A RANDOMIZED DOUBLE-BLIND PHASE IIA STUDY EVALUATING THE EFFICACY, SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF CROVALIMAB AS ADJUNCT TREATMENT IN PREVENTION OF VASO-OCCLUSIVE EPISODES (VOE) IN SICKLE CELL DISEASE (SCD)

24/10/2025 21:34:18

Main Information

Primary registry identifying number
LBCTR2023115331

Protocol number
BO42451

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
13/08/2024

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

Public title
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Acronym
Crosswalk-c

Scientific title
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Brief summary of the study: English
Sickle cell disease (SCD) is an autosomal recessive genetic disorder caused by the inheritance of a point mutation at position 6 in the □-globin gene, replacing a glutamic acid with a valine (S). SCD affects millions of patients worldwide, with an estimated incidence of 300,000-400,000 affected neonates annually
The SCD phenotype is seen with multiple genotypes, including homozygous inheritance of S (HbSS), or heterozygous coinheritance of S with other □-globin variants including C (HbSC), E (HbSE), or -thalassemia (HbS0, or HbS+) . The expression of

sickle □-globin in these genotypes results in the formation of hemoglobin S (HbS), a tetramer of α-globin and sickle □-globin molecules.
HbS, compared to normal adult hemoglobin (HbA and HbA2) has reduced solubility and polymerizes within the RBC when deoxygenated in acidic pH.
The polymerized HbS distorts the Red Blood Cells (RBC) 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 (VOEs) in patients with SCD. Further, sickled RBCs promote abnormal adhesion of erythrocytes with platelets, neutrophils, and endothelial cells that participate in the pathophysiology of vascular occlusion.
VOEs are marked by ischemia and reperfusion injury, which can affect any organ system in the body. Acute painful episodes can range in severity, from being managed at home to requiring hospital admission for pain control, and can be complicated by additional acute sickle cell manifestations including acute chest syndrome (ACS) and hepatic and/or splenic sequestration.
Sickled RBCs have a significantly shorter lifespan as a result of chronic intravascular and extravascular hemolysis causing chronic anemia. The chronic hemolysis generates high levels of circulating free hemoglobin and heme, which saturate natural scavenging mechanisms (haptoglobin, hemopexin) and cause 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
The driving events of sickled, rheologically abnormal RBCs and chronic hemolysis result in broad, multisystem clinical complications of SCD. In addition to the acute painful crises being the most common symptom for which patients seek care, SCD 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 SCD contribute to the significant morbidity and mortality in this patient population.
The management and treatment of SCD is complex and depends on patient features including 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 approaches to SCD are limited to hydroxyurea, which has disease-modifying efficacy, blood transfusion, and other supportive care for acute and chronic complications. In the United States, three additional disease-modifying therapies with non-overlapping mechanisms have been recently approved for the treatment of SCD. These are hydroxyurea, L-glutamine, crizanlizumab, and voxelotor. 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 SCD. Although medical advances have significantly improved life expectancy in patients with HbSS or HbS 0 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
Accumulating nonclinical evidence suggests a role for complement in SCD pathophysiology. Complement activation has been described in patients with SCD at baseline, in acute pain crisis , and in those with a delayed hemolytic transfusion reaction (DHTR) . Complement inhibition may provide a novel mechanism to target SCD
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 RecyclingTechnology (SMART-Ig) (Recycling Antibody) 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.
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.
Published evidence supports exploratory trials of complement inhibition in patients with
SCD, which may address the unmet medical need in this disease, employing a mechanism that does not overlap with current therapies. 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 SCD.
This randomized, multicenter, placebo-controlled, double-blinded Phase IIa study is designed to evaluate the efficacy, safety, and pharmacokinetics of crovalimab compared with placebo as adjunct therapy in the prevention of VOEs in patients with SCD.
The study will enroll approximately 90 patients at approximately 30 sites globally.
The primary efficacy objective for this study is to evaluate the efficacy of crovalimab compared with placebo on the basis of the following endpoint:Annualized rate of medical facility VOEs (AVR).
The secondary efficacy objective for this study is to evaluate the efficacy of crovalimab compared with placebo on the basis of the following endpoints:Annualized rate of home VOE captured by patient report on a handheld device at home; Annualized rate of uncomplicated medical facility VOE (described in primary efficacy objective above); Annualized rate of ACS; Annualized rate of days hospitalized for medical facility VOE (described in primary efficacy objective above); Annualized rate of days hospitalized for treatment of non-VOE complications of SCD; Change in hematologic measures from baseline to Week 49;Time to first medical facility VOE from randomization (described in primary efficacy objective above); Change in urinary albumin-creatinine ratio from baseline to Week 49; Change from baseline to Week 49 in tricuspid regurgitant jet velocity (TRV); Proportion of patients with TRV > 2.5 m/s at Week 49; Change from baseline to Week 49 in Patient-Reported Outcomes Measurement Information System (PROMIS)-Fatigue score in adults.

Study has additional exploratory efficacy objectives. Safety objectives, Pharmacokinetic objective, immunogenicity objective, biomarker objectives.

