Crosswalk-a

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Main Information

Primary registry identifying number
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Protocol number
BO42452

MOH registration number

Study registered at the country of origin
Yes

Study registered at the country of origin: Specify

Type of registration
Prospective

Type of registration: Justify
N/A

Date of registration in national regulatory agency
15/01/2021

Primary sponsor
F. Hoffmann-La Roche Ltd

Primary sponsor: Country of origin
Switzerland

Date of registration in primary registry
19/07/2024

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15/01/2021

Public title
Crosswalk-a

Acronym
Crosswalk-a

Scientific title
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)

Acronym
Crosswalk-a

Brief summary of the study: English

Background on Sickle Cell Disease:
Sickle cell disease (SCD) is an autosomal recessive genetic disorder caused by the inheritance of a point mutation at position 6 in the β-globin gene, replacing a glutamic acid with a valine (βS). It affects millions of patients with an estimated incidence of 300,000-400,000 affected neonates annually.

The polymerized HbS distorts the Red Blood Cells into a sickled shape with abnormal rheology. The increased rigidity and decreased deformability of sickled RBCs contribute to microvascular occlusions and the hallmark presentation of acute painful vaso-occlusive episodes in patients with Sickle Cell Disease. Vaso-occlusive episodes are marked by ischemia and reperfusion injury, which can affect any organ system in the body.

Acute painful episodes can range, from being managed at home to requiring hospital admission, and can be complicated by additional acute sickle cell manifestations including acute chest syndrome and hepatic and/or splenic sequestration. Sickled Red blood Cells have a significantly shorter lifespan as a result of chronic intravascular and extravascular hemolysis causing chronic anemia. The chronic hemolysis causes chronic endothelial activation leading to vascular dysfunction that can manifest clinically as vascular stiffness, pulmonary hypertension, diastolic heart failure, and renal damage.

The release of intracellular contents also results in chronic sterile inflammation with activation of leukocytes, platelets, endothelial cells, and generation of reactive oxygen species. In addition, Sickle Cell Disease May also result in moderate to severe chronic anemia, immune dysfunction, chronic pain, and progressive end-organ damage in the lungs, heart, kidney, and central nervous system

These acute and chronic complications of Sickle Cell Disease contribute to the significant morbidity and mortality in this patient population.

The management/ treatment of Sickle Cell disease is complex and depends on the patient's age, comorbidities, and disease phenotype. In patients diagnosed in the neonatal period, anticipatory guidance and supportive care with antibiotic prophylaxis and vaccinations has improved childhood outcomes.

Globally, treatment of Sickle Cell Disease is limited to hydroxyurea, which has disease-modifying efficacy, blood transfusion, and other supportive care for acute and chronic complications. Hematopoietic stem cell transplantation (HSCT) is the only available curative intervention; however, it is limited by donor availability and procedure-associated toxicity.

Morbidity and mortality data highlight the unmet need in Sickle Cell Disease. Although medical advances have significantly improved life expectancy in patients with HbSS or HbSβ0 to a median of more than 60 years, especially in high-resource countries, life expectancy remains about 30 years less than in the general population and morbidity burden of disease remains high.

Complement Inhibition C5 on sickle cell disease
Taken together, the available data from patients with Sickle Cell Disease, and in vitro and in vivo nonclinical models indicate that complement is activated in patients with Sickle Cell Disease And suggest a role in its pathophysiology in multiple domains. Complement activation is detected in patients at steady state in Sickle Cell Disease And in association with acute vaso-occlusive episodes . In vitro and in vivo models of complement inhibition suggest multiple potential downstream effects of C5 inhibition in patients with Sickle Cell Disease That include prevention of endothelial activation by free heme, reduction in rate of hemolysis, reduction in vaso-occlusion, improvement in chronic inflammation, and reduction in end-organ damage.Published evidence supports exploratory trials of complement inhibition in patients with Sickle Cell Disease, which may address the unmet medical need in this disease, employing a mechanism that does not overlap with current therapies.

Crovalimab effect:
Crovalimab induces rapid and complete inhibition of the terminal complement pathway by targeting C5, making it a suitable candidate for exploration of the role of targeting complement in treatment for Sickle Cell Disease .

BO42452 Study Objective
BO42452 will evaluate the safety, pharmacokinetics, pharmacodynamics, and efficacy of crovalimab compared with placebo for the management of acute uncomplicated Vaso-occulsive episodes in patients with sickle cell disease . (Kindly check the objectives and endpoint in protocol section 2 page 34). This randomized, multicenter, placebo-controlled, double-blinded Phase Ib study is designed to evaluate the safety (primary study objective), pharmacokinetics, pharmacodynamics, and efficacy of crovalimab compared with placebo for the management of an acute uncomplicated vaso-occulsive episodes in adult and adolescent patients with sickle cell disease.

BO42452 Design
This study will enroll approximately 30 patients (at approximately 10 -15 sites globally), aged 12-55 years old and ≥40 kg, with sickle cell disease genotype of HbSS or HbSβ0, presenting to the ER/ED or acute medical facility with an acute uncomplicated vaso-occulsive episodes. Patients who present with acute complications such as

acute chest syndrome, priapism, hepatic or splenic sequestration etc., or present with pain atypical of or unrelated to an acute uncomplicated vaso-occulsive episodes will be excluded at screening. Complications of the vaso-occulsive episodes that develop after study treatment administration and during hospitalization will be documented. Patients who develop complications after screening, but before study treatment administration, may no longer be eligible.

