to 23.26].



Listing of Crovalimab Serum Concentrations, Pharmacokinetic Analysis Set
Protocol: BO42452

Treatment Group: Crova (N=20)

Center/Patient - Age/Sex/Race	Visit / Timepoint	Study Day	Concentration of Crovalimab (ug/mL)
[redacted]	Baseline	1	BLQ
	Day 1 / within 30 mins after end of infusion	1	147
	Day 1 / 12h after end of infusion	1	143
	Discharge	2	132
	Observation Day28	31	37.4
	Observation Day84	101	6
[redacted]	Baseline	1	BLQ
	Day 1 / 12h after end of infusion	2	177
	Hospitalization Day2	2	167
	Hospitalization Day6	6	112
	Discharge	10	104
	Observation Day84	87	14.5
[redacted]	Baseline	1	BLQ
	Day 1 / within 30 mins after end of infusion	1	196
	Day 1 / 12h after end of infusion	2	185
	Hospitalization Day2	2	194
	Discharge	7	157
	Observation Day28	31	55.7
	Observation Day84	85	11
[redacted]	Baseline	1	BLQ
	Day 1 / within 30 mins after end of infusion	1	398
	Hospitalization Day2	2	258
	Hospitalization Day6	6	190
	Hospitalization Day10	10	146
	Hospitalization Day14	15	126
	Discharge	16	130
	Observation Day28	29	67.4
	Observation Day84	85	14.3

BLQ: Below limit of quantification: 0.05 ug/mL.
Baseline visit is the patient's last observation prior to initiation of study drug.
CCOD: 18AUG2025 Data Extract Date: 18SEPT2025

Listing of Crovalimab Serum Concentrations, Pharmacokinetic Analysis Set
Protocol: BO42452

Treatment Group: Crova (N=20)

Center/Patient - Age/Sex/Race	Visit / Timepoint	Study Day	Concentration of Crovalimab (ug/mL)
[redacted]	Baseline	1	BLQ
	Day 1 / 12h after end of infusion	2	162
	Hospitalization Day2	2	155
	Observation Day28	32	72.6
[redacted]	Baseline	1	BLQ
	Day 1 / within 30 mins after end of infusion	1	252
	Day 1 / 12h after end of infusion	2	165
	Hospitalization Day2	2	157
	Hospitalization Day6	7	116
	Discharge	7	110
	Observation Day28	18	106
	Observation Day84	84	14.7
[redacted]	Baseline	1	BLQ
	Day 1 / within 30 mins after end of infusion	1	253
	Day 1 / 12h after end of infusion	2	232
	Hospitalization Day2	2	179
	Discharge	3	229
	Observation Day84	91	21.5
[redacted]	Baseline	1	BLQ
	Day 1 / within 30 mins after end of infusion	1	323
	Day 1 / 12h after end of infusion	2	213
	Hospitalization Day2	2	218
	Discharge	3	196
	Observation Day28	29	89.9
	Observation Day84	85	12.8
[redacted]	Baseline	1	BLQ
	Day 1 / within 30 mins after end of infusion	1	405
	Day 1 / 12h after end of infusion	2	293

BLQ: Below limit of quantification: 0.05 ug/mL.
Baseline visit is the patient's last observation prior to initiation of study drug.
CCOD: 18AUG2025 Data Extract Date: 18SEPT2025

Listing of Crovalimab Serum Concentrations, Pharmacokinetic Analysis Set
Protocol: BO42452

Treatment Group: Crova (N=20)

Center/Patient - Age/Sex/Race	Visit / Timepoint	Study Day	Concentration of Crovalimab (ug/mL)
[redacted]	Hospitalization Day2	2	294
	Observation Day28	29	141
	Observation Day84	85	17.2
[redacted]	Baseline	1	BLQ
	Day 1 / within 30 mins after end of infusion	1	188
	Day 1 / 12h after end of infusion	2	169
	Hospitalization Day2	2	163
	Observation Day28	30	61.8
	Observation Day84	87	19.9
[redacted]	Baseline	1	BLQ
	Day 1 / within 30 mins after end of infusion	1	214
	Day 1 / 12h after end of infusion	2	209
	Hospitalization Day2	2	172
	Discharge	3	151
	Observation Day84	80	30.3
[redacted]	Day 1 / within 30 mins after end of infusion	1	207
	Day 1 / 12h after end of infusion	2	174
	Observation Day28	36	44.1
[redacted]	Baseline	1	BLQ
	Day 1 / within 30 mins after end of infusion	1	234
	Day 1 / 12h after end of infusion	2	163
	Hospitalization Day2	2	180
	Discharge	3	149

BLQ: Below limit of quantification: 0.05 ug/mL.
Baseline visit is the patient's last observation prior to initiation of study drug.
CCOD: 18AUG2025 Data Extract Date: 18SEPT2025

Listing of Crovalimab Serum Concentrations, Pharmacokinetic Analysis Set
Protocol: BO42452

Treatment Group: Crova (N=20)

Center/Patient - Age/Sex/Race	Visit / Timepoint	Study Day	Concentration of Crovalimab (ug/mL)
[redacted]	Baseline	1	BLQ
	Day 1 / within 30 mins after end of infusion	1	291
	Discharge	2	216
	Observation Day28	30	134
	Observation Day84	86	22.8
[redacted]	Baseline	1	BLQ
	Day 1 / within 30 mins after end of infusion	1	206
	Hospitalization Day2	2	87.8
	Discharge	3	198
	Observation Day28	30	113
	Observation Day84	86	35.6
[redacted]	Baseline	1	BLQ
	Day 1 / within 30 mins after end of infusion	1	222
	Day 1 / 12h after end of infusion	2	148
	Discharge	2	152
	Observation Day28	18	95.6
	Observation Day84	88	12.7
[redacted]	Baseline	1	BLQ
	Day 1 / within 30 mins after end of infusion	1	239
	Day 1 / 12h after end of infusion	2	161
	Discharge	3	163
	Observation Day28	30	90.5
	Observation Day84	89	21.3
[redacted]	Baseline	1	BLQ
	Day 1 / within 30 mins after end of infusion	1	247
	Day 1 / 12h after end of infusion	2	205
	Observation Day84	121	6.45

BLQ: Below limit of quantification: 0.05 ug/mL.
Baseline visit is the patient's last observation prior to initiation of study drug.
CCOD: 18AUG2025 Data Extract Date: 18SEPT2025

Listing of Crovalimab Serum Concentrations, Pharmacokinetic Analysis Set
Protocol: BO42452

Treatment Group: Crova (N=20)

Center/Patient - Age/Sex/Race	Visit / Timepoint	Study Day	Concentration of Crovalimab (ug/mL)
[redacted]	Day 1 / within 30 mins after end of infusion	1	200
	Day 1 / 12h after end of infusion	2	198
	Hospitalization Day2	3	128
	Observation Day28	28	97.4
	Observation Day84	84	27.2
[redacted]	Baseline	1	BLQ
	Day 1 / within 30 mins after end of infusion	1	204
	Observation Day28	31	73.6
	Observation Day84	81	31.7

BLQ: Below limit of quantification: 0.05 ug/mL.
Baseline visit is the patient's last observation prior to initiation of study drug.
CCOD: 18AUG2025 Data Extract Date: 18SEPT2025

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In addition, immunogenicity of crovalimab was assessed (anti-drug antibodies against crovalimab). At baseline, 10.5% of participants displayed ADA positive status for crovalimab. Treatment-emergent ADA were observed in 20% of subjects and developed after a mean (SD) time of 13.22 weeks (8.61).