The screening period of the study will be up to 28 days in length. Patients who do not meet the criteria for participation in this study (screen failure) may qualify for two rescreening opportunities (for a total of three screenings per patient) at the investigator's discretion. The investigator will maintain a record of reasons for screen failures.
Eligible patients will be randomized 1:1 to receive either crovalimab or placebo in addition to their current SCD therapy. Patients in both treatment arms will receive standard treatment for SCD as guided by the treating physician and/or institutional guidelines, including but not limited to treatments currently approved for SCD within each country participating in this study (e.g., hydroxyurea, L-glutamine, crizanlizumab, or voxelotor), pain management treatment (e.g., opioid analgesics, nonsteroidal anti-inflammatory drugs [NSAIDs]), hydration, oxygen, and other BSC.
The primary analysis will be performed when all patients have either completed 48 weeks of the study treatment or have discontinued from the study, whichever occurs first.An initial crovalimab(or matching placebo) intravenous (IV) loading dose will be administered on Week 1 Day 1 followed by 4 once weekly SC doses of the study treatment (refers to crovalimab or placebo) on Week 1 Day 2, then on Weeks 2, 3, and 4. Maintenance dosing will begin at Week 5 and will continue Q4W thereafter, for a total of 48 weeks of treatment. All patients will receive the study treatment according to a weight-based tiered dosing schedule. Study treatment dosing will continue per protocol schedule during any medical facility or home VOE occurring on treatment.

Efficacy assessments will include details of medical facility VOEs (home VOEs, and
hospitalizations for non-VOE complications of SCD (see Section 4.5.1 for definitions).
Additional efficacy assessments will include urinary albumin-creatinine ratio, hematologic
parameters, RBC transfusions, TRV, PRO assessments, and serum and urine Biomarkers.
Safety assessments will include monitoring of risks associated with crovalimab and adverse events including those of special interest vital signs, ECG, physical examination, blood sample analysis for hematologic and biochemical abnormalities, urine analysis, and concomitant medication use.

The proposed dosing for crovalimab in this study is designed to achieve complete
terminal complement activity inhibition across body weights. 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. Potential clinical benefits of C5 inhibition in SCD will be assessed in this study. The proposed dose for this study was selected to achieve complete complement activity inhibition throughout the dosing interval. Dose selection was based on previous data obtained from Studies BP39144 and YO42311 in healthy subjects and PNH patients. The PK/PD relationship established in Studies BP39144 and YO42311 indicated that a serum crovalimab concentration of approximately 100 g/mL achieves complete complement inhibition. The PK/PD relationship is not dependent on the disease; similar PK/PD
relationship is expected in PNH and SCD patients. Similarly to PNH, the objective of crovalimab treatment in SCD patients is to achieve complete complement inhibition, which is achieved with similar crovalimab serum concentrations (i.e., 100 µg/mL); therefore, same dose and dosing regimen as in other indications is proposed in this study
he study plans to enroll patients with SCD (HbSS and HbS0) aged 12-55 years with 2-10 documented VOEs in the 12 months prior to randomization. This exploratory study aims to target a homogenous population related to age and SCD genotype, to minimize interpatient variability and facilitate the interpretation of endpoints. Patients with genotype HbSS or HbS0 were chosen to be the study population to minimize interpatient variability in clinical phenotype. Given the generally milder clinical phenotype of HbS+ SCD and the distinct pathophysiology of hemoglobin SC (HbSC) , patients with these genotypes will not be included for this exploratory study. Enrollment will focus on moderate to severe disease, with a target of 2 but 10 VOEs in the 12 months prior to randomization. Fewer than 2 VOEs in 12 months will not result in sufficient measurable events during the randomized treatment period. Acknowledging the difficulty with distinguishing acute from chronic pain in SCD, patients with 10 VOEs within 12 months prior to randomization will be excluded due to this being potentially indicative of chronic pain or disease control challenges that may not respond to complement inhibition. This approach has been used in other similar studies of VOE prevention.

Brief summary of the study: Arabic

مرض الخلايا المنجلية (SCD) هو اضطراب وراثي جسمي متنحي ناجم عن وراثة طفرة نقطية في الموضع 6 في جين□-جلوبين، مما يؤدي إلى استبدال حمض الجلوتاميك بحمض فالين (S). يؤثر مرض فقر الدم المنجلي على ملايين المرضى في جميع أنحاء العالم، حيث يقدر معدل طفل حديث الولادة سنويا300.000 إلى 400.000 الإصابة بـ
أو الوراثة المتغايرة الزيجوت لـ S (HbSS)، مع أنماط وراثية متعددة، بما في ذلك الوراثة المتماثلة الزيجوت لـ SCD يُرى النمط الظاهري لـ SCD مع متغيرات S □-globin الأخرى بما في ذلك C (HbSC)، أو E (HbSE)، أو الثلاسيميا (HbS0، أو HbS+). يؤدي التعبير عن □-globin وجزيئات S (HbS)، الجلوبين المنجلي في هذه الأنماط الجينية إلى تكوين الهيموجلوبين المنجلية. وهو رباعي جزيئات □-globin قد قلل من قابلية الذوبان والبلمرة داخل كرات الدم الحمراء عند نزع الأكسجين (HbA2 وHbA) مقارنة بالهيموجلوبين الطبيعي البالغ، إن HbS في درجة الحموضة الحمضية.
يشوه HbS خلايا الدم الحمراء (RBC) المبلمر إلى شكل منجل مع ريولوجيا غير طبيعية.
تساهم زيادة صلابة خلايا الدم الحمراء المنجلية وانخفاض تشوهها في انسداد الأوعية الدموية الدقيقة والتمثيل المميز لنوبات الانسداد الوعائي في المرضى المصابين بمرض الخلايا المنجلية. علاوة على ذلك، تعزز خلايا الدم الحمراء المنجلية الالتصاق غير الطبيعي للخلايا الحمراء بالصفائح الدموية والعدلات والخلايا البطانية التي تشارك في الفيزيولوجيا المرضية لانسداد الأوعية الدموية. تتميز (VOEs) المؤلمة الحادة