A 2-step process for screening procedures is encouraged to preliminarily identity and consent patients for the study prior to vaso occlusive episodes presentation:
Screening Visit #1 (initial screening) is conducted at an outpatient visit (i.e., when the patient is not experiencing a vaso occlusive episode), where the main Informed Consent Form is signed and preliminary eligibility is assessed. During this visit, preliminary screening assessments can be conducted, and a steady state sickle cell disease exploratory biomarker sample will be collected (only after consent is received), No additional assessments are required until Screening Visit #2.
Eligibility at Screening Visit #1 does not guarantee eligibility at Screening Visit #2.

Screening Visit #2 (vaso-occlusive episodes crisis screen) is then conducted when the patient presents with a vaso-occulsive episodes to the ER/ED or acute medical facility. The patient consent from Screening Visit #1 must be confirmed prior to starting study assessments (this confirmation must be documented). Once patient consent is confirmed, all remaining eligibility criteria must be assessed. (Refer to study design for more info in protocol page 37)

The patients enrolled in the study will be randomized 2:1 in this study.

Crovalimab dosing
A single IV dose of crovalimab at 1000 mg (≥ 40 to ≤100 kg) or 1500 mg (≥ 100 kg) will be administered in this study. The goal of the single dose treatment is to achieve rapid and complete C5 activity inhibition for a short term.
Data from Studies BP39144 and YO42311 in healthy subjects and PNH patients indicate that crovalimab serum concentration above 100 g/mL achieves complete complement inhibition. In the therapeutic use of C5 inhibitors, regardless of indication (e.g., PNH, aHUS, neuromyelitis optica, myasthenia gravis), there has been minimal evidence to date to support that less-than-complete complement inhibition is an acceptable therapeutic approach.

End of the study
The end of this study is defined as the date when the last patient's last visit occurs, or
the date at which the last data point is received from the last patient on study, whichever occurs later. The end of the study is expected to occur approximately 322 days or approximately 10.5 months after the last patient is enrolled.

Brief summary of the study: Arabic

خلفية عن مرض الخلايا المنجلية
مرض الخلايا المنجلية (SCD) هو اضطراب وراثي جسمي متنحي ناجم عن وراثة طفرة نقطية في الموضع 6 في جين β-globin، مما يؤدي إلى استبدال حمض الجلوتاميك بحمض أميني أساسي (βS). إنه يؤثر على ملايين المرضى الذين يقدر عددهم بحوالي 300.000 إلى 400.000 طفل حديث الولادة سنويًا.

يقوم المبلمر بتشويه خلايا الدم الحمراء إلى شكل منجل مع ريولوجيا غير طبيعية. تساهم الصلابة المتزايدة وانخفاض تشوه كرات الدم HbS الحمراء المنجلية في انسداد الأوعية الدموية الدقيقة والعرض المميز لنوبات انسداد الأوعية الدموية الحادة المؤلمة لدى المرضى الذين يعانون من مرض فقر الدم المنجلي. تتميز نوبات انسداد الأوعية الدموية بنقص التروية وإصابة إعادة ضخ الدم، والتي يمكن أن تؤثر على أي جهاز عضوي في الجسم.

يمكن أن تتراوح النوبات المؤلمة الحادة، من العلاج في المنزل إلى الحاجة إلى دخول المستشفى، ويمكن أن تكون معقدة بسبب مظاهر الخلايا المنجلية الحادة الإضافية بما في ذلك متلازمة الصدر الحادة وعزل الكبد و/أو الطحال. تتمتع خلايا الدم الحمراء المنجلية بعمر أقصر بكثير نتيجة لانحلال الدم المزمن داخل الأوعية وخارج الأوعية الدموية الذي يسبب فقر الدم المزمن. يتسبب انحلال الدم المزمن في تنشيط بطانة الأوعية الدموية المزمن مما يؤدي إلى خلل في الأوعية الدموية يمكن أن يظهر سريريًا على شكل تصلب الأوعية الدموية وارتفاع ضغط الدم الرئوي وفشل القلب الانبساطي وتلف الكلى. يؤدي إطلاق المحتويات داخل الخلايا أيضًا إلى التهاب مزمن معقم مع تنشيط كريات الدم البيضاء والصفائح الدموية والخلايا البطانية وتوليد أنواع الأكسجين التفاعلية. بالإضافة إلى ذلك، قد يؤدي مرض فقر الدم المنجلي أيضًا إلى فقر دم مزمن متوسط إلى شديد، وخلل في المناعة، وألم مزمن، وتلف تدريجي للأعضاء النهائية في الرئتين والقلب والكلى والجهاز العصبي المركزي.

تساهم هذه المضاعفات الحادة والمزمنة لمرض فقر الدم المنجلي في ارتفاع معدلات الإصابة بالمرض والوفيات بين هذه الفئة من المرضى.