Efficacy results

All exploratory efficacy endpoints were analysed in the ITT Population. These analyses were descriptive in nature. The interpretation of the exploratory efficacy results should be taken with caution due to the small sample size of the study and high variability in the assessment of efficacy variables, which may be due to a variety of factors.

The benefit of crovalimab in the management of acute VOEs is inconclusive:

- Key exploratory efficacy endpoint results showed that the HRs were <1 for time to improvement of VOE, time to hospital discharge, and time to readiness for hospital discharge, but the respective 95% CIs included HR=1, indicating no clear benefit of crovalimab over placebo (**Table 5**).
- Median time to event was numerically longer for the crovalimab arm compared with the placebo arm across all key exploratory efficacy endpoints.

Table 5. Summary of Key Efficacy Endpoint Results, Intent-to-Treat

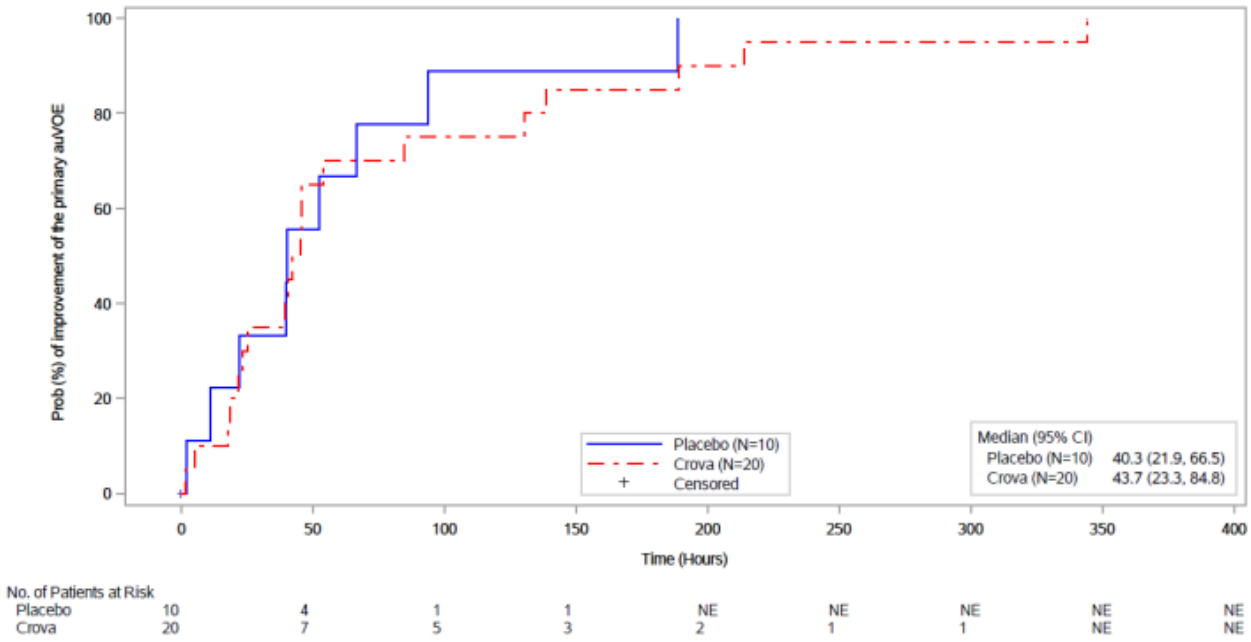
Parameter	**Placebo (n=10)[a]**	**Crova (n=20)**
Time to improvement of VOE • Median, hours (95% CI) • HR (95% CI)	40.3 (21.9, 66.5)	43.7 (23.3,84.8) 0.77 (0.34, 1.74)
Time to hospital discharge • Median, hours (95% CI) • HR (95% CI)	41.2 (26.9, 72.5)	46.5 (26.1, 90.3) 0.79 (0.35, 1.79)
Time to readiness for hospital discharge • Median, hours (95% CI) • HR (95% CI)	40.3 (21.9, 66.5)	43.9 (23.3, 130.2) 0.70 (0.30, 1.60)

Crova = Crovalimab; HR = Hazard Ratio; ITT = Intent-To-Treat; VOE = Vaso-Occlusive Episode.
[a] In the placebo arm, 10 participants were enrolled and included in the ITT Population, but 1 participant was not dosed due to meeting an exclusion criterion (fever) after screening. For time-to-event analyses, the data from this participant were censored at date of randomization.

Time to improvement of VOE

Participants in the placebo arm reported a shorter median time to improvement of VOE (40.3 hours [95% CI: 21.9 to 66.5]) compared with participants in the crovalimab arm (43.7 hours [95% CI: 23.3 to 84.8]). The HR was 0.77 (95% CI: 0.34 to 1.74; **Figure 3**).

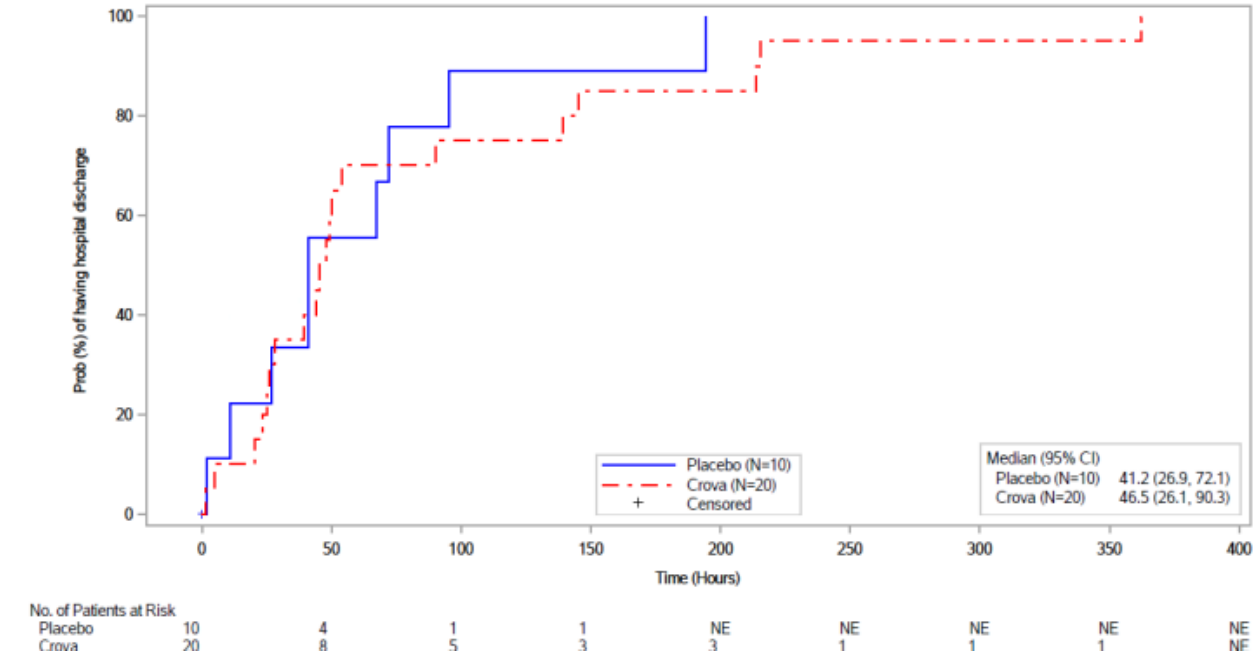
Figure 3. Kaplan-Meier Plot: Time to Improvement of VOE, Intent-to-Treat



Time to Hospital Discharge

Participants in the placebo arm reported a shorter median time to hospital discharge (41.2 hours [95% CI: 26.9 to 72.1]) compared with participants in the crovalimab arm (46.5 hours [95% CI: 26.1 to 90.3]). The HR was 0.79 (95% CI: 0.35 to 1.79; **Figure 4**).

