Characterizing Pyoderma Gangrenosum Lesion Regression and Remission by IL-36 Receptor Targeting With Spesolimab
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NCT06092216
Document Date: 2/27/2024

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Protocol Version: October 1st, 2023

Amendment 1: August 10, 2023

Amendment 2: December 21, 2023

Effective Date: 2/27/2024
End Date:8/14/2024

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BACKGROUND:

Pyoderma gangrenosum (PG) is a rare, inflammatory neutrophilic disease that is characterized by rapidly developing, painful and necrotizing skin ulcers with peripheral, violaceous erythema and undermined or "rolled" borders[1]. The condition most frequently occurs in adults between the ages of 41-72 years of age with a predisposition to the female sex[2]. It is estimated that 3-10 people per million are diagnosed with PG each year[3].

PG is often a chronic condition harboring a significant impact on patient mortality and quality of life[4]. Approximately 30% of individuals with PG have co-existing immune-mediated conditions such as inflammatory bowel disease, rheumatoid arthritis, or myeloproliferative disorders[4]. Clinically, the lesions appear as non-healing wounds or pustule eruptions that slowly ulcerate into crater-like holes and fistular tracks[5]. While rarely diagnostic, histopathology of PG lesions may show prominent dermal neutrophilic infiltrate with abscess formation in conjunction with a lack of signs for infection or vasculopathies[1]. Thus, the diagnosis of PG is most often one of exclusion.

The PARACELSUS scoring tool is a diagnostic tool that helps distinguish PG from ulcers caused by a different etiology[6]. The tool consists of three major diagnostic criteria (3 points each) and seven minor criteria (2 points each)[6]. Major criteria include: progressing disease, assessment of relevant differential diagnosis, and reddish-violaceous wound borders[6]. Minor criteria include: amelioration by immunosuppressant drugs, characteristically irregular shape of ulceration, extreme pain >4/10 on a visual analogue scale, localization of lesion at site of trauma, suppurative inflammation on histopathology, undermined wound borders, and associated systemic diseases such as inflammatory bowel disease or rheumatoid arthritis[6]. If a patient had a score greater than or equal to 10 points, the patient had a high likelihood of having PG[6]. Biopsy has not been found to a reliable diagnostic criterion[7].

While the mechanism of PG has not been fully elucidated, there has already been significant progress. PG is a destructive autoinflammatory process driven by the innate immune system. The process is attributed to pathergy in which initial insult releases cytokines and danger signals that result into aberrant inflammation and cutaneous neutrophilic infiltration[1]. Ulcerative PG occurs in response to pathergy, often in the postoperative setting. Upon trauma, keratinocytes release interleukin-36 (IL-36) which is thought to play a central role in PG pathogenesis and neutrophil recruitment[8].

To date, there is no gold standard for treatment of PG. Rapidly progressing cases require early systemic therapies such as prednisone and cyclosporine to contain lesions and halt spread[1]. On the contrary, slowly progressing, smaller areas may be conservatively managed with topical corticosteroids or calcineurin inhibitors as well as intralesional corticosteroid injections[9,10]. More recently, anti-TNF-α therapies such as infliximab, adalimumab and etanercept have also been used in refractory cases with moderate success[11,12,13,]. Patients with pyoderma gangrenosum suffer from severe pain and poor quality of life due to frequent dressing changes and disfiguring lesions. More importantly, rapidly progressing ulcers present an important risk for infection, morbidity, and mortality for patients.

Spesolimab is humanized antagonistic monoclonal IgG1 antibody that blocks human IL36R signalling and subsequent downstream pro-inflammatory pathways[14]. The IL-36 receptor blocker was recently approved for generalized pustular psoriasis (GPP)[15]. Similar to ulcerative PG, IL-36 cytokines are aberrantly expressed in GPP skin lesions[8]. In 2021, Bachelez et al. demonstrated in a phase 2 randomized trial that spesolimab treatment resulted in significant clearing of GPP lesions compared to placebo[15]. In the same vein, we hypothesized that targeting IL-36 in refractory, ulcerative postoperative PG may result in regression and resolution of a patient's lesions.