نوبات انسداد الأوعية الدموية بإصابة نقص التروية الدموية ونقص التروية، والتي يمكن أن تؤثر على أي جهاز عضوي في الجسم. يمكن أن تتراوح النوبات المؤلمة الحادة في شدتها، من أن تدار في المنزل إلى أن تتطلب دخول المستشفى للسيطرة على الألم، ويمكن أن تكون معقدة والاحتجاز الكبدي و/أو الطحالي (ACS) بمظاهر إضافية للخلايا المنجلية الحادة بما في ذلك متلازمة الصدر الحادة.

تتمتع كرات الدم الحمراء المنجلية بعمر أقصر بكثير نتيجة لانحلال الدم المزمن داخل الأوعية وخارج الأوعية الدموية الذي يسبب فقر الدم المزمن. يولد انحلال الدم المزمن مستويات عالية من الهيموجلوبين الحر والهيم، مما يشبع آليات الكسح الطبيعية (هابتوغلوبين، الهيموبكسين) ويسبب 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 معقم مزمن مع تنشيط كريات الدم البيضاء والصفائح الدموية والخلايا البطانية وتوليد أنواع الأكسجين التفاعلية

تؤدي الأحداث الدافعة لخلايا الدم الحمراء المنجلية غير الطبيعية الروماتيزمية وانحلال الدم المزمن إلى مضاعفات سريرية واسعة ومتعددة الأجهزة لمرض الخلايا المنجلية. وبالإضافة إلى أن الأزمات الحادة المؤلمة هي أكثر الأعراض شيوعا التي يسعى المرضى للحصول على الرعاية منها، قد يؤدي مرض الخلايا المنجلية أيضا إلى فقر الدم المزمن المعتدل إلى الشديد والخلل الوظيفي في المناعة والألم المزمن وضرر تدريجي في الأعضاء في الرئتين والقلب والكلى والجهاز العصبي المركزي. تساهم هذه المضاعفات الحادة والمزمنة لمرض الخلايا المنجلية في معدلات الاعتلال والوفاة الكبيرة في هذه الفئة من المرضى.

إن التعامل مع مرض الخلايا المنجلية وعلاجه أمر معقد ويعتمد على خصائص المريض بما في ذلك العمر والأمراض المصاحبة والنمط الظاهري للمرض. في المرضى الذين شخصت حالتهم في فترة ما بعد الولادة، أدى التوجيه التمهيدي والرعاية الداعمة باستخدام العلاج الوقائي بالمضادات الحيوية واللقاحات إلى تحسين نتائج مرحلة الطفولة

على الصعيد العالمي، تقتصر طرق علاج مرض الخلايا المنجلية على هيدروكسي يوريا، والتي تتميز بفاعلية معدلة للمرض، ونقل الدم، وغيرها من الرعاية الداعمة للمضاعفات الحادة والمزمنة. في الولايات المتحدة، تمت الموافقة مؤخرا على ثلاثة علاجات إضافية لتعديل المرض مع آليات غير متداخلة لعلاج مرض الخلايا المنجلية. هذه هيدروكسي يوريا، ل-غلوتامين، كريزانليزوماب، فوكسيلوتور. يعد زرع الخلايا الجذعية المكونة للدم (HSCT) هو التدخل العلاجي الوحيد المتاح؛ ومع ذلك، فهو محدود بسبب توافر المانحين والسمية المرتبطة بالعمليات.