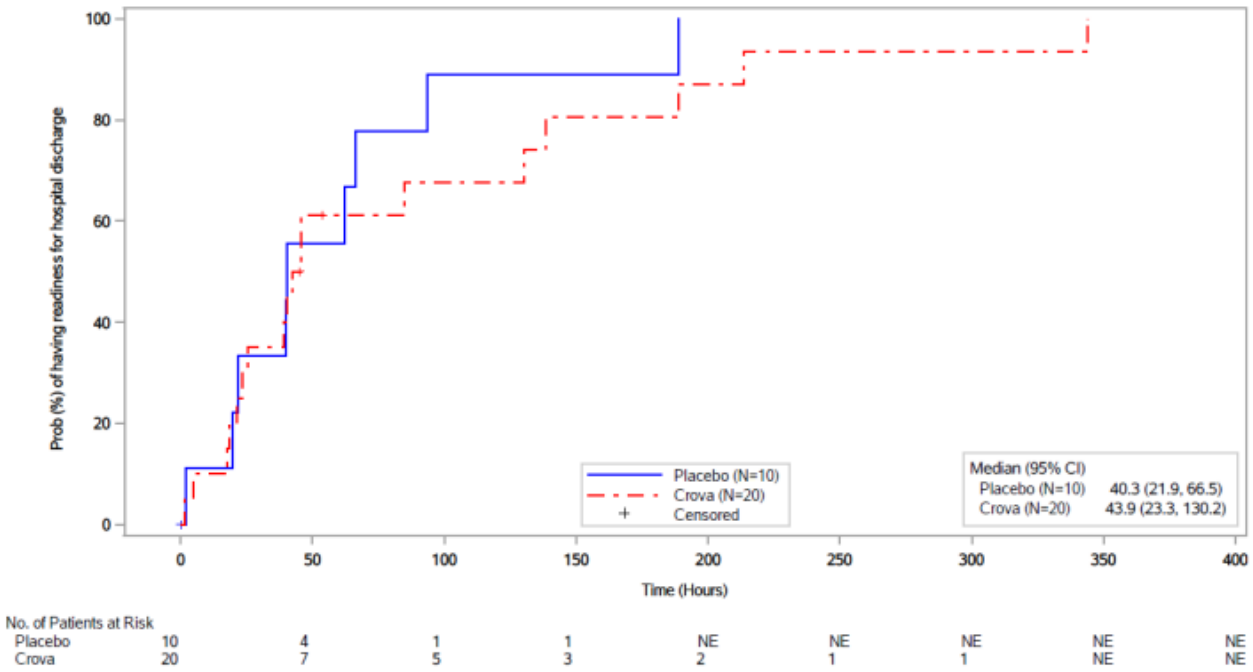
Figure 4. Kaplan-Meier Plot: Time to Hospital Discharge, Intent-to-Treat



Time to Readiness for Hospital Discharge

Participants in the placebo arm reported a shorter median time to readiness for hospital discharge (40.3 hours [95% CI: 21.9 to 66.5]) compared with participants in the crovalimab arm (43.9 hours [95% CI: 23.3 to 130.2]). The HR was 0.70 (95% CI: 0.30 to 1.60; **Figure 5**).

Figure 5. Kaplan-Meier Plot: Time to Readiness for Hospital Discharge, Intent-to-Treat



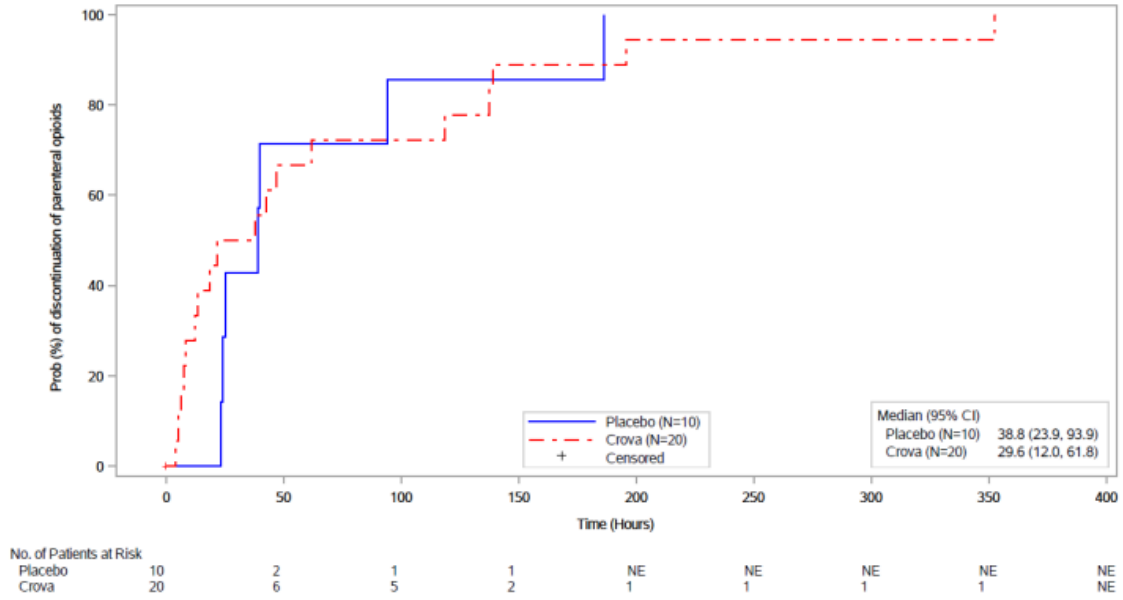
Total Cumulative Opioid Use

There were 18 participants (90.0%) and 8 participants (80.0%) in the crovalimab and placebo arms, respectively, who received at least 1 dose of opioid analgesic from baseline to hospital discharge. The median (minimum−maximum) total cumulative opioid dose (parenteral and oral) from baseline to hospital discharge was numerically higher in the crovalimab arm (3.33 MEU/kg [0.1−61.0 MEU/kg]) than in the placebo arm (2.03 MEU/kg [0.0−19.8 MEU/kg]).

Time to Discontinuation of all Parenteral Opioids

Participants in the crovalimab arm reported a shorter median time to discontinuation of all parenteral opioids (29.6 hours [95% CI: 12.0 to 61.8]) compared with participants in the placebo arm (38.8 hours [95% CI: 23.9 to 93.9]). The HR was 1.01 (95% CI: 0.41 to 2.49; **Figure 6**).