TREATMENT RATIONALE:

To date, there is a lack of specific, efficacious, and safe treatment options for severe PG. Treatment of the condition largely consists of immunosuppressants such as prednisone and cyclosporine, both of which harbor side effect profiles that render them not suitable for long-term use[16]. For patients with refractory PG, long-term use of these immunosuppressants may lead to development of Cushing syndrome and osteoporosis in the case of prednisone and nephrotoxicity and malignancy in long-term use of cyclosporine[16,17]. More recently, TNF-α blockers (adalimumab, infliximab, etanercept) have seen moderate success in treatment of pyoderma gangrenosum[10-13]. However, while safer than cyclosporine and prednisone for long term use, TNF-α blockers also harbor risk for malignancy[16]. It is imperative to find safe, alternative treatment for chronic, severe pyoderma gangrenosum refractory to current treatment therapies.

In addition, given the rarity and difficult diagnostic nature of this disease, there are very few clinical trials that exist for pyoderma gangrenosum. Literature concerning therapies for PG consists mostly of case reports and case series. Thus, it is essential that we conduct clinical trials in order to investigate safer, alternative therapies for those suffering from this debilitating disease.

While the pathogenesis of pyoderma gangrenosum has not been fully elucidated, pathergy has been thought to play a large role. Upon trauma, keratinocytes release IL-36 which triggers both the innate and adaptive immune system into a positive feedback loop (Figure 1)[8].

IL-36 is a member of the interleukin-1 cytokine family, which has been implicated in neutrophilic inflammation and the pathogenesis of PG. Lacking a specific caspase-cleavage motif, IL-36 requires proteolytic cleavage by surrounding neutrophil-derived proteases: Cathepsin G, elastase, and proteinase-3[8]. Once cleaved and activated, IL-36 upregulates expression of inflammatory cytokines and chemokine release resulting in increased neutrophil recruitment[8]. In response to IL-36, human keratinocytes have been shown to produce increased levels of TNF, IL-17A, IL-6, IL-8, and CXCL8, which propagate pro-inflammatory signals and recruitment of immune cells such as neutrophils, macrophages, and T cells [4, 18, 19]. Recruited neutrophils degranulate and result in increased levels of activated IL-36, leading the cycle to repeat itself. At the same time, IL-36 has been reported to skew T cell differentiation towards Th1 and away from Treg, which further propagates aberrant, pro-inflammatory signaling[20,21]. Taken together, IL-36 appears to play a central role in propagation of a pro-inflammatory cycle in PG, which leadings to neutrophil recruitment and skin ulceration (Figure 1). To further confirm this,

biopsies of PG skin ulcers demonstrate elevated levels of IL-36 [22]. Thus, targeting IL-36 downstream signaling is likely to halt disease propagation and lead to skin healing.