تعد إدارة/علاج مرض الخلايا المرضية أمرًا معقدًا ويعتمد على عمر المريض والأمراض المصاحبة والنمط الظاهري للمرض. في المرضى الذين تم تشخيصهم في فترة حديثي الولادة، أدى التوجيه الاستباقي والرعاية الداعمة بالعلاج الوقائي بالمضادات الحيوية واللقاحات إلى تحسين نتائج الطفولة.

على الصعيد العالمي، يقتصر علاج مرض فقر الدم المنجلي على الهيدروكسي يوريا، الذي يتمتع بفعالية في تعديل المرض، ونقل الدم، وغيرها هو التدخل العلاجي الوحيد المتاح؛ ومع (HSCT) من الرعاية الداعمة للمضاعفات الحادة والمزمنة. يعتبر زرع الخلايا الجذعية المكونة للدم ذلك، فهو محدود بتوافر الجهات المانحة والسمية المرتبطة بالإجراءات.
تسلط بيانات معدلات المراضة والوفيات الضوء على الاحتياجات غير الملباة في مرض فقر الدم المنجلي. على الرغم من أن التقدم الطبي قد أدى عامًا، خاصة في60إلى متوسط يزيد عن HbSβ0 أو HbSS إلى تحسين كبير في متوسط العمر المتوقع لدى المرضى الذين يعانون من عامًا من عامة السكان ويظل عبء المراضة الناتج عن المرض30البلدان ذات الموارد العالية، إلا أن متوسط العمر المتوقع لا يزال أقل بنحو مرتفعًا.

لمرض فقر الدم المنجلي - C5 - تثبيط المكمل
مجتمعة، تشير البيانات المتاحة من المرضى الذين يعانون من مرض فقر الدم المنجلي، وفي النماذج غير السريرية في المختبر وفي الجسم الحي إلى أن المكمل يتم تنشيطه في المرضى الذين يعانون من مرض فقر الدم المنجلي، وتشير إلى دور في الفسيولوجيا المرضية في مجالات متعددة. تم الكشف عن التنشيط التكميلي في المرضى الذين يعانون من حالة مستقرة في مرض الخلايا المنجلية وبالتزامن مع نوبات انسداد الأوعية الدموية في المرضى الذين يعانون من مرض C5 الحادة. تشير نماذج التنشيط التكميلي في المختبر وفي الجسم الحي إلى تأثيرات متعددة محتملة لتثبيط الخلايا المنجلية، والتي تشمل الوقاية من تنشيط بطانة الأوعية الدموية عن طريق الهيم الحر، وانخفاض معدل انحلال الدم، وانخفاض انسداد الأوعية الدموية، وتحسين الالتهاب المزمن، و تقليل تلف الأعضاء النهائية. تدعم الأدلة المنشورة التجارب الاستكشافية للتثبيط التكميلي في المرضى الذين يعانون من مرض فقر الدم المنجلي، والتي قد تلبي الاحتياجات الطبية غير الملباة في هذا المرض، وذلك باستخدام آلية لا تتداخل مع العلاجات الحالية.

تأثير كروفاليماب
مما يجعله مرشحًا مناسبًا لاستكشاف دور مكمل C5، يحث كروفاليماب على تثبيط سريع وكامل للمسار المكمل الطرفي من خلال استهداف الاستهداف في علاج مرض فقر الدم المنجلي.

هدف الدراسة BO42452
بتقييم السلامة والحركية الدوائية والديناميكية الدوائية وفعالية كروفاليماب مقارنة مع الدواء الوهمي لإدارة نوبات انسداد BO42452 ستقوم الأوعية الدموية الحادة غير المعقدة في المرضى الذين يعانون من مرض فقر الدم المنجلي. (يرجى التحقق من الأهداف ونقطة النهاية في قسم 34، الصفحة 2البروتوكول).
تم تصميم هذه الدراسة العشوائية متعددة المراكز والمضبوطة بالعلاج الوهمي ومزدوجة التعمية لتقييم سلامة (هدف الدراسة الأساسي) والحركية الدوائية والديناميكا الدوائية وفعالية كروفاليماب مقارنة مع الدواء الوهمي لإدارة نوبات انسداد الأوعية الدموية الحادة غير المعقدة في المرضى البالغين والمراهقين الذين يعانون من مرض فقر الدم المنجلي.