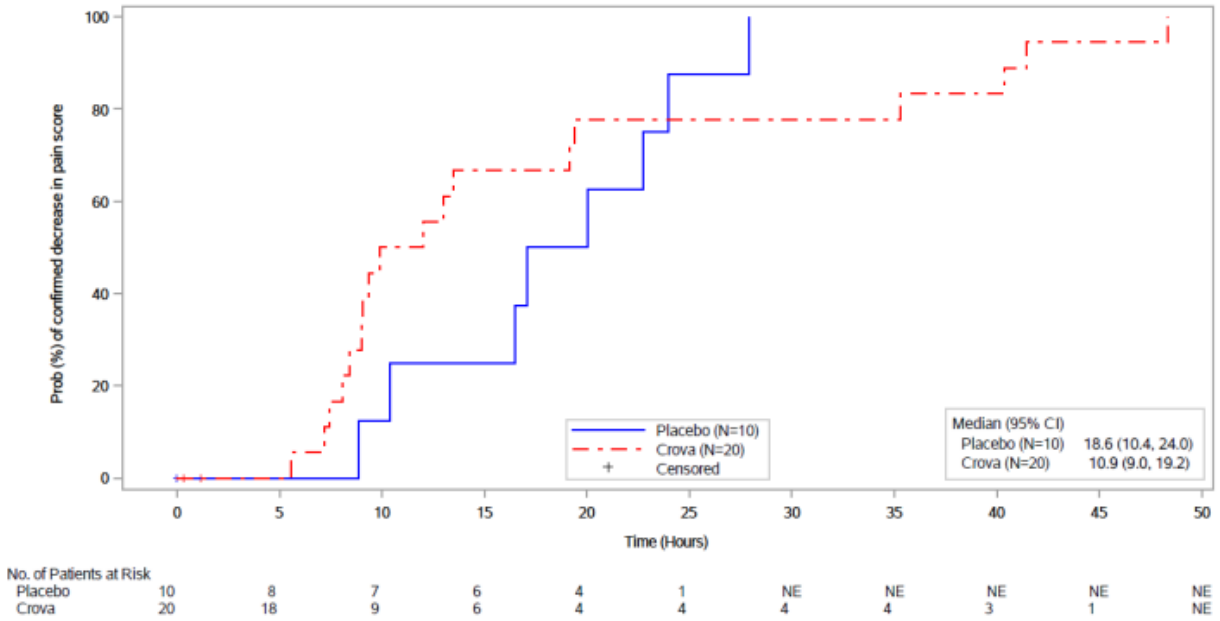
Figure 6. Kaplan-Meier Plot: Time to Discontinuation of Parenteral Opioids, Intent-to-Treat



Time to a Confirmed Decrease in Pain Score

There was a numerical improvement in the time to a confirmed decrease in pain score in the crovalimab arm compared with the placebo arm. The median time to a confirmed decrease in pain score was 10.9 hours (95% CI: 9.0 to 19.2) and 18.6 hours (95% CI: 10.4 to 24.0) in the crovalimab and placebo arms, respectively, with a difference of 7.7 hours in the medians. The HR was 1.12 (95% CI: 0.46 to 2.68; **Figure 7**).

Figure 7. Kaplan-Meier Plot: Time to Confirmed Decrease in Pain Score, Intent-to-Treat



Change in Pain Score from the Maximal Predose Pain Score to the Score at Hospital Discharge

There was a numerically larger reduction in the crovalimab arm compared with the placebo arm for both the mean (SD) (−6.37 [2.61] vs. −5.33 [2.65]) and the median (minimum−maximum) (−7.0 [−10.0 to −2.0] vs. −5.0 [−10.0 to −2.0]) differences in pain scores from the maximal predose pain score to the pain score at hospital discharge.

Readmission Rate for a VOE or VOE-related Event within 28 Days of Discharge after the Primary Acute Uncomplicated VOE

The percentage of participants who had a readmission for a VOE or VOE-related event within 28 days of discharge was numerically higher in the crovalimab arm. The re-admission rates were 35.0% (95% CI: 15.39 to 59.22) and 20.0% (95% CI: 2.52 to 55.61) in the crovalimab and placebo arms, respectively.

Other Exploratory Efficacy Endpoints

In the context of very low incidence rates, there was no meaningful difference between the crovalimab and placebo arms in results for the following exploratory efficacy endpoints:

- Proportion of patients who develop ACS from baseline to Day 28
- Proportion of patients requiring ICU/critical care admission for SCD-related complications from baseline to hospital discharge
- Proportion of patients requiring blood transfusion for SCD-related complications from baseline to hospital discharge

***CHMP comment*:**

Overall, the efficacy results remain inconclusive. Numerically, treatment did not appear to improve clinically relevant outcomes related to resolution of the VOE, such as time to improvement of VOE or time to hospital discharge, which were slightly shorter in the placebo arm (43.7 h vs 40.3h and 46.5 h vs 41.2 h respectively). The proportion of participants with readmission for a VOE within 28 days was also numerically higher in the crovalimab arm (35.0% vs 20.0%).

In contrast, some numerical improvements were observed in pain-related outcomes in the crovalimab arm, including a shorter time to confirmed decrease in pain score (10.9 h vs 18.6 h) and earlier discontinuation of parenteral opioid use (29.6 h vs 38.8h). These findings suggest a possible effect on pain management.

However, the overall interpretation remains limited due to the very small sample size, the apparent inconsistency between endpoints (improvement in opioid use and pain scores but not in crisis resolution or discharge), and the wide confidence intervals, which included 1. Therefore, no conclusions on efficacy can be drawn from this study.

Safety results

The overall safety profile of crovalimab was consistent with the known safety profile of crovalimab in PNH and of other C5 inhibitors. In Study BO42452, the safety results in the Safety Analysis Set indicated that crovalimab was well tolerated. No new safety signals were identified compared with studies of crovalimab in participants with PNH.

An overview of the safety results in the Safety Analysis Set (crovalimab: 20 participants; placebo: 9 participants) is provided in Table 5. The key safety findings are as follows:

- In the crovalimab arm, the most frequently occurring AEs were in the Blood and lymphatic system disorders System Organ Class (SOC) (18 participants [90.0%]); Gastrointestinal

disorders SOC (8 participants [40.0%]); and Infections and infestations and Respiratory, thoracic and mediastinal disorders SOCs (7 participants [35.0%] each). In the placebo arm, the most frequently occurring AEs were in the Blood and lymphatic system disorders; Gastrointestinal disorders; Infections and infestations; and Respiratory, thoracic and mediastinal disorders SOCs (4 participants [44.4%] each)

- The proportion of participants with Grade≥3 AEs was higher in the crovalimab arm (100.0% [20 participants]) than in the placebo arm (55.6% [5 participants]). After the hospitalization period, a higher rate of sickle cell anaemia with crisis was reported in the crovalimab arm, leading to a higher rate of Grade ≥3 AEs compared with placebo (as only serious [i.e., Grade ≥3] VOEs [sickle cell anaemia with crisis] were reported as AEs).

- In the crovalimab arm, 2 participants (10.0%) experienced treatment-related Grade 3 AEs. One of these participants (5.0%) also experienced a Grade 2 treatment-related event. In the placebo arm, 1 participant (11.1%) experienced a treatment-related Grade 3 AE, 1 participant (11.1%) experienced a treatment-related Grade 2 AE, and 1 participant (11.1%) experienced a treatment-related Grade 1 AE.

- No deaths were reported in either treatment arm.

- In total, 1 participant (5.0%) in the crovalimab arm and 1 participant (11.1%) in the placebo arm experienced SAEs considered by the investigator to be related to treatment.

- No participants were withdrawn from the study due to AEs.