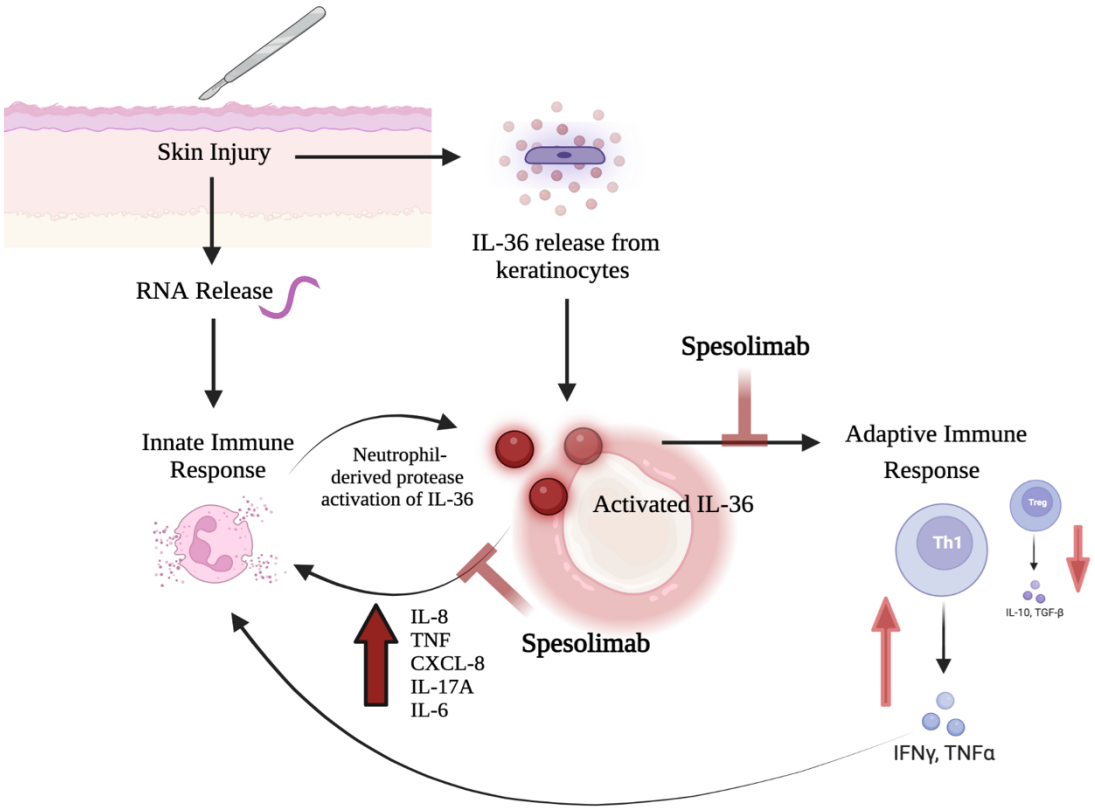

Figure 1. Proposed Mechanism: IL-36 Plays Key Role in the Inflammatory Cycle of Pyoderma Gangrenosum[8, 18-21]
Upon skin injury, there is RNA release which activates the innate immune response and leads to neutrophil activation and degranulation. At the same time, keratinocyte injury leads to IL-36 release. Simultaneous occurrence of these events leads to activation of IL-36 by neutrophil-derived proteases. Activated IL-36 leads to increased expression of pro-inflammatory, neutrophil recruiting cytokines IL-8, TNF, CXCL-8, IL-17A, and IL-6. Further, IL-36 activation also leads to skewed Th1 differentiation with decreased Treg differentiation; thereby amplifying the inflammatory response and progression of disease. Spesolimab, an IL-36 receptor blocker, inhibits pro-inflammatory downstream effects of activated IL-36; thereby breaking the inflammatory cycle in pyoderma gangrenosum. (Figure made courtesy of Biorender.com)

Already, we have seen successful treatment of two of our patients with severe PG with spesolimab. The first patient had severe, refractory PG on his face and chest, which showed marked improvement within five weeks of his first spesolimab infusion (Figure 2). A second spesolimab-treated patient with pyoderma gangrenosum also saw near resolution of PG lesions after two spesolimab infusions at week 0 and week 4.

The first patient treated with spesolimab for severe, refractory PG was started on 900mg IV spesolimab every 4 weeks. However, it was noted that he began seeing signs of purulence by week 3 post-treatment. Thus, approval was obtained from Boehringer

Ingelheim and the FDA for 900mg q3 week dosing and we anticipate this dosing to better control his disease process.

The successful treatment of these two patients suggests that spesolimab effectively blocks the IL-36 receptor and thereby halts the PG inflammatory cycle. Their rapid response also suggests that IL-36 plays a crucial role in the pathogenesis of PG and may be a worthwhile target for future PG therapies. Further, the lack of severe adverse effects in our patient demonstrates that spesolimab may be a safe, alternative to long-term, systemic immunosuppressive therapies that have well-established, dangerous side effects. This will be an important study that will help fill the gap in available clinical trial evidence for pyoderma gangrenosum treatment.