وتسلط بيانات معدلات المراضة والوفيات الضوء على الاحتياجات غير الملباة لداء الخلية المنجلية. على الرغم من أن التطورات الطبية قد حسنت إلى أكثر 0 (HBs) أو النزلة النزفية (HBs) بشكل ملحوظ من متوسط العمر المتوقع للمرضى الذين يعانون من متلازمة الهنتافيروس الرئوية 60من عاما من عامة السكان، ويظل عبء المرض30 عاما، خاصة في البلدان ذات الموارد العالية، لا يزال متوسط العمر المتوقع أقل بنحو المرتفع

تشير مجموعة من الأدلة غير السريرية إلى دور للمكمل في الفيزيولوجيا المرضية لأمراض الخلايا المنجلية. تم وصف التنشيط المتمم لدى المرضى المصابين بمرض الخلايا المنجلية في الوضع الأولي، وفي أزمة الألم الحادة، وفي أولئك الذين لديهم تفاعل مؤخر لنقل الدم (DHTR) . قد يوفر التثبيط المكمل آلية جديدة لاستهداف مرض الخلايا المنجلية

بألفة عالية، مما يمنع انشقاقه إلى C5 يرتبط كروفاليماب ب ب .(C5) 5كروفاليماب هو جسم مضاد أحادي النسيلة، مكون بشري مضاد للمكمل يعتمد كروفاليماب على تقنية إعادة تدوير الأجسام .([MAC] مركب هجوم الغشاء) C5b-9 ويمنع تكوين مركب المكمل الطرفي C5b و C5a (الجسم المضاد لإعادة التدوير) مع ربط المستضد المعتمد على درجة الحموضة مما يسمح بالتخلص (SMART-Ig) المضادة وحيدة النسيلة الفعال من الهدف، وتعزيز ربط المستقبل القابل للتبلور الوليدي لتحسين كفاءة إعادة تدوير الأجسام المضادة. تؤدي هذه الخصائص إلى عمر نصفي طويل وتثبيط المكمل مل مل مل طويل.

ومعطيات علم الأدوية غير السريري ،(PNH) بناء على البيانات السريرية من المرضى الذين يعانون من بيلة الهيموغلوبين الليلي الانتيابي ثابت طوال فترة الجرعات C5 من المتوقع أن يحقق كروفاليماب تثبيط ،(PD) والديناميكا الدوائية.

تدعم الأدلة المنشورة التجارب الاستكشافية للتثبيط التكميلي في المرضى المصابين بمرض الخلايا المنجلية، والتي قد تلبي الاحتياجات الطبية غير الملباة في هذا المرض، باستخدام آلية لا تتداخل مع العلاجات الحالية. يحفز كروفاليماب التثبيط السريع والكامل للمسار التكميلي الطرفي باستهدافه C5، مما يجعله مرشحا مناسبا لاستكشاف دور الاستهداف التكميلي في علاج مرض الخلايا المنجلية.

هذه الدراسة عشوائية، متعددة المراكز ، مراقبة مقابل دواء وهمي، مزدوجة التعمية، المرحلة الثانية، صممت لتقييم فعالية وسلامة وحرائك الدواء لكروفاليماب مقارنة بالدواء الوهمي كعلاج مساعد في الوقاية من نوبات حصر الأوعية الدموية في المرضى المصابين بمرض الخلايا المنجلية.

يوما. يمكن28 موقعا على مستوى العالم. سيكون طول فترة الفحص للدراسة حتى 30 مريضا في نحو 90وستسجل الدراسة ما يقرب من للمرضى الذين لا يستوفون معايير المشاركة في هذه الدراسة (فشل الفحص) أن يكونوا مؤهلين لفرصتي إعادة فحص (لمدة إجمالية تبلغ ثلاثة فحوصات لكل مريض) وفقا لتقدير الباحث. سيحتفظ الباحث بسجل للأسباب التي أدت إلى فشل الفحص.

لتلقي إما كروفاليماب أو الدواء الوهمي بالإضافة إلى علاجهم الحالي لمرض الخلايا1:1سيتم اختيار المرضى المؤهلين بشكل عشوائي بنسبة المنجلية. سيحصل المرضى في كلا جناحي العلاج على علاج قياسي لمرض فقر الدم المنجلي وفقًا لتوجيهات الطبيب المعالج و/أو الإرشادات المؤسسية، بما في ذلك على سبيل المثال لا الحصر العلاجات المعتمدة حاليًا لمرض فقر الدم المنجلي داخل كل بلد مشارك في هذه الدراسة (على سبيل المثال، هيدروكسي يوريا، ل- الجلوتامين، أو كريزانليزوماب، أو فوكسيلوتور)، وعلاج إدارة الألم (مثل المسكنات الأفيونية، والأدوية المضادة للالتهابات غير الستيرويدية [مضادات الالتهاب غير الستيروئيدية])، والترطيب، والأكسجين، وغيرها من BSC.

أسبوعا من علاج الدراسة أو توقفوا عن الدراسة، أيهما يحدث أولا. سيتم48سيتم إجراء التحليل الأولي عندما يكون جميع المرضى قد أكملوا جرعات تحت4 متبوعة ب 1 اليوم 1في الأسبوع (IV) إعطاء جرعة تحميل أولية من دواء فالوريدي (أو دواء وهمي مطابق) عبر الوريد . ستبدأ4 و 3 و 2، ثم في الأسابيع 2 اليوم 1جلدية مرة واحدة أسبوعيا من علاج الدراسة (تشير إلى دواء فالومي أو دواء وهمي) في الأسبوع أسبوعا من العلاج. سيحصل جميع المرضى على علاج48 أسابيع بعد ذلك، لمدة إجمالي 4 وستستمر كل 5جرعات المداومة في الأسبوع الدراسة وفقا لجدول الجرعات المقام على أساس الوزن. ستستمر جرعات العلاج موضوع الدراسة وفقا لجدول البروتوكولات خلال أي نوبة سرية لفازو منزلية أو منشأة طبية تحدث أثناء العلاج.