- AEs of special interest (all of them severe infections) were experienced by 3 participants (15.0%) in the crovalimab arm and 2 participants (22.2%) in the placebo arm.

- The rate of serious infections per 100 PY was higher for crovalimab-treated participants (62.95 per 100 PY) compared with placebo-treated participants (39.80 per 100 PY). The infection incidence rate was higher in the crovalimab arm (91.57 per 100 PY) than in the placebo arm (66.34 per 100 PY). In the crovalimab arm, 4 participants (20.0%) had 11 total SAEs of infections; however, of the 4 participants in the crovalimab arm that experienced serious infections, 1 participant had 8 of the 11 total SAEs of infections (72.7%). This participant experienced 1 SAE during the hospitalization and observation periods (onset on Day 6, lasting 13 days), and the remaining 7 SAEs during the safety follow-up period (onset between Days 139−310). In the placebo arm, 2 participants (22.2%) experienced 3 total SAEs of infection.

- No participants in the crovalimab arm and 2 participants in the placebo arm experienced infusion-related reactions (Grades 1 and 2).

- There were no clinically meaningful changes from baseline in haematology, chemistry, or vital sign parameters in either treatment arm.

- No pregnancies were reported during the study period.

Table 6. Overview of Deaths and Adverse Events - Safety Analysis Set

	Placebo (N=9)	Crova (N=20)
Total number of patients with at least one AE	8 (88.9%)	20 (100%)
Total number of AEs	41	122
Total number of grade 3-5 AEs	19	80
Total number of deaths	0	0
Total number of patients withdrawn from study due to an AE	0	0
Total number of patients with at least one		
AE with fatal outcome	0	0
Serious AE	5 (55.6%)	20 (100%)
Serious AE leading to withdrawal from treatment	0	0
Serious AE leading to withdrawal from study	0	0
Serious AE leading to dose modification/interruption	0	0
Related Serious AE	1 (11.1%)	1 (5.0%)
AE leading to withdrawal from treatment	0	0
AE leading to withdrawal from study	0	0
AE leading to dose modification/interruption	0	0
Related AE	3 (33.3%)	2 (10.0%)
Related AE leading to withdrawal from treatment	0	0
Related AE leading to withdrawal from study	0	0
Related AE leading to dose modification/interruption	0	0
Grade 3-5 AE	5 (55.6%)	20 (100%)
Adverse Events of Special Interest		
Case of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in protocol	0	0
Suspected transmission of an infectious agent by the study drug	0	0
Severe infections (>=NCI CTCAE Grade 3) including Meningococcal infections	2 (22.2%)	3 (15.0%)

Investigator text for AEs encoded using MedDRA version 28.0. Percentages are based on N in the column headings.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
CCOD: 18AUG2025 Data Extract Date: 18SEPT2025

Frequency of Adverse Events by System Organ Class and Preferred Term

For the crovalimab arm, the most frequently occurring AEs were in the Blood and lymphatic system disorders SOC (18 participants [90.0%]); Gastrointestinal disorders SOC (8 participants [40.0%]); and Infections and infestations and Respiratory, thoracic and mediastinal disorders SOCs (7 participants [35.0%] each). For the placebo arm, the most frequently occurring AEs were in the Blood and lymphatic system disorders; Gastrointestinal disorders, Infections and infestations; and Respiratory, thoracic and mediastinal disorders SOCs (4 participants [44.4%] each).

An overall summary of AEs by SOC/Preferred Term (PT) is presented in **Table 7**. Proportion of patients requiring blood transfusion for SCD-related complications from baseline to the time of hospital discharge is presented in **Table 8**.

Table 7. Summary of Adverse Events, Safety Analysis Set

MedDRA System Organ Class MedDRA Preferred Term	Placebo (N=9)	Crova (N=20)
Total number of patients with at least one adverse event	8 (88.9%)	20 (100%)
Overall total number of events	41	122
Blood and lymphatic system disorders		
Total number of patients with at least one adverse event	4 (44.4%)	18 (90.0%)
Total number of events	13	57
Sickle cell anaemia with crisis	4 (44.4%)	16 (80.0%)
Anaemia	0	3 (15.0%)
Agranulocytosis	0	1 (5.0%)
Coagulopathy	0	1 (5.0%)
Neutropenia	0	1 (5.0%)
Gastrointestinal disorders		
Total number of patients with at least one adverse event	4 (44.4%)	8 (40.0%)
Total number of events	7	11
Nausea	1 (11.1%)	3 (15.0%)
Abdominal pain upper	2 (22.2%)	1 (5.0%)
Vomiting	0	3 (15.0%)
Constipation	1 (11.1%)	1 (5.0%)
Gastritis	2 (22.2%)	0
Abdominal pain	0	1 (5.0%)
Gingival bleeding	0	1 (5.0%)
Toothache	0	1 (5.0%)
Infections and infestations		
Total number of patients with at least one adverse event	4 (44.4%)	7 (35.0%)
Total number of events	5	16
Influenza	0	2 (10.0%)
Bacteraemia	0	1 (5.0%)
Bacterial disease carrier	0	1 (5.0%)
Bacterial sepsis	0	1 (5.0%)
COVID-19	0	1 (5.0%)
Cellulitis	0	1 (5.0%)
Device related bacteraemia	0	1 (5.0%)
Lower respiratory tract infection	0	1 (5.0%)
Oral herpes	1 (11.1%)	0
Pharyngitis	0	1 (5.0%)
Pharyngitis streptococcal	1 (11.1%)	0
Staphylococcal bacteraemia	0	1 (5.0%)
Streptococcal sepsis	1 (11.1%)	0
Subperiosteal abscess	1 (11.1%)	0
Systemic candida	0	1 (5.0%)
Vascular device infection	0	1 (5.0%)
Viraemia	1 (11.1%)	0
Viral upper respiratory tract infection	0	1 (5.0%)

Respiratory, thoracic and mediastinal disorders		
Total number of patients with at least one adverse event	4 (44.4%)	7 (35.0%)
Total number of events	4	12
Acute chest syndrome	3 (33.3%)	5 (25.0%)
Cough	1 (11.1%)	1 (5.0%)
Oropharyngeal pain	0	1 (5.0%)
Sleep apnoea syndrome	0	1 (5.0%)
Injury, poisoning and procedural complications		
Total number of patients with at least one adverse event	2 (22.2%)	4 (20.0%)
Total number of events	2	4
Infusion related reaction	2 (22.2%)	0
Toxicity to various agents	0	2 (10.0%)
Fat embolism	0	1 (5.0%)
Radius fracture	0	1 (5.0%)
Nervous system disorders		
Total number of patients with at least one adverse event	2 (22.2%)	3 (15.0%)
Total number of events	4	5
Headache	2 (22.2%)	2 (10.0%)
Depressed level of consciousness	0	1 (5.0%)
Dizziness	1 (11.1%)	0
Lethargy	1 (11.1%)	0
Loss of consciousness	0	1 (5.0%)
Metabolism and nutrition disorders		
Total number of patients with at least one adverse event	1 (11.1%)	3 (15.0%)
Total number of events	1	4
Vitamin B12 deficiency	0	2 (10.0%)
Decreased appetite	1 (11.1%)	0
Hyperkalaemia	0	1 (5.0%)
Hyperuricaemia	0	1 (5.0%)
Musculoskeletal and connective tissue disorders		
Total number of patients with at least one adverse event	0	4 (20.0%)
Total number of events	0	4
Osteonecrosis	0	2 (10.0%)
Arthralgia	0	1 (5.0%)
Osteoarthritis	0	1 (5.0%)
Psychiatric disorders		
Total number of patients with at least one adverse event	2 (22.2%)	1 (5.0%)
Total number of events	2	1
Insomnia	1 (11.1%)	1 (5.0%)
Confusional state	1 (11.1%)	0
Investigations		
Total number of patients with at least one adverse event	0	2 (10.0%)
Total number of events	0	4
Blood creatinine increased	0	1 (5.0%)
Troponin increased	0	1 (5.0%)
Viral test positive	0	1 (5.0%)
Eye disorders		
Total number of patients with at least one adverse event	1 (11.1%)	0
Total number of events	1	0
Ocular hyperaemia	1 (11.1%)	0
General disorders and administration site conditions		
Total number of patients with at least one adverse event	1 (11.1%)	0
Total number of events	1	0
Fatigue	1 (11.1%)	0
Hepatobiliary disorders		
Total number of patients with at least one adverse event	1 (11.1%)	0
Total number of events	1	0
Drug-induced liver injury	1 (11.1%)	0
Immune system disorders		
Total number of patients with at least one adverse event	0	1 (5.0%)
Total number of events	0	1
Seasonal allergy	0	1 (5.0%)
Reproductive system and breast disorders		
Total number of patients with at least one adverse event	0	1 (5.0%)
Total number of events	0	1
Priapism	0	1 (5.0%)