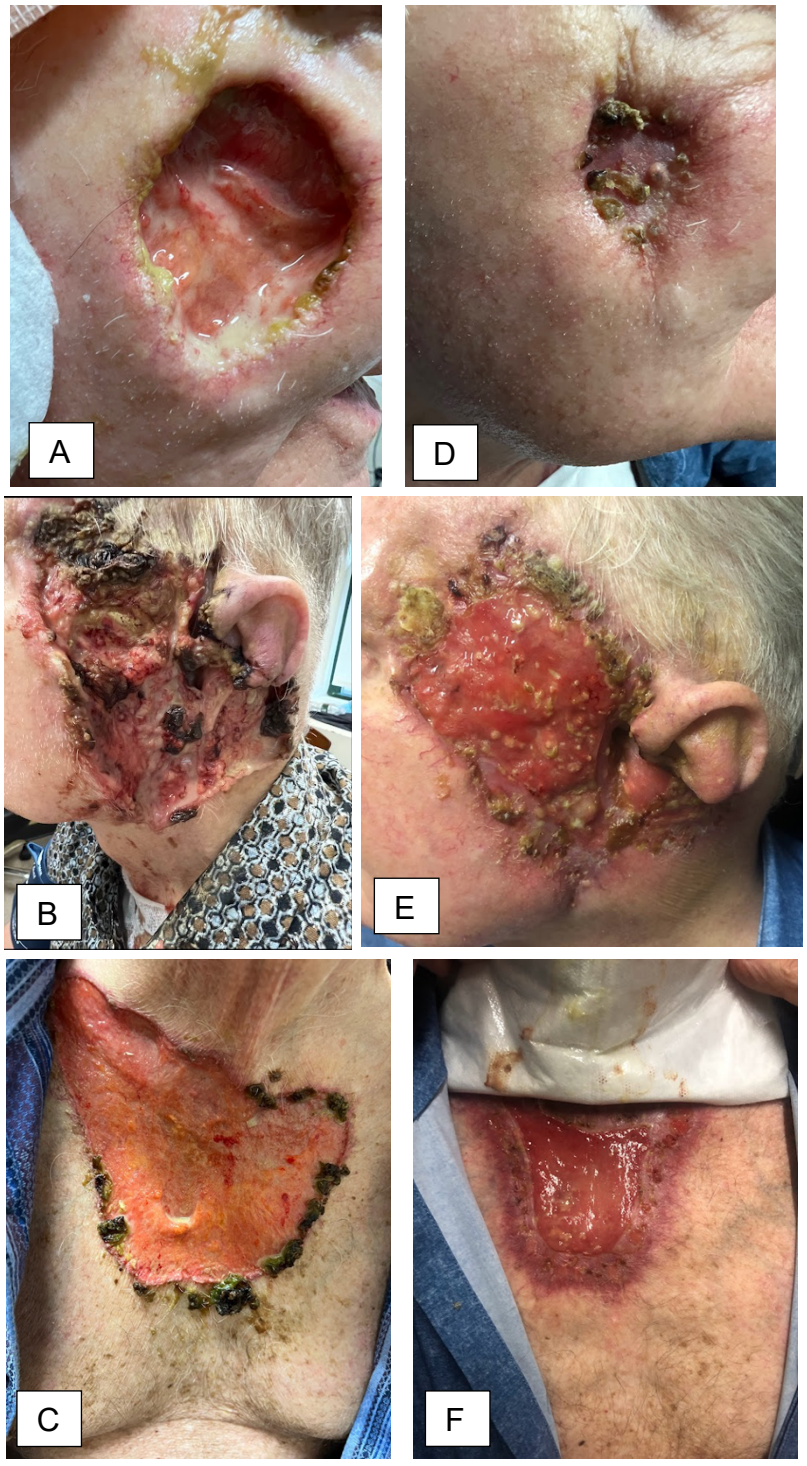

Figure 2. 75-year-old male Pyoderma Gangrenosum
A-C. Prior to Spesolimab treatment (A. Right Cheek, B. Left Face, C. Chest)
D-F. Five weeks after first 900mg infusion of spesolimab (D. Right Cheek, E. Left Face, F. Chest)

HYPOTHESIS:

Primary Hypothesis:

- Blocking the IL-36 receptor with spesolimab will be effective in improving and/or resolving PG lesions and their associated morbidities.

OBJECTIVES:

Primary Objectives:

- To study the rate of improvement of patients with pyoderma gangrenosum lesions treated with 900 mg infusions of spesolimab at week 16

Secondary Objectives

- To evaluate the rate of complete re-epithelization of PG lesions to spesolimab treatment
- To evaluate the rate of recurrence of PG lesions upon spesolimab treatment cessation and over 4-month follow-up period
- To evaluate safety spesolimab treatment in patients with pyoderma gangrenosum
- To evaluate change in patient pain severity
- To evaluate the change in patient-reported symptoms and impact of skin problems on quality of life

ENDPOINTS:

Primary Endpoint

- One point decrease from baseline in target lesion Global PG (GPG) Severity Score at Week 16

Secondary Endpoints

- Complete re-epithelization of PG lesions (GPG Severity Score of 0) at visits 3, 4, 5, 6, 7, 8, and 9.
- Absolute change from baseline in patient-reported pain severity (Pain-VAS) at visits 3, 4, 5, 6, 7, 8, and 9 and at complete re-epithelization of ulcer.
- Absolute change in quality of life (DLQI) from baseline at visits 3, 4, 5, 6, 7, 8, and 9 and at complete re-epithelization of ulcer.
- Recurrence of PG lesions after complete re-epithelization (GPG score 0) of all lesions and spesolimab cessation

- Time to worsening (1 or more GPG point increase) of target PG lesion from spesolimab cessation

STUDY DESIGN OVERVIEW:

This study is a prospective, proof-of-concept, open label clinical trial. The study will take place at Icahn School of Medicine at Mount Sinai.