ستتضمن تقييمات الفعالية تفاصيل النوبات الغشائية الوعائية للمنشأة الطبية (النوبات الغشائية الوعائية المنزلية، وحالات دخول المستشفى ،لمضاعفات النوبات الغشائية غير الوعائية لمرض الخلايا المنجلية. ستتضمن تقييمات الفعالية الإضافية نسبة الألبومين-الكرياتينين في البول والمؤشرات الحيوية للمصل والبول. ستتضمن تقييمات PRO، ومؤشرات TRV، ومعايير أمراض الدم، ونقل خلايا الدم الحمراء، وتقييمات السلامة مراقبة المخاطر المرتبطة بالتكروفاليماب والأحداث الضارة بما في ذلك تلك ذات العلامات الحيوية ذات الاهتمام الخاص، ومخطط كهربية القلب، والفحص البدني، وتحليل عينة الدم للكشف عن التشوهات الدموية والكيميائية الحيوية، وتحليل البول، واستخدام الأدوية بالتزامن.

تم تصميم الجرعات المقترحة للكروفاليماب في هذه الدراسة لتحقيق تثبيط كامل لنشاط المكمل النهائي عبر أوزان الجسم. في الاستخدام العلاجي كان ،(التهاب النخاع العصبي البصري، الوهن العضلي الوبيل ،PNH، aHUS، على سبيل المثال) بغض النظر عن الإشارة ،C5 لمثبطات هناك الحد الأدنى من الأدلة حتى الآن لدعم أن تثبيط المكمل الأقل من الكامل هو نهج علاجي مقبول. سيتم تقييم الفوائد السريرية المحتملة لتثبيط في مرض الخلايا المنجلية في هذه الدراسة. تم اختيار الجرعة المقترحة لهذه الدراسة لتحقيق تثبيط كامل للنشاط التكميلي طوال فترة C5 في الأشخاص الأصحاء YO42311وBP39144 الجرعات. يعتمد اختيار الجرعة على البيانات السابقة التي تم الحصول عليها من الدراسات إلى أن تركيز الكروفاليماب في المصل YO42311وBP39144 التي تم تحديدها في الدراسات PK/PD أشارت العلاقة. PNH ومرضى مماثلة في مرضى PK/PD لا تعتمد على المرض؛ من المتوقع وجود علاقة PK/PD جم/مل يحقق تثبيطا مكملا كاملا. علاقة100بحوالي فإن الهدف من علاج كروفاليماب في مرضى فقر الدم المنجلي هو تحقيق تثبيط مكمل ،PNH ومرضى الخلايا المنجلية. على غرار PNH ميكروغرام / مل)؛ لذلك، يتم اقتراح نفس الجرعة ونظام الجرعات كما100كامل، والذي يتم تحقيقه بتركيزات مصل كروفاليماب مماثلة (أي HbSS) هو الحال في المؤشرات الأخرى في هذه الدراسةتعتزم الدراسة تسجيل المرضى المصابين بمتلازمة الانحلال الورمي التقدمي الثانوي أشهر قبل التوزيع10 عاما مع نوبتين موثقتين الانسداد الوعائي يتراوح عمرهما بين 55 و 12الذين تتراوح أعمارهم بين (HbS0 و العشوائي. تهدف هذه الدراسة الاستكشافية إلى إستهداف مجموعة متجانسة مرتبطة بالسن والنمط الجيني للداء السكري غير صغير الخلايا، لتقليل ليكونوا فئة الدراسة HbS0 أو HbSS التباين بين المرضى وتسهيل تفسير نقاط النهاية. وقد تم إختيار المرضى الذين يعانون من النمط الوراثي S+ لتقليل التباين بين المرضى في النمط الظاهري السريري. وبالنظر إلى النمط الظاهري السريري الأخف بوجه عام لفيروس التهاب الكبد لن يتم تضمين المرضى الذين يعانون من هذه الأنماط الجينية ، (HbSC) SC والفيزيولوجيا المرضية المميزة للهيموغلوبين تحت الجلد SCD نوبات انسداد وعائي في10في هذه الدراسة الاستكشافية. سيركز التسجيل على المرض المتوسط إلى الشديد، مع هدف يتمثل في نوبتين ولكن

شهرا إلى أحداث كافية قابلة للقياس12 السابقة للتوزيع العشوائي. لن يؤدي أقل من نوبتين من نوبات الجهاز الوعائي الخفي خلال 12الأشهر ال 10سيتم إستبعاد المرضى الذين يعانون من ،SCD خلال فترة العلاج العشوائية. إدراكا لصعوبة التمييز بين الألم الحاد والألم المزمن في مرض شهرا قبل التوزيع العشوائي لأن هذا قد يكون مؤشرا على تحديات الألم المزمن أو السيطرة على المرض12نوبات احتكاسية وعائية في غضون .التي قد لا تستجيب للتثبيط المكمل. تم إستخدام هذا النهج في دراسات أخرى مماثلة للوقاية من النوبات الوعائية الخفية

Health conditions/problem studied: Specify

patients with SCD (HbSS and HbSb0) aged 12-55 years with 2-10 documented VOEs in the 12 months prior to randomization. This exploratory study aims to target a homogenous population related to age and SCD genotype, to minimize interpatient variability and facilitate the interpretation of endpoints.

Interventions: Specify

The investigational medicinal products (IMPs) for this study are crovalimab and placebo.
Crovalimab vials will be supplied by the Sponsor as a solution for IV infusion/SC injection from a single-use vial, which contains an extractable volume of 2 mL or 340 mg (nominal) crovalimab. For IV infusion, the crovalimab solution is diluted in 0.9% (w/v) sodium chloride. For SC injection, the crovalimab solution is used undiluted. Patients in this study will receive crovalimab according to a weight-based tiered dosing approach schedule for 48 weeks.
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 and SC injection with equal volume dosing as the weight-based crovalimab.

Eligible patients will be randomized 1:1 to receive either crovalimab or placebo in addition to their current SCD therapy. Patients in both treatment arms will receive standard treatment for SCD as guided by the treating physician and/or institutional guidelines, including but not limited to treatments currently approved for SCD within each country participating in this study (e.g., hydroxyurea, L-glutamine, crizanlizumab, or voxelotor), pain management treatment (e.g., opioid analgesics, nonsteroidal anti-inflammatory drugs [NSAIDs]), hydration, oxygen, and other BSC.

Stratification factors at randomization are:
● Number of VOEs in the 12 months prior to enrollment (< 4 vs. >= 4 VOEs)
● Use of concurrent SCD-directed therapy in any combination (e.g., hydroxyurea, L-glutamine, crizanlizumab, or voxelotor) (yes vs. no)
The primary analysis will be performed when all patients have either completed 48 weeks of the study treatment or have discontinued from the study, whichever occurs first.

An initial crovalimab (or matching placebo) intravenous (IV) loading dose will be administered on Week 1 Day 1 followed by 4 once weekly SC doses of the study treatment (refers to crovalimab or placebo) on Week 1 Day 2, then on Weeks 2, 3, and 4. Maintenance dosing will begin at Week 5 and will continue Q4W thereafter, for a total of 48 weeks of treatment (see Section 4.3.2 for study treatment dosing). All patients will receive the study treatment according to a weight-based tiered dosing schedule. Study treatment dosing will continue per protocol schedule during any medical facility or home VOE occurring on treatment.

Key inclusion and exclusion criteria: Inclusion criteria

Inclusion Criteria
Patients must meet the following criteria for study entry:
●Signed Informed Consent Form (ICF)
●Signed Assent Form when appropriate, 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
●Body weight ≥ 40 kg at screening
●Willingness and ability to comply with the study protocol including scheduled visits, treatment plans, laboratory tests, and other study procedures, including the completion of the HVQ and PRO questionnaires through the use of an electronic device
●Male or female with confirmed diagnosis of sickle cell anemia (HbSS or HbSβ0)
●Two or more (≥ 2) to ≤10 documented VOEs in the 12 months prior to randomization as determined by medical history (VOE should include the occurrence of typical symptoms, a visit to a specific medical facility and/or healthcare professional, and receipt of pain medication as defined for the medical facility VOE endpoint in
●If receiving concurrent SCD-directed therapy (e.g., hydroxyurea, L-glutamine, crizanlizumab, or voxelotor), the patient must have been on a stable dose, except for weight-based titration, with good adherence by the investigator's assessment for a minimum of 3 months prior to study enrollment (Day 1). There should be no plans to modify the patients' dosing throughout the study duration, other than for safety reasons.
●If receiving erythropoietin, the patient must have been prescribed this medication for the preceding 3 months and be dose-stabilized for at least 3 months prior to study enrollment (Day 1).
●Vaccinations:
oVaccination against N. meningitidis serotypes A, C, W, and Y prior to initiation of 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.
oVaccinations against H. influenza type B and S. pneumonia 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.
oNote, if any of the above vaccinations are received < 2 weeks before initiating treatment, appropriate antibiotic prophylaxis per local standard of practice must be initiated. Antibiotic prophylaxis should be continued until 2 weeks after the vaccination is complete.