Skin and subcutaneous tissue disorders			
Total number of patients with at least one adverse event	0		1 (5.0%)
Total number of events		0	1
Pruritus	0		1 (5.0%)
Vascular disorders			
Total number of patients with at least one adverse event	0		1 (5.0%)
Total number of events		0	1
Deep vein thrombosis	0		1 (5.0%)

Table 8. Proportion of patients requiring blood transfusion for SCD-related complications from baseline to the time of hospital discharge, Intent-to-treat

Number of patients with blood transfusion for SCD-related complication:	**Placebo (n=10)**	**Crova (n=20)**
n (%) **95% CI**	1 (10.0%) (0.25,44.50)	5 (25.0%) (8.66, 49.10)

None of the participants required intensive care unit (ICU) or critical care admission for SCD-related complications.

Adverse Events by Intensity

The proportion of participants with Grade≥3 AEs was higher in the crovalimab arm (20 participants [100.0%]) than in the placebo arm (5 participants [55.6%]). Participants in both arms reported Grade≥3 AEs most frequently in the following SOCs:

- Blood and lymphatic system disorders: 18 participants (90.0%) in the crovalimab arm and 4 participants (44.4%) in the placebo arm.
- Respiratory, thoracic, and mediastinal disorders: 5 participants (25.0%) in the crovalimab arm and 3 participants (33.3%) in the placebo arm.

The most frequently reported Grade ≥3 AEs by PT in the crovalimab arm were sickle cell anaemia with crisis (16 participants [80.0%]), acute chest syndrome (5 participants [25.0%]), and anaemia (3 participants [15.0%]). The most frequently reported Grade ≥3 AEs by PT in the placebo arm were sickle cell anaemia with crisis (4 participants [44.4%]) and acute chest syndrome (3 participants [33.3%]).

No Grade 5 AEs were reported.

Adverse Events Related to Treatment

The proportion of participants with treatment-related AEs was lower in the crovalimab arm (10.0%) than in the placebo arm (33.3%).

In the crovalimab arm, 2 participants (10.0%) experienced treatment-related AEs of anaemia (each Grade 3). One of these participants (5.0%) also experienced a treatment-related AE of pharyngitis (Grade 2).

In the placebo arm, 3 participants (33.3%) experienced treatment-related AEs. Two participants experienced infusion-related reaction (Grades 1 and 2), and 1 participant experienced subperiosteal abscess (Grade 3).

Deaths

There were no deaths reported in the study.

Serious Adverse Events

The proportion of participants experiencing SAEs was higher in the crovalimab arm (100.0%) than in the placebo arm (55.6%); however, this difference was mainly driven by sickle cell anaemia with crisis being more frequent in the crovalimab arm than in the placebo arm (**Table 9**).

For both treatment arms, participants reported the most SAEs in the following SOCs:

- Blood and lymphatic system disorders: 17 crovalimab-treated participants (85.0%) and 4 placebo-treated participants (44.4%)
- Respiratory, thoracic and mediastinal disorders: 5 crovalimab-treated participants (25.0%) and 2 placebo-treated participants (22.2%)
- Infections and infestations: 4 crovalimab-treated participants (20.0%) and 2 placebo-treated participants (22.2%)

Table 9. Summary of Serious Adverse Events, Safety Analysis Set

MedDRA System Organ Class MedDRA Preferred Term	Placebo (N=9)	Crova (N=20)
Total number of patients with at least one adverse event	5 (55.6%)	20 (100%)
Overall total number of events	18	78
Blood and lymphatic system disorders		
Total number of patients with at least one adverse event	4 (44.4%)	17 (85.0%)
Total number of events	13	53
Sickle cell anaemia with crisis	4 (44.4%)	16 (80.0%)
Anaemia	0	2 (10.0%)
Agranulocytosis	0	1 (5.0%)
Respiratory, thoracic and mediastinal disorders		
Total number of patients with at least one adverse event	2 (22.2%)	5 (25.0%)
Total number of events	2	9
Acute chest syndrome	2 (22.2%)	5 (25.0%)
Infections and infestations		
Total number of patients with at least one adverse event	2 (22.2%)	4 (20.0%)
Total number of events	3	11
Bacteraemia	0	1 (5.0%)
Bacterial sepsis	0	1 (5.0%)
Cellulitis	0	1 (5.0%)
Device related bacteraemia	0	1 (5.0%)
Lower respiratory tract infection	0	1 (5.0%)
Staphylococcal bacteraemia	0	1 (5.0%)
Streptococcal sepsis	1 (11.1%)	0
Subperiosteal abscess	1 (11.1%)	0
Systemic candida	0	1 (5.0%)
Vascular device infection	0	1 (5.0%)
Viraemia	1 (11.1%)	0
Viral upper respiratory tract infection	0	1 (5.0%)
Nervous system disorders		
Total number of patients with at least one adverse event	0	2 (10.0%)
Total number of events	0	2
Headache	0	1 (5.0%)
Loss of consciousness	0	1 (5.0%)
Injury, poisoning and procedural complications		
Total number of patients with at least one adverse event	0	1 (5.0%)
Total number of events	0	1
Fat embolism	0	1 (5.0%)
Reproductive system and breast disorders		
Total number of patients with at least one adverse event	0	1 (5.0%)
Total number of events	0	1
Priapism	0	1 (5.0%)
Vascular disorders		
Total number of patients with at least one adverse event	0	1 (5.0%)
Total number of events	0	1
Deep vein thrombosis	0	1 (5.0%)

Only 1 participant (5.0%) in the crovalimab arm reported a treatment-related SAE (Grade 3 anaemia, which required hospitalization and was recovered/resolved after 3 days). One participant (11.1%) in the placebo arm reported a treatment-related SAE.

(Grade 3 subperiosteal abscess, which required hospitalization and was reported as recovering/resolving).

There were no participants who had to be discontinued from either treatment or study due to SAEs in the study.