The study will screen up to 25 subjects in order to enroll a total of up to 20 patients with at least one clinically measurable ulcerative PG lesion. Subjects will receive 900 mg of spesolimab intravenously (IV) over 90 minutes at a frequency of every 4 weeks until Week 28 with the following exceptions:

- At the Week 8 visit, subjects who do not show any improvement, show only minimal improvement, or those that begin to lose their initial improvement response (decrease in pain or wound drainage), may be switched to a dosing frequency of every 3 weeks through Week 26, at the discretion of the investigator. These subjects will still return at Week 16 for an endpoint visit, but will not receive treatment at this visit. Refer to Tables 3 and 4 for schedule of events.

All subjects will be monitored monthly for 4 months subsequent to treatment cessation.

Subjects who reach GPG score 0 at anytime during the study will continue to receive treatments until week 28 (or Week 26 depending on dosing frequency) and will then be monitored for 4 months subsequent to treatment cessation.

Subjects who are experiencing improvement in their PG but who have not reached complete wound healing will continue treatment until Week 28 (or Week 26 for those who were switched to every 3 week dosing), even if primary endpoint has been achieved. These subjects will then be monitored for 4 months subsequent to treatment cessation.

Subjects who have not improved and not worsened significantly will also continue to receive treatments until week 28 (or Week 26 depending on dosing frequency) and will then be monitored for 4 months subsequent to treatment cessation.

Any subject that experiences significant worsening will be discontinued from the study.

After providing consent, subjects will be assessed for study eligibility during the screening period (within 28 days of baseline). The screening visit includes a review of the subject's past and current medical conditions as well as a review of family history of associated relevant diagnoses such as inflammatory bowel disease, rheumatoid arthritis, and hematological malignancy. Subjects will also be asked to review past surgical history and history of any relevant skin trauma. Subjects will also be asked to report past and current treatment regimens of their PG and their perception of response to each treatment trialed. A limited physical exam will be performed, vitals collected, blood samples collected for safety tests (including screenings for HIV, hepatitis B and C and tuberculosis), and the physician will assess number, location, and severity of PG lesions.

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Subjects who meet inclusion criteria for eligibility will undergo Baseline assessments at Week 0, including clinical assessments, review of concomitant medications, limited physical examination, vitals, standardized clinical photography, questionnaires (patient PG questionnaire, pain VAS and DLQI). Blood samples (CBC, CMP, CRP, serum cytokine profiles, pharmacokinetics, Nab, ADA) will be collected to monitor for adverse effects of medication and overall inflammatory response.

During each treatment visit the subject will undergo clinical assessments (number, location, measurement of lesions, and GPG Score (Appendix 1)). Each visit will also consist of vitals, medication review, blood collection, patient PG questionnaire (wound dressings, pain VAS and DLQI (Appendix 2) and monitoring for adverse events. O-Link ® Inflammatory Serum Cytokine Panel, IL-1ß, and IL-36 subtype cytokine levels will be run from blood serum samples collected at Baseline/Week 0, Week 16, all follow-up visits, and/or at early termination visits. Blood samples for pharmacokinetics and antibody testing (Nab and ADA) will be collected at Baseline, Week 8, Week 16, Week 28 (or Week 26 depending on dosing frequency) and/or early termination visit. An extra 10mL aliquot of serum sample will be reserved for any additional exploratory serum testing done in the future.

PATIENT POPULATION:

Prior to enrollment, all subjects must meet the following inclusion and exclusion criteria:

Inclusion Criteria:

1) Male or female subjects ≥ 18 years of age at the time of signing the informed consent document
2) Subject is able to understand and voluntarily sign an informed consent document prior to participation in any study assessments or procedures
3) Subject is able to adhere to the study visit schedule and other protocol requirements.
4) Subject has clinically diagnosed ulcerative PG with PARACELSUS score greater than or equal to 10 [6]
5) Subject has at least one clinically measurable ulcerative PG lesion on his/her/their body that has failed to respond to at least one prior therapy such as (but not limited to) topical corticosteroids, intralesional triamcinolone, prednisone, cyclosporine, IL-23 inhibitor, IL-17 inhibitors, IL-1 inhibitors, or TNF-α blocker therapy
6) Subject has moderate to severe PG as determined by a GPG severity score of ≥3
7) Subject is judged to be in otherwise good overall health as judged by the investigator, based on medical history, limited physical examination, and laboratory testing. (NOTE: The definition of good health means a subject does not have uncontrolled significant co-morbid conditions).
8) Females of childbearing potential (FCBP) must have a negative pregnancy test at Screening and Baseline. While on investigational product and for at least 28 days after taking the last dose of investigational product, FCBP who engage in activity in which conception is possible must use one of the approved contraceptive options described below:

Option 1: Any one of the following highly effective contraceptive methods: hormonal contraception (oral, injection, implant, transdermal patch, vaginal ring); intrauterine device (IUD); tubal ligation; or partner's vasectomy.

OR

Option 2: Male or female condom (latex condom or nonlatex condom NOT made out of natural [animal] membrane [for example, polyurethane]); PLUS one additional barrier method: (a) diaphragm with spermicide; (b) cervical cap with spermicide; or (c) contraceptive sponge with spermicide.

The female subject's chosen form of contraception must be effective by the time the female subject presents for her Baseline visit (for example, hormonal contraception should be initiated at least 28 days before first spesolimab infusion at Baseline).

Exclusion Criteria:

The presence of any of the following will exclude a subject from enrollment:

1) Subject has a persistent or recurring bacterial infection requiring systemic antibiotics, or clinically significant viral or fungal or helminth parasitic infections, within 2 weeks of the Screening Visit. Any treatment of such infections must have been completed at least 2 weeks prior to the Screening Visit and no new/recurrent infections should have occurred prior to the Baseline Visit.
2) Subject with current or history of positive human immunodeficiency virus (HIV), or congenital or acquired immunodeficiency (i.e. Common Variable Immunodeficiency [CVID]), hepatitis B or C, or active or untreated latent tuberculosis.
3) Subject has clinically significant (as determined by the investigator) renal, hepatic, hematologic, intestinal, endocrine, pulmonary, cardiovascular, neurological, psychiatric, immunologic, or other major uncontrolled diseases that will affect the health of the subject during the study, or interfere with the interpretation of study results. Uncontrolled disease defined as hospitalization within 1 month of screening visit or determined by specialist (rheumatologist, gastroenterologist) consulted prior to study start.
4) Subject has presence of acute demyelinating neuropathy
5) Major surgery (according to the investigator's assessment) performed within 12 weeks prior to receiving first dose of spesolimab or planned during trial such as hip replacement, aneurysm removal, stomach ligation, or otherwise determined by investigator
6) Subject has a suspected or active lymphoproliferative disorder or malignancy
7) Subject was treated previously with spesolimab or another IL-36R inhibitor biologic
8) Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treatment basal or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix.
9) Subject has received a live attenuated vaccine ≤ 30 days prior to study initiation.
10) History of adverse systemic or allergic reactions to any component of the study drug.

11) Female subject who is pregnant or breast feeding

POTENTIAL RISKS OF SPESOLIMAB

Preclinical and clinical data demonstrates that spesolimab is safe for chronic use in humans with a good safety profile and minimal anticipated adverse events (AE). Animal studies demonstrated that administration of 1 and 10mg/kg/dose of spesolimab to mice twice per week for 4 weeks was well tolerated without any signs of toxicity[14]. Further, there was no clinical signs of toxicity in mice after administration of spesolimab for 26 weeks. Spesolimab is not expected to be carcinogenic or teratogenic in mouse models; however, further studies in humans are still required[14].

Specific adverse reactions for spesolimab include infection, risk of tuberculosis, and hypersensitivity and infusion-related reactions. Of note, the two reported cases of 6DRESS were categorized as “no” DRESS and “possible” DRESS with the RegiSCAR DRESS validation scoring. Other previously reported potential adverse events include Guillan-Barre Syndrome and other peripheral neuropathy.