●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, 3 days or longer after inoculation

●Otherwise appropriate medical history and physical and laboratory evaluation that are acceptable for inclusion in this clinical trial
●Adequate hepatic function, with ALT < 3 xULN at the time of screening; no clinical signs or known laboratory/radiographic evidence consistent with cirrhosis
●Adequate renal function, defined as creatinine clearance ≥ 30 mL/min/1.73 m2 by Chronic Kidney Disease Epidemiology Collaboration formula; patients on dialysis will not be eligible for the study
●For women of childbearing potential, agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:
oWomen must remain abstinent or use contraceptive methods with a failure rate of □ 1% per year during the treatment period and for 46 weeks (approximately 10.5 months) after the final dose of study treatment.
oA woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal 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.
oExamples 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.
oThe 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, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local ICF.
Kindly refer to the inclusion criteria in the protocol p 44

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:
Patients who meet any of the following criteria will be excluded from study entry:
●History of hematopoietic stem cell transplant
●Participating in a chronic transfusion program (preplanned series of transfusions for prophylactic purposes) and/or planning on undergoing an exchange transfusion during the duration of the study. Episodic simple transfusion is permitted.
●History of hypersensitivity, allergic, or anaphylactic reactions to any ingredient contained in the study treatment (crovalimab or placebo), including hypersensitivity to human, humanized, or murine monoclonal antibodies or known hypersensitivity to any constituent of the product
●Received active treatment on another investigational trial within 28 days (or within five half-lives of that agent, whichever is greater) prior to screening visit, or plans to participate in another investigational drug trial
●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
●Hemoglobin <6 g/dL
●Substance abuse within 12 months prior to screening, in the investigator's judgment
●Received prior treatment with crovalimab or other complement inhibitor therapy
●Known or suspected hereditary complement deficiency
●Active systemic bacterial, viral, or fungal infection within 14 days before first drug administration
●Presence of fever (≥380C) within 7 days before the first drug administration
●Immunized with a live attenuated vaccine within 1 month before first drug administration
●Pregnant or breastfeeding, or intending to become pregnant during the study or within 46 weeks (approximately 10.5 months) after the final dose of study treatment
oWomen of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.
●History of malignancy within 5 years prior to screening and up to the first drug administration (Day 1), with the following exceptions:
oPatients with any malignancy appropriately treated with curative intent and the malignancy has been in remission without treatment for > 5 years prior to study drug administration (Day 1) are eligible.
oPatients with curatively treated basal or squamous cell carcinoma of the skin or in situ carcinoma of the cervix at any time prior to study drug administration (Day 1) are eligible.
oPatients with low-grade, early-stage prostate cancer (Gleason score 6 or below, Stage 1 or 2) with no requirement for therapy at any time prior to study drug administration (Day 1) are eligible
●Known HIV infection with documented CD4 count <200 cells/μL within 24 weeks prior to screening
●History of N. meningitidis infection within the prior 6 months

Kindly refer to the exclusion criteria p 46 on the protocol

Type of study

Interventional

Type of intervention

Pharmaceutical

Type of intervention: Specify type

N/A

Trial scope

Trial scope: Specify scope

Other

Study design: Allocation

Randomized controlled trial

Study design: Masking

Blinded (masking used)

Study design: Control

Placebo

Study phase

2

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

BO42451 Study indication: Crovalimab is under development for the treatment of vaso-occlusive crisis associated with sickle cell disease. (Therapeutic indication for the submitted study BO42451) ,

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. 2017; 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 delayed hemolytic transfusion reaction (DHTR) (Roumenina et al. 2019). The available nonclinical data with complement inhibition in SCD suggests a multimodal role for crovalimab on disease pathophysiology of vaso-occlusion, hemolysis, inflammation, thrombogenicity, endothelial activation, ischemia-reperfusion, and end-organ damage (Tampaki et al. 2021). The evidence supports exploratory trials of complement inhibition in patients with SCD,employing a therapeutic mechanism that does not overlap with current therapies.
Crovalimab induces rapid and complete inhibition of the terminal complement pathway by targeting C5, making it a suitable candidate for exploring the role of complement inhibition for the treatment of SCD.

Study model

N/A

Study model: Explain model

Study model: Specify model

N/A

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

Blood sample (about 0.5-2.5 tablespoons (for an adult) and 0.5-2 tablespoons (for a child) or less at each visit):
 Standard laboratory tests
 Biomarkers (gaining additional information about sickle cell disease and the study treatment)
 Pharmacokinetic and pharmacodynamic tests (measuring amount of drug in your body and markers of drug activity)

Upon screening and Every visit (weekly up to Week 5, then every 4 weeks) for a total 48 weeks

Urine sample for monitoring
 Kidney health
 Kidney biomarkers (gaining additional knowledge about sickle cell disease and the study drug

upon screening and on Week 1 and every 4 weeks for a total of 48 weeks

Urine pregnancy test (for women who can become pregnant) on Week 1 and then every 4 weeks for a total of 48 weeks and Safety upon follow-up visit 24 weeks after the final dose of study treatment
upon Safety follow-up telephone call 46 weeks after the final dose of study treatment: a urine pregnancy test will be provided to you that must be completed at home within 2 days before the follow-up telephone call.
 and During the telephone call, you will be asked to report the results of the pregnancy test

Biomarker testing may involve analysis of your genome (DNA), an "instruction book" for the cells in your body. Your blood samples may be tested for inherited genome variations associated with sickle cell disease and the complement protein system. Analyses of samples from a large number of people may help researchers learn more about crovalimab and similar drugs, sickle cell disease and other diseases, possible links among diseases, genome variations and how they might affect a disease or a person's response to treatment, and new avenues for drug development and personalized therapies.

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to crovalimab or SCD, diseases, or drug safety:
 Leftover blood from clinical genotyping samples and any derivatives thereof (DNA)

Target sample size

90

Actual enrollment target size

Date of first enrollment: Type

Actual

Date of first enrollment: Date

09/03/2022

Date of study closure: Type

Actual

Date of study closure: Date

30/12/2025

Recruitment status

Recruiting

Recruitment status: Specify

Date of completion

IPD sharing statement plan

Yes

IPD sharing statement description

Information technology systems used to collect, process, and store study -related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or
access. In the event of a data security breach, appropriate mitigation measures will be implemented.

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 data sets 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
EUDRACT	2020-004839-25

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	Hemtologist - Oncologist	Approved

Ethics Review

Ethics approval obtained	Approval date	Contact name	Contact email	Contact phone
Nini Hospital	01/08/2023	IRB	NA	+9616431400 ext 3165
American University of Beirut Medical Center	20/02/2024	IRB	nkbci-irb@aub.edu.lb	T +961 1 35 00 00 – Ext 5445

Countries of Recruitment

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

Health Conditions or Problems Studied

Condition	Code	Keyword
TREATMENT IN PREVENTION OF VASO-OCCLUSIVE EPISODES (VOE) IN SICKLE CELL DISEASE (SCD)	Sigmoid colon (C18.7)	sickle cell disease

Interventions

Intervention	Description	Keyword
crovalimab	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.	crovalimab

Primary Outcomes

Name	Time Points	Measure
The primary efficacy objective for this study is to evaluate the efficacy of crovalimab compared with placebo	end of study	Annualized rate of medical facility VOEs (AVR)

Key Secondary Outcomes

Name	Time Points	Measure
The secondary efficacy objective for this study is to evaluate the efficacy of crovalimab compared with placebo	end of study	Annualized rate of home VOE captured by patient report on a handheld device at home □ Annualized rate of uncomplicated medical facility VOE □ Annualized rate of ACS □ Annualized rate of days hospitalized for medical facility VOE (□ Annualized rate of days hospitalized for treatment of non-VOE complications of SCD □ Change in hematologic measures from baseline to Week 49 □ Time to first medical facility VOE from randomization as defined in primary efficacy endpoint □ Change in urinary albumin-creatinine ratio from baseline to Week 49 □ Change from baseline to Week 49 in tricuspid regurgitant jet velocity (TRV) □ Proportion of patients with TRV □2.5 m/s at Week 49 □ Change from baseline to Week 49 in Patient-Reported Outcomes Measurement Information System (PROMIS)-Fatigue score in adults
The exploratory efficacy objective for this study is to evaluate the efficacy of crovalimab compared with placebo	end of study	Combined rate of VOEs leading to medical facility visit or treated only at home □ Annualized rate of home VOE captured by patient recall at study clinic visits □ Annualized number of RBC transfusions □ Endpoints collected during any medical facility VOE and requiring hospitalization between baseline visit and Week 49: o Re-admission rate for a subsequent medical facility VOE within 28 days of discharge o Duration in days of hospitalization for each medical facility VOE o Need for RBC transfusion during admission for each medical facility VOE □ Change from baseline to Week 49 in the scores of the following PROs: o Emotional impact and stiffness impact as assessed by the Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me) in adults Physical functioning as assessed by the PROMIS Physical Function in adults o Physical functioning as assessed by the Pediatric Quality of Life Inventory (PedsQL) Core in adolescents o Fatigue as assessed by the PROMIS Pediatric Fatigue in adolescents
The safety objective for this study is to evaluate the safety and tolerability of crovalimab compared with placebo	end of study	Incidence and severity of adverse events with severity determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0) □ Change from baseline in targeted vital signs and clinical laboratory test results of clinical significance □ Incidence and severity of injection-site reactions, infusion-related reactions (IRRs), hypersensitivity, and infections (including meningococcal meningitis)
The PK objective for this study is to evaluate the pharmacokinetics of crovalimab	end of study	Serum concentrations of crovalimab over time The exploratory PK objective for this study is: □ To evaluate potential relationships between drug exposure, pharmacodynamics, efficacy, and safety of crovalimab (in patients randomized to crovalimab)
The immunogenicity objective for this study is to evaluate the immune response to crovalimab	end of study	Prevalence of ADAs at baseline and incidence of ADAs during the study (patients randomized to crovalimab) The exploratory immunogenicity objective for this study is: □ To evaluate the potential effects of ADA on PD, efficacy, safety, and PK endpoints
The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that are predictive of a 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), can provide evidence of crovalimab activity (i.e., PD biomarkers), or can increase the knowledge and understanding of disease biology	end of study	Change over time in PD biomarkers, including CH50 measured by a LIA, total and free C5 concentrations, and sC5b-9 concentration □ Change over time in additional 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 urine and efficacy, safety, PK, immunogenicity, or other biomarker endpoints □ Change in biomarkers collected during hospitalization for medical facility VOE, from baseline to discharge

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