Adverse Events That Led to Discontinuation of Treatment

In both treatment arms, there were no AEs that led to discontinuation of treatment.

Adverse Events That Led to Dose Modification

In both treatment arms, there were no AEs that led to dose modification.

Adverse Events of Special Interest

Overall, 3 participants (15.0%) in the crovalimab arm and 2 participants (22.2%) in the placebo arm experienced AEs of special interest. All AEs of special interest were Grade 3 in severity, none led to treatment or study discontinuation, and one (in the placebo arm) was considered related to study treatment.

Three participants (15.0%) in the crovalimab arm experienced AEs of special interest:

- One participant (5.0%) experienced a Grade 3 serious event of staphylococcal bacteraemia.
- One participant (5.0%) experienced 6 Grade 3 serious events: bacteraemia, bacterial sepsis, cellulitis, device related bacteraemia, systemic candida, and vascular device infection.
- One participant (5.0%) experienced a Grade 3 serious event of lower respiratory tract infection.

Two participants (22.2%) in the placebo arm experienced AEs of special interest:

- One participant (11.1%) experienced a Grade 3 serious event of streptococcal sepsis.
- One participant (11.1%) experienced two Grade 3 serious events: subperiosteal abscess (considered related to study treatment) and viraemia

Selected AEs: Infection AEs

Overall, the exposure-adjusted incidence of infection AEs was higher in the crovalimab arm. The infection incidence rate was 91.57 per 100 PY (16 infection AEs in total) in the crovalimab arm and 66.34 per 100 PY (5 infection AEs) in the placebo arm; however, 9 (56.3%) of the 16 infection events in the crovalimab arm occurred in a single participant.

The rate of serious infections (per 100 PY) was also higher in the crovalimab arm: 62.95 per 100 PY in the crovalimab arm and 39.80 per 100 PY in the placebo arm. In the crovalimab arm, 4 participants (20.0%) had 11 total SAEs of infections: Grade 3 events of bacteraemia and vascular device infection, bacterial sepsis, cellulitis, device related bacteraemia, lower respiratory tract infection, staphylococcal bacteraemia, systemic candida, and vascular device infection (1 event each), and a Grade 2 event of viral upper respiratory tract infection. One participant experienced 8 of these events, with 1 SAE during the hospitalization and observation periods (onset on Day 6, lasting 13 days) and the remaining 7 SAEs during the safety follow-up period (onset between Days 139–310). In the placebo arm, 2 participants (22.2%) experienced 3 total SAEs of infection: Grade 3 events of streptococcal sepsis, subperiosteal abscess, and viremia. Mean (SD) time to onset of first serious infection was 19.93 weeks (22.81) in the crovalimab arm and 1.43 weeks (1.82) in the placebo arm. One non-serious event of pharyngitis in the crovalimab arm was considered related to study treatment, and one serious event of subperiosteal abscess was considered related to study treatment in the placebo arm.

***CHMP comment*:**

In the treatment arm, 100% of subjects reported AEs: the most commonly (≥ 15%) reported AEs were Sickle cell anaemia with crisis (16 participants [80.0%]), Acute chest syndrome (5 participants [25.0%]) and Anaemia (3 participants [15.0%]). All of these were Grade ≥ 3.

The AEs for which the difference between treatment and placebo was substantial (≥ 15%) are: sickle cell anaemia with crisis (80.0% vs. 44.4%), anaemia (15.0% vs. 0), and vomiting (15.0% vs. 0).

Sickle cell anaemia with crisis was the most frequent reported Serious AE in both arm and with the largest difference between arms (16 [80.0%] treatment vs. 4 [44.4%] placebo). However, only 2 participants (10.0%) in the crovalimab arm experienced an SAE that was considered related to study drug (anaemia).

As stated in the study CSR, most of sickle cell anaemia with crisis event occurred after the hospitalization period. Based on the narratives of SAE, overall, 2 cases involved paediatric participants (16 y.o) and most events occurred during the later follow-up period rather than in the early post-dose phase (after Day 30 and up to Day 314). Only a few events were reported early observation period (Day 3–Day 10).

Five participants in the crovalimab arm (25.0%) required transfusion for SCD-related complication versus 1 in the placebo arm (10.0%).

Infection is highlighted as a special warning in the SmPC. Serious or fatal meningococcal infections, including sepsis, have been reported and is a known class effect. Patients may have an increased susceptibility to infections, particularly with Neisseria species and other encapsulated bacteria.

Adverse events of special interest (AESIs) in the study included severe infections such as meningococcal infections, suspected transmission of an infectious agent by the study drug, and elevated ALT or AST in combination with either elevated bilirubin or clinical jaundice. Only one AESI, a subperiosteal abscess, was considered related to the study treatment and occurred in the placebo arm. Overall, three participants (15.0%) in the treatment arm and two participants (22.2%) in the placebo arm experienced AESIs, all of which were infection related.

The rate of serious infections per 100 PY was almost 1.6 times higher in the crovalimab arm (62.95 versus 39.80 per 100 PY). Although 4 participants (20%) in the crovalimab arm experienced serious infections, most events were driven by a single individual, with only one event occurring during the hospitalization/observation period and the remaining events arising later during the safety follow-up. Serious infection reported were Grade 3 events of bacteraemia and vascular device infection, bacterial sepsis, cellulitis, device related bacteraemia, lower respiratory tract infection, staphylococcal bacteraemia, systemic candida, and vascular device infection (1 event each), and a Grade 2 event of viral upper respiratory tract infection. These events represent infectious risks associated with the treatment. However, they do not correspond to the **s**pecific infections highlighted as special warnings in the SmPC.

Clinical Laboratory Evaluation

- **Haematology**

The data showed no clinically meaningful changes from baseline in haematology parameters. The results were comparable across both treatment arms. As previously mentioned, after the hospitalization period, participants in the crovalimab arm experienced more events of sickle cell anaemia with crisis than participants in the placebo arm. As such, crovalimab arm participants experienced more AEs in the Blood and lymphatic system disorders SOC (18 participants [90.0%]) than placebo arm participants (4 participants [44.4%]).

However, only 2 participants (10.0%) in the crovalimab arm experienced an SAE that was considered related to study drug (anaemia). All other haematology-related AEs were not clinically significant.

- **Chemistry**

The data showed no clinically meaningful changes from baseline in chemistry values. The results were comparable across both treatment arms. One participant in the placebo arm had a non-serious AE of drug-induced liver injury (hydroxyurea toxicity). The event was resolved after 10 days and was not

related to study treatment. No participants in the crovalimab arm had laboratory values meeting Hy's law criteria for drug-induced liver injury.

Other Safety Evaluations

- **Vital Signs**

There were no clinically meaningful findings in the vital signs measurements or other observations related to safety in this study. The assessments and observations were comparable across both treatment arms. No clinically meaningful difference from baseline to Day 28 was observed between the treatment arms in blood pressure, pulse rate, respiratory rate, temperature, or oxygen saturation. Vital sign abnormalities were balanced between treatment arms. No abnormalities were considered clinically significant or related to study treatment (**Table 10**).