In the phase 2 trial investigating spesolimab use in GPP, there were no serious adverse events in the spesolimab 900mg intravenous infusion group[15]. Serious adverse events reported included: drug reaction with eosinophilia and systemic symptoms, urinary tract infection, drug induced hepatic injury, arthritis, influenza, worsening of chronic plaque psoriasis and squamous cell carcinomas of skin[15]. The most common selected adverse reactions occurring in >1% of spesolimab treated individuals in the Effisayil-1 trial when compared to placebo was: asthenia and fatigue, nausea and vomiting, headache, pruritus and prurigo, infusion site hematoma and bruising, urinary tract infection, bacteremia, bacteriuria, cellulitis, herpes dermatitis and oral herpes, upper respiratory tract infection, dyspnea, eye edema, and urticaria[14]. The most common adverse reactions noted in the package insert for spesolimab are: asthenia and fatigue, nausea and vomiting, headache, pruritus and prurigo, infusion site hematoma and bruising and urinary tract infection[14].

The paragraphs above provide the safety information described in the US PI (spesolimab label in US) according to the FDA approval process. However, Boehringer-Ingelheim´s position concerning the adverse drug reactions of spesolimab in patients with flares of Generalized Pustular Psoriasis is described in the table 1 below:

Table 1 Summary of Adverse Reactions

MedDRA System Organ Class terminology	Spesolimab adverse reactions
Infections and infestations	Urinary tract infection Upper respiratory tract infection
Skin and subcutaneous tissue disorders	Pruritus

General disorders and administration site conditions	Injection site reactions Fatigue

Moreover, there are some important potential risks still under evaluation for spesolimab which are part of its core Risk Management Plan. These important potential risks are the following:

- **Serious or opportunistic infections**
- **Systemic hypersensitivity reactions**
- **Malignancy**
- **Peripheral Neuropathy**

Contraindications to spesolimab treatment include patients with severe or life-threatening hypersensitivity to spesolimab or to any of the excipients in spesolimab[14]. In our experience, patients infused with spesolimab exhibited no adverse reactions during or after treatment with no pre-medication required. There is limited data available on the impact of antidrug antibodies on safety and efficacy upon retreatment. Furthermore, it is not known whether spesolimab increases or decreases the efficacy of other medications.

PRIOR TREATMENT:

All relevant treatment received by the subject within 30 days before screening will be recorded.

CONCOMITANT TREATMENT:

Concomitant medications are permitted for the treatment of stable, chronic illness as well as for pyoderma gangrenosum. Concomitant treatments for pyoderma gangrenosum will tapered over spesolimab treatment course as tolerated. Use of such concomitant medication or other medications that may be required throughout the study will be recorded (including the reason for treatment and name, dose, unit, route, and the date of treatment as appropriate) until treatment termination and throughout follow-up period. Patients will be allowed to continue with biologic therapies used to treat comorbidities.

PROHIBITED TREATMENT:

All treatments prohibited by clinician during the screening period are also prohibited throughout the course of the study. No live attenuated vaccinations are permitted throughout the study.

PROCEDURES:

Monitoring of AEs will begin at the time of signing the informed consent form and will be continued throughout the course of the study. All study procedures will be completed at designated times during the study period (see Tables 3 and 4). Subjects will receive 900mg IV spesolimab at a frequency of every 4 weeks through Week 8, at which time, at the discretion of the investigator, dosing frequency may be increased to every 3 weeks. Subjects will continue to dose every 4 or 3 weeks through Week 28 or 26 (depending on

dosing frequency). Subjects will be monitored once a month, for 4 months after treatment cessation. Patients that, in the opinion of the investigator, are benefiting from treatment at week 28 but need more therapy to achieve wound closure may be eligible to continue on treatment (on case-by-case basis) to a maximum of 52 week after discussion with Boehringer Ingelheim trial team.

Trained assessors will perform clinical assessments. It is strongly recommended that the same assessor/s perform clinical assessments for a subject at all study visits. The following procedures will be performed at each visit:

Screening

Visit 1 – Screening (within 4 weeks of Baseline)*

- Obtain signed IRB-approved informed consent and HIPPA agreement
- Review Inclusion and Exclusion Criteria
- Review PARACELSUS Criteria and confirm the PARACELSUS score for patient and target lesion is greater than or equal to 10
- Record gender, race, ethnicity, and medical history
- Review personal and family history of PG, inflammatory bowel disease, rheumatoid arthritis, hematological, and autoimmune diseases as well as personal lifetime surgical history
- Perform limited physical exam and vitals, including blood pressure and heart rate
- Record all concomitant medications as well as all those received within the three months prior to screening; assess adverse events.
- PG history assessment (date of onset for each PG lesion) extracted from electronic medical records or obtained from referring provider