تصميم الدراسة BO42452
40 عامًا ووزن ≥12-55 موقعًا على مستوى العالم)، تتراوح أعمارهم بين 15-10 مريضًا (في حوالي 30ستسجل هذه الدراسة ما يقرب من وسيقدمون إلى غرفة الطوارئ/الطوارئ أو إلى منشأة طبية حادة مع HbSβ0، HbSS أو كجم، مصابين بالنمط الجيني لمرض الخلايا المنجلية، نوبات انسداد الأوعية الدموية الحادة غير المعقدة. سيتم استبعاد المرضى الذين يعانون من مضاعفات حادة مثل متلازمة الصدر الحادة، أو القساح أو عزل الكبد أو الطحال وما إلى ذلك، أو الذين يعانون من آلام غير نمطية أو غير مرتبطة بنوبات انسداد الأوعية الدموية الحادة غير المعقدة، من الفحص. سيتم توثيق مضاعفات نوبات انسداد الأوعية الدموية التي تتطور بعد إدارة علاج الدراسة وأثناء العلاج في المستشفى. المرضى الذين يصابون بمضاعفات بعد الفحص، ولكن قبل إدارة علاج الدراسة، قد لا يعودون مؤهلين.
(فحص أزمة نوبات انسداد الأوعية الدموية) عندما يعاني المريض من نوبات انسداد الأوعية الدموية إلى2يتم بعد ذلك إجراء زيارة الفحص رقم قبل بدء تقييمات الدراسة (يجب توثيق هذا1غرفة الطوارئ/الطوارئ أو المنشأة الطبية الحادة. يجب تأكيد موافقة المريض من زيارة الفحص رقم التأكيد). بمجرد تأكيد موافقة المريض، يجب تقييم جميع معايير الأهلية المتبقية. (ارجع إلى تصميم الدراسة لمزيد من المعلومات في صفحة 37البروتوكول)

في هذه الدراسة2:1سيتم اختيارهم بصورة عشوائية المرضى المسجلين في الدراسة .

جرعات كروفاليماب
كجم) في هذه100 مجم (≤ 1500 كجم) أو 100 إلى ≤40 مجم (≥ 1000سيتم إعطاء جرعة واحدة من كروفاليماب في الوريد بمقدار لفترة قصيرة C5 الدراسة. الهدف من العلاج بجرعة واحدة هو تحقيق تثبيط سريع وكامل لنشاط.
إلى أن تركيز مصل كروفاليماب PNH في الأشخاص الأصحاء ومرضى YO42311 وBP39144 تشير البيانات المستمدة من الدراسات PNH، بغض النظر عن الإشارة (على سبيل المثال، C5 جم / مل يحقق تثبيطًا مكملاً كاملاً. في الاستخدام العلاجي لمثبطات100أعلى من التهاب النخاع العصبي البصري، الوهن العضلي الوبيل)، كان هناك الحد الأدنى من الأدلة حتى الآن لدعم أن تثبيط المكمل الأقل من aHUS، الكامل هو نهج علاجي مقبول.

نهاية الدراسة
يتم تعريف نهاية هذه الدراسة على أنها تاريخ آخر زيارة للمريض، أو التاريخ الذي يتم فيه استلام آخر نقطة بيانات من آخر مريض قيد الدراسة، شهرًا من تسجيل آخر مريض10.5 يومًا أو حوالي 322أيهما يحدث لاحقًا. ومن المتوقع أن تتم نهاية الدراسة بعد حوالي .

Health conditions/problem studied: Specify

This study is tackling the management of acute uncomplicated vaso occlusive episodes (voe) in patients with sickle cell disease (SCD). This study will enroll approximately 30 patients (at approximately 10-15 sites globally), aged 12-55 years old and ≥40 kg, with sickle cell disease genotype of HbSS or HbSβ0, presenting to the ER/ED or acute medical facility with an acute uncomplicated vaso-occulsive episodes.

Interventions: Specify

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

The placebo will be an aqueous, isotonic, and sterile solution with a similar pH value as the crovalimab drug product. It should be handled, stored, and used in the same manner as crovalimab. The placebo will be filled into the same primary container as the crovalimab drug product and will be administered by IV infusion with the same volume as weight-based crovalimab.

Approximately 30 patients with SCD presenting to an ER/ED or acute medical facility with an acute uncomplicated VOE and meeting all eligibility criteria will be randomized 2:1 in this study.

Patients in this study will receive a single IV dose of crovalimab or placebo according to a weight-based dosing approach
A single IV dose of crovalimab at 1000 mg (≥ 40 to ≤100 kg) or 1500 mg (≥ 100 kg) will be administered in this study.

Study treatment should be administered no longer than 12 hours following the initial evaluation in the ER/ED or acute medical facility for the VOE

Key inclusion and exclusion criteria: Inclusion criteria

Key Inclusion Criteria

Screen Visit #1 (Initial Screen)
●Signed ICF or Assent Form (as determined by patient's age and individual site and country standards)
●Age >= 12 to <=55 years at time of signing ICF or Assent Form, and VOE presentation
●Body weight >=40 kg
●Willingness and ability to comply with all study visits and procedures
●Confirmed diagnosis of HbSS (SCD genotype of sickle cell anemia) or HbSβ0 (SCD genotype of sickle cell beta zero thalassemia)
●Vaccination against N. meningitidis serotypes A, C, W, and Y prior to initiation of study treatment. Vaccination against serotypes A, C, W, and Y should have been received < 3 years prior to initiation of study treatment, or must be up to date in accordance with the most current local guidelines or SOC, as applicable for patients with complement deficiency and SCD. If vaccination against serotypes A, C, W, and Y is not required per local SOC, the Advisory Committee on Immunization Practices (ACIP) 2020 guidelines should be used. Vaccination against serotype B should be administered in accordance with the most current local guidelines or SOC for patients with complement deficiency and SCD. Vaccination currency against serotypes A, C, W, Y, and B should be maintained throughout the study, including the safety follow-up, per local guidelines.

– If vaccination(s) are incomplete or vaccination status is unknown at VOE presentation, or vaccination(s) were received < 2 weeks before treatment administration, appropriate antibiotic prophylaxis per local clinical practice must be initiated. Antibiotic prophylaxis should be continued until the required vaccination(s) are completed and for an additional 2 weeks after completion

●Vaccinations against H. influenzae type B and S. pneumoniae in accordance with most current SCD-specific guidelines or local SOC. If the vaccination(s) are not required per local guidelines, the ACIP guidelines should be used. Vaccination currency should be maintained throughout the study, including the safety follow-up, per local guidelines.

– If vaccination(s) are incomplete or vaccination status is unknown at VOE presentation, or vaccination(s) were received < 2 weeks before treatment administration, appropriate antibiotic prophylaxis per local clinical practice must be initiated. Antibiotic prophylaxis should be continued until the required vaccination(s) are completed and for an additional 2 weeks after completion

●Patients who have been vaccinated (partially or in full) against SARS-CoV-2 with a locally approved vaccine are eligible to be enrolled in the study, as long as it has been 3 days or more after inoculation with the vaccine.

Screen Visit #2 (VOE Presentation Screen)
●All criteria from Screen Visit #1 must be reconfirmed at Screen Visit #2
●Diagnosis of an acute uncomplicated VOE (for definition see Section 2.4.1), that requires admission to a hospital and treatment with parenteral opioid analgesics
●Pain score >= 2 as measured with the NRS on a 0-10 scale
●Ability to receive the single dose of study treatment within 12 hours from initial evaluation in the ER/ED or acute medical facility for the VOE (i.e., first vital signs measurements or first evaluation by a medical professional, whichever is first)
●Adequate hepatic function, including ALT < 3 x ULN and no clinical signs or known laboratory/radiographic evidence that are consistent with cirrhosis
●Adequate renal function, defined as creatinine clearance by the Chronic Kidney Disease Epidemiology Collaboration formula >= 30 mL/min/1.73 m2; patients on dialysis will not be eligible for the study
●Hemoglobin >=5 g/dL
●Platelet count >=100,000/µL
●Patients receiving sickle cell therapies (e.g., hydroxyurea, crizanlizumab, L-glutamine, voxelotor, etc.) must be on a stable dose for >= 28 days prior to VOE presentation
●For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception as defined below:
– Women must remain abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for 322 days (approximately 10.5 months) after the dose of study treatment
– A woman is considered to be of childbearing potential if she is post-menarchal, has not reached a post-menopausal state (>= 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations
– Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices
– The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and

information about the reliability of abstinence will be described in the local ICF.

Kindly refer to the inclusion criteria protocol in section 4.1.1

Key inclusion and exclusion criteria: Gender

Both

Key inclusion and exclusion criteria: Specify gender

Key inclusion and exclusion criteria: Age minimum

12

Key inclusion and exclusion criteria: Age maximum

55

Key inclusion and exclusion criteria: Exclusion criteria

Exclusion Criteria:
Screen Visit #1 (Initial Screen)
●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 center, day hospital, etc.), as determined by medical history or by patient recall
●History of hematopoietic stem cell transplant
●Known or suspected hereditary complement deficiency
●History of hypersensitivity, allergic, or anaphylactic reactions to any ingredient contained in crovalimab, including hypersensitivity to human, humanized, or murine monoclonal antibodies or known hypersensitivity to any constituent of the product
●Current or previous treatment with a complement inhibitor therapy (e.g., crovalimab, eculizumab, or ravulizumab)
Screen Visit #2 (VOE Presentation Screen)
●All criteria from Screen Visit #1 must be reconfirmed at Screen Visit #2
●pain related to the current VOE ongoing for > 48 hours prior to VOE presentation
●Major surgery and/or hospitalization for any reason within 30 days prior to VOE presentation
●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
●Presentation with a critical illness necessitating ICU or critical care admission
●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 >= 38.5oC (101.3oF), 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
- Patients with uncomplicated infections (e.g., uncomplicated urinary tract infections, uncomplicated acute otitis media, streptococcal pharyngitis, minor viral infections) may be included as per investigator assessment
●Presence of fever >= 38oC (100.oF)
●Infection requiring hospitalization or treatment with IV antibiotics within the prior 28 days, or oral antibiotics within the prior 14 days of VOE presentation
– Patients on prophylactic antibiotics may be included
●History of N. meningitidis infection within 6 months prior to VOE presentation
●Known HIV infection with a documented CD4 count <200 cells/µL within 24 weeks prior to VOE presentation
●Transfusion or receipt of blood products within 3 months prior to VOE presentation or as part of BSC regimen for the current VOE, or current participation in a chronic transfusion protocol
●Immunized with a live attenuated vaccine within 30 days prior to VOE presentation
●Pregnant or breastfeeding, or intending to become pregnant during the study or within 322 days (approximately 10.5 months) after the study drug administration
– Women of childbearing potential must have a documented negative pregnancy test result (urine or serum). If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test
●Participation in another interventional treatment study with an investigational agent or use of any experimental therapy within the prior 28 days of VOE presentation or within five half-lives of that investigational product, whichever was greater
●Substance abuse within 12 months prior to VOE presentation, in the investigator's judgment
●Concurrent disease, treatment, procedure, surgery, or abnormality in clinical laboratory tests that could interfere with the conduct of the study, may pose any additional risk for the patient, or would, in the opinion of the investigator, preclude the patient's safe participation in and completion of the study
●
Kindly refer to the inclusion criteria in protocol in section 4.1.1

Type of study

Interventional

Type of intervention

Pharmaceutical

Type of intervention: Specify type

N/A

Trial scope

Other

Trial scope: Specify scope

N/A

Study design: Allocation

Randomized controlled trial

Study design: Masking

Blinded (masking used)

Study design: Control

Placebo

Study phase

1

Study design: Purpose

Treatment

Study design: Specify purpose

N/A

Study design: Assignment

Parallel

Study design: Specify assignment

N/A

IMP has market authorization

No

IMP has market authorization: Specify

Name of IMP

Crovalimab

Year of authorization

Month of authorization

Type of IMP

Others

Pharmaceutical class

Crovalimab is a novel, humanized anti-complement component 5 (C5) monoclonal antibody. Crovalimab binds to C5 with high affinity, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9 (membrane attack complex [MAC]). Crovalimab is based on Sequential Monoclonal Antibody Recycling Technology (SMART-Ig) (Recycling Antibody) (Fukuzawa et al. 2017) with pH-dependent antigen binding allowing for efficient target disposal, and enhancement of neonatal fragment crystallizable receptor binding to improve antibody recycling efficiency. These characteristics result in a prolonged half-life and prolonged complement inhibition.The physicochemical properties of crovalimab support the development of a high concentration formulation. The combination of the SMART-Ig and the highly concentrated formulation will enable up to every 4 weeks (Q4W) subcutaneous (SC) dosing. Based on clinical data from patients with paroxysmal nocturnal hemoglobinuria (PNH), nonclinical pharmacology and pharmacodynamic (PD) data, crovalimab is expected to achieve consistent C5 inhibition throughout the dosing interval.

Therapeutic indication

Study indication: Crovalimab is under developement for the Management of Acute Uncomplicated Vaso-Occlusive Episodes (VOE) in Patients With Sickle Cell Disease (SCD) (Therapeutic indication for the submitted study BO42452)

Therapeutic benefit

Multiple studies have demonstrated markers of alternative pathway and terminal complement pathway activation in patients with SCD (Chudwin et al. 1994; Mold et al. 1995; Wang et al. 2011; Gavriilaki et al. 2019; Roumenina et al. 2020). Complement activation has been described in patients with SCD at baseline (Roumenina et al. 2020), in acute pain crisis (Mold et al. 1995), and in those with DHTR (Roumenina et al. 2019). Mechanisms for complement activation in patients with SCD may be multi-factorial. A recent study found that the complement activation in SCD may be occurring on endothelial cells as a result of free heme activation of toll-like receptor 4,
leading to increased P-selectin expression, which anchors activated C3 fragments C3b and C3(H2O), triggering alternative pathway activity on endothelial cells (Merle et al. 2019). This suggests a mechanism for complement activation in the chronic
steady state in SCD from products of chronic hemolysis. This mechanism is supported by in vitro studies in whole blood of healthy volunteers, which have shown dose-response activation of terminal complement triggered by increasing amounts of
free heme (Thomas et al. 2019). Other studies have shown complement pathway activation through the alternative pathway from membrane phospholipid changes occurring in HbSS RBCs (Wang et al. 1993; Chudwin et al. 1994). Further, sickled RBCs have been shown to have increased susceptibility compared with normal erythrocytes to lysis by the terminal complement complex (Test and Woolworth 1994), suggesting a possible amplification loop in which hemolysis products activate complement, which promotes further destruction of sickled RBCs. Lastly, a link between complement activation and the dense, dehydrated cells that play a role in the pathophysiology of SCD has been demonstrated in whole blood of patients with SCD. Blood levels of soluble complement 5b 9 (sC5b-9), a marker of terminal complement pathway activation, were positively correlated with the percentage of dense sickle cells (Roumenina et al. 2020). In addition, expression of complement regulators on dense sickle cells is reduced (Roumenina et al. 2020). This could make these cells more susceptible to complement -mediated lysis.

Study model

N/A

Study model: Explain model

N/A

Study model: Specify model

N/A

Time perspective

N/A

Time perspective: Explain time perspective

N/A

Time perspective: Specify perspective

N/A

Target follow-up duration

Target follow-up duration: Unit

Number of groups/cohorts

Biospecimen retention

Samples with DNA**

Biospecimen description

Samples for laboratory assessments for hematology (including reticulocytes), chemistry
(including LDH), pharmacokinetics, ADA, pharmacodynamics and biomarkers will be
taken as per schedule of assessment in the protocol

Local Laboratory Assessments
Samples for the following laboratory tests will be sent to the study site's local laboratory
for analysis:
- Hematology: RBC count, hemoglobin, hematocrit, platelet count, WBC count, and
differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes,
other cells), and reticulocytes
- Chemistry panel (serum or plasma): sodium, potassium, chloride, bicarbonate, or
total carbon dioxide (if considered SOC for the region), glucose,

BUN or urea,
creatinine, magnesium, total and direct bilirubin, alkaline phosphatase, ALT, AST,
and LDH
- Patients living in and/or traveling to/from a malaria endemic area within
1 month prior to enrollment will have a malaria microscopy or malaria RDT
performed per local guidelines (on Day 1 prior to randomization)
- Pregnancy test: All women of childbearing potential will have a pregnancy test at
screening (serum or urine). Additionally at the end of the study, a urine pregnancy
test will be performed by the patient at home no more than 2 days before the
Day 322 telephone call. The patient should report the result of the pregnancy test
during the telephone call. At sites in France, the urine pregnancy test at the end of
the study will be performed at the Day 322 site visit. If a urine pregnancy test is
positive, it must be confirmed by a serum pregnancy test.

Hematology and chemistry labs that are not mandatory per protocol during
hospitalization, but are conducted as routine assessments according to local clinical practice, should be documented on the eCRF.

Central Laboratory Assessments
The following samples will be sent to one or several central laboratories, to the Sponsor,
or to a designee for analysis:
- Serum PK samples
- Serum ADA samples
- Plasma and serum samples for PD biomarkers (including total CH50 measurement
by LIA, total and free complement C5 concentration, and sC5-b9 concentration)
- Plasma and serum samples for exploratory biomarkers
- Urine samples for exploratory biomarkers
- Blood sample for clinical genotyping

Exploratory biomarker research may include, but will not be limited to markers of
hemolysis, immune cell activation, inflammation, endothelial/vascular damage, and
end-organ (e.g., kidney) injury.
The PK, PD, ADA, and exploratory biomarker assessments will be conducted as
described in Appendix 1 and Appendix 2 during the hospitalization period, and
Appendix 3 during the observational period. Whenever possible, PK, PD and ADA
samples should be collected at the same time. Steady state SCD exploratory biomarker
samples (plasma/serum and urine) at Screen Visit #1 (initial screen) should only be
collected if this visit is conducted at an outpatient visit prior to VOE presentation, and
only after the main ICF is signed; it should otherwise be skipped. All pre-dose baseline
samples at VOE presentation must only be collected after the patient has been enrolled
on the study and must be within 24 hours before study treatment administration. Day 28
and Day 84 PK, PD, ADA, and biomarker samples will be collected at study site visits
during the observational period. However, if the patient continues to be hospitalized at
Day 28 and/or Day 84 for any reason, these samples should be collected in the hospital
on these days.

A mandatory blood sample for clinical genotyping will be collected at screening
(see Appendix 1 of the protocol) or if the sample is missed at screening, it can be collected at any other
timepoint during hospitalization or after discharge. Whole genome sequencing (WGS)
data may be generated from the DNA obtained from blood, but with the objective to
analyze C5 polymorphisms and other complement or SCD-related gene polymorphisms.
Only one clinical genotyping sample is required per patient. If the patient gives consent,
the remainder of the clinical genotyping samples (blood) and their derivatives (DNA) will
be stored under the Research Biosample Repository (RBR) policy, otherwise the
remainder will be destroyed.
For sampling procedures, storage conditions, and shipment instructions, see the
laboratory manual. Unless the patient gives specific consent for his or her leftover
samples to be stored for optional exploratory research (see Section 4.5.14),
biological samples will be destroyed no later than 5 years after the final Clinical Study
Report has been completed.
When a patient withdraws from the study, samples collected prior to the date of
withdrawal may still be analyzed, unless the patient specifically requests that the
samples be destroyed, or local laws require destruction of the samples. However,
if samples have been tested prior to withdrawal, results from those tests will remain as
part of the overall research data. Data arising from sample analysis, including data on
genomic variants, will be subject to the confidentiality standards described in
Section 8.4 of the protocol
Given the complexity and exploratory nature of exploratory biomarker analyses, data
derived from these analyses will generally not be provided to study investigators or
patients unless required by law. The aggregate results of any conducted research will
be available in accordance with the effective Sponsor policy on study data publication.

Target sample size

30

Actual enrollment target size

Date of first enrollment: Type

Actual

Date of first enrollment: Date

26/03/2022

Date of study closure: Type

Actual

Date of study closure: Date

30/04/2025

Recruitment status

Recruiting

Recruitment status: Specify

Date of completion

IPD sharing statement plan

Yes

IPD sharing statement description

The Sponsor maintains confidentiality standards by coding each patient enrolled in the
study through assignment of a unique patient identification number. This means that
patient names are not included in datasets that are transmitted to any Sponsor location.
Patient medical information obtained by this study is confidential and may be disclosed
to third parties only as permitted by the ICF (or separate authorization for use and
disclosure of personal health information) signed by the patient, unless permitted or
required by law.
Medical information may be given to a patient's personal physician or other appropriate
medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data
derived from these analyses will generally not be provided to study investigators or
patients unless required by law. The aggregate results of any conducted research will
be available in accordance with the effective Sponsor policy on study data publication.
Data generated by this study must be available for inspection upon request by
representatives of national and local health authorities, Sponsor monitors,
representatives, and collaborators, and the IRB/EC for each study site, as appropriate.
Study data, which may include data on genomic variants, may be submitted to
government or other health research databases or shared with researchers, government
agencies, companies, or other groups that are not participating in this study. These data
may be combined with or linked to other data and used for research purposes, to
advance science and public health, or for analysis, development, and commercialization
of products to treat and diagnose disease. In addition, redacted Clinical Study Reports
and other summary reports will be provided upon request.

Additional data URL

Admin comments

Trial status

Approved

Secondary Identifying Numbers

Full name of issuing authority	Secondary identifying number
EU CT NUMBER	2022-502546-26-00

Sources of Monetary or Material Support

Name
F. HOFFMANN-LA ROCHE LTD

Secondary Sponsors

No Sponsors

Contact for Public/Scientific Queries

Contact type	Contact full name	Address	Country	Telephone	Email	Affiliation
Public	Adlette Inati	Tripoli, El Maarad street - Tripoli Lebanon	Lebanon	+961 3228033	adletteinati@outlook.com	Hematologist at NINI Hospital
Scientific	Adlette Inati	Tripoli, El Maarad street - Tripoli Lebanon	Lebanon	+961 3228033	adletteinati@outlook.com	Hematologist at NINI Hospital
Public	Ali Taher	AUBMC - Cairo STreet - Beirut Lebanon	Lebanon	00961-1-350000	ataher@aub.edu.lb	Oncologist - Hematologist at AUBMC
Scientific	Ali Taher	AUBMC - Cairo STreet - Beirut Lebanon	Lebanon	00961-1-350000	ataher@aub.edu.lb	Oncologist - Hematologist at AUBMC

Centers/Hospitals Involved in the Study

Center/Hospital name	Name of principles investigator	Principles investigator speciality	Ethical approval
NINI HOSPITAL	Adlette Inati	Hematologist	Approved
AUBMC	Ali Taher	Hematologist - Oncologist	Approved

Ethics Review

Ethics approval obtained	Approval date	Contact name	Contact email	Contact phone
American University of Beirut Medical Center	20/02/2024	AUB IRB	irb@aub.edu.lb	T +961 1 35 00 00 – Ext 5445
Nini Hospital	25/03/2024	Dr Elias Bitar	NA	06431400

Countries of Recruitment

Name
Brazil
France
Italy
South Africa
Spain
Netherlands
United Kingdom
United States of America
Lebanon
Kenya

Health Conditions or Problems Studied

Condition	Code	Keyword
Acute Uncomplicated Vaso-Occlusive Episodes (VOE) in Patients With Sickle Cell Disease (SCD)	Sickle-cell disorders (D57)	sickle cell disease

Interventions

Intervention	Description	Keyword
Crovalimab	Crovalimab will be 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.	Crovalimab
Placebo	The placebo will be an aqueous, isotonic, and sterile solution with a similar pH value as the crovalimab drug product. It should be handled, stored, and used in the same manner as crovalimab. The placebo will be filled into the same primary container as the crovalimab drug product and will be administered by IV infusion with the same volume as weight-based crovalimab	Placebo

Primary Outcomes

Name	Time Points	Measure
The safety objective for this study is to evaluate the safety of crovalimab compared with placebo	end of study	Incidence and severity of adverse events, with severity determined according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 5.0 (CTCAE v5.0) Change from baseline in targeted vital signs and clinical laboratory test results Incidence and severity of infusion-related reactions and hypersensitivity
The PK objective for this study is to characterize the crovalimab PK profile	end of study	Serum concentrations of crovalimab over time Relationships between drug exposure and pharmacodynamics, efficacy or safety endpoints of crovalimab (patients randomized to crovalimab)
The PD objective for this study is to evaluate PD biomarkers that can provide evidence of crovalimab activity	end of study	Change over time in PD biomarkers, including total complement activity (CH50) measured by a LIA, total and free complement component 5 (C5) concentration, and sC5b-9 concentration
The efficacy objective for this study is to characterize the efficacy of crovalimab compared with placebo	end of study	Time to improvement of the primary acute uncomplicated VOE (for definition, see Section 2.4.1) from baseline, defined as the first achieved from the following criteria: – Confirmed decrease in pain score of at least 2 points from the maximal pre-dose 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 Numerical Rating Scale [NRS] on a 0□10 scale) AND transition to oral pain medications for a minimum of 6 hours after the completion of 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 equivalents per kilogram units (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 pre-dose 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 (ICU)/critical care admission for SCD-related complications from baseline to the 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

Key Secondary Outcomes

Name	Time Points	Measure
The immunogenicity objective for this study is to evaluate the immune response to crovalimab	End of study	Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs during the study (patients randomized to crovalimab) Potential effects of ADAs on efficacy, safety, or PK endpoints
The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that are predictive of response to crovalimab (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with resistance to crovalimab, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), or can increase the knowledge and understanding of disease biology and drug safety,	End of study	Observed value and change over time in exploratory biomarkers including but not limited to markers of hemolysis, immune cell activation, inflammation, endothelial/vascular damage, and end-organ injury Relationship between biomarkers in blood and efficacy, safety, pharmacokinetics, immunogenicity, or other biomarker endpoints

Trial Results

Summary results

Study results globally

Date of posting of results summaries

Date of first journal publication of results

Results URL link

Baseline characteristics

Participant flow

Adverse events

Outcome measures

URL to protocol files