Table 10. Vital Sign Abnormalities, Safety Analysis Set

Assessment	Direction of Abnormality	Placebo (N=9)	Crova (N=20)
Oxygen Saturation (%)	Low	3/8 (37.5%)	6/15 (40.0%)
	High	0/9	0/20
Diastolic Blood Pressure (mmHg)	Low	4/6 (66.7%)	11/16 (68.8%)
	High	3/8 (37.5%)	7/18 (38.9%)
Systolic Blood Pressure (mmHg)	Low	1/8 (12.5%)	1/19 (5.3%)
	High	4/7 (57.1%)	8/19 (42.1%)
Pulse Rate (beats/min)	Low	2/9 (22.2%)	2/19 (10.5%)
	High	2/8 (25.0%)	7/19 (36.8%)
Respiratory Rate (breaths/min)	Low	0/9	0/20
	High	0/8	5/19 (26.3%)
Temperature (C)	Low	4/5 (80.0%)	12/13 (92.3%)
	High	1/9 (11.1%)	6/19 (31.6%)

Pregnancies

No pregnancies were reported during the study period.

CHMP comment:

No substantial changes were observed in vital signs (oxygen saturation, Diastolic/systolic blood pressure, pulse rate, respiratory rate and temperature), chemistry values or haematological parameter except for 2 Grade 3 serious adverse events of anaemia considered related to crovalimab.

Conclusions

In light of the low sample size and high variability in the assessment of efficacy endpoints, no clear conclusions could be drawn regarding the assessment of the benefit−risk of crovalimab in acute SCD.

2.3.3. Discussion on clinical aspects

This P46 submission is based on Study BO42452, a Phase IB Randomized, Placebo-Controlled Study aimed to evaluate the safety, pharmacokinetics, pharmacodynamics, and efficacy of Crovalimab for the management of Acute Uncomplicated Vaso-Occlusive Episodes (VOE) in adult and paediatric patients (12−55 years old) with Sickle Cell Disease (SCD).

Participants were randomly assigned in a 2:1 ratio to crovalimab or placebo and received a single IV dose of 1000 mg of the experimental treatment. In total, 30 participants were randomized (20 to crovalimab and 10 to placebo).

Participants aged 12–17 years represented 15% (3/20) of the crovalimab arm and 40% (4/10) of the placebo arm. Paediatric data are therefore very limited and were not analysed separately from the overall dataset. As a result, no robust conclusions can be drawn regarding efficacy or safety in this age subgroup.

The primary objective of this study was safety while efficacy analyses were exploratory and descriptive.

In terms of pharmacokinetics, sample collection times spanned the full course of the study, from predose to Day 84. The duration of the study represented 1.58 times the half-life of crovalimab (terminal half-life of crovalimab was estimated as 53.1 days [CV%: 39.9]) and 3 times the duration of the loading dose phase recommended by SmPC (28 days). Therefore, this study duration was considered sufficient to assess serum concentrations of crovamilab in patients with SCD.

A validated analytical method was used for serum quantification of crovalimab (ELISA, calibration range from 50.0 ng/mL (LLOQ) to 3200 ng/mL (ULOQ)) in line with the previously validated method during MAA application (Method ID: M08.RO7112689.huse.1). A validated method was used for detection of anti-RO7112689 antibodies in human serum by ELISA assay. Validated analytical methods and certificates of analysis were provided and considered acceptable.

Crovalimab serum concentrations in participants with SCD was 187.31 µg/mL [95% CI: 167.24 to 207.38] on Day 1 and reached approximately 60% of C_{max} observed in PNH patients (cf. study BP39144 part 4).

Crovalimab serum concentration–time curves were compared by ADA status: a small number of participants displayed ADA+ results (N=4, 20%) and were comprised in the previously known range. It appears that no neutralizing ADAs was observed in this study. These observations were coherent with overlapping pharmacokinetics profiles. Systemic exposure to crovalimab did not appear impacted by ADA status, with N=16 ADA negative and N=4 ADA positive subjects.

Efficacy analyses were descriptive and primarily focused on evaluating reduction of pain intensity and opioid use, time to hospital discharge, and the proportion of disease-related complications, including acute chest syndrome (ACS). The assessment of benefits of crovalimab in the management of acute VOEs was inconclusive. Exploratory efficacy results in the ITT Population indicated no clear benefit of crovalimab over placebo, with wide 95% CIs for HRs that included HR=1 indicating no treatment benefit. This being said, there was a numerically larger reduction in the crovalimab arm in pain scores from the maximal predose pain score to the pain score at hospital discharge.

Regarding safety results, all participants (100%) in the crovalimab arm reported AEs. The most frequently reported AE was sickle cell anaemia with crisis (16/20 [80.0%] vs 4/9 [44.4%] in the placebo arm), which also showed the largest difference between groups. While these events were not considered treatment-related, these finding are of concern given that crovalimab is intended to reduce such complications. Interpretation of this difference should nevertheless be made with caution due to the small study size.

Other commonly reported AEs in the treatment arm (≥15%) were acute chest syndrome (5 participants [25.0%]), and anaemia (3 participants [15.0%]), all of which were Grade ≥3. Compared with placebo, the largest differences (≥15%) were observed for sickle cell anaemia with crisis (80.0% vs. 44.4%), anaemia (15.0% vs. 0), and vomiting (15.0% vs. 0). Most other differences between groups were limited to one or two participants.

Although certain AEs were numerically more frequent in the treatment arm, most were not considered directly attributable to treatment. Treatment-related AEs were reported in 10.0% in the crovalimab arm (n=2), both corresponding to Grade 3 anaemia, compared with 33.3% in the placebo arm (n=3). In the

placebo arm, treatment-related AEs consisted of low-grade infusion-related reactions (IRR) and one Grade 3 subperiosteal abscess.

Adverse events of special interest (AESIs) included severe infections such as meningococcal infections, suspected transmission of an infectious agent by the study drug, and elevated ALT or AST in combination with either elevated bilirubin or clinical jaundice. No specific observation could be identified. Only one AESI, a subperiosteal abscess, was considered related to the study treatment and occurred in the placebo arm. Overall, three participants (15.0%) in the treatment arm and two participants (22.2%) in the placebo arm experienced AESIs, all of which were infection related.

The rate of serious infections per 100 PY was almost 1.6 times higher in the crovalimab arm (62.95 versus 39.80 per 100 PY). Although 4 participants (20%) in the crovalimab arm experienced serious infections, most events were driven by a single individual, with only one event occurring during the hospitalization/observation period and the remaining events arising later during the safety follow-up.

The data showed no clinically meaningful changes from baseline in haematology parameters, chemistry values, or vital signs parameters.

No death occurred and no adverse events (AEs) led to treatment discontinuation or dose modification.

Overall, given the very limited study population and the specific characteristics of patients with sickle cell disease, most of the reported AEs correspond to complications commonly associated with the underlying disease. However, this does not fully explain the numerical imbalance observed between the treatment arm and placebo arms.
Similarly, anaemia, which represents a frequent clinical manifestation of SCD, was reported as Grade 3 event in 3 patients in the treatment arm (including 2 considered treatment-related), while no events were reported in the placebo arm. Nevertheless, these findings are based on very small numbers of patients enrolled (3/20 patients) and should therefore be interpreted with caution.

Overall, the very limited number of patients enrolled, especially paediatric patients, does not allow to draw clear conclusions on B/R, however, some safety signals (SCD-related events, infections…) emerging from the study are of concern and should not be overlooked if further development is intended in SCD settings.

3. Rapporteur's overall conclusion and recommendation

Overall, paediatric data are very limited and were not analysed separately from the overall dataset. As a result, no robust conclusions can be drawn regarding efficacy or safety in this age subgroup.

☒ **Fulfilled:**

No regulatory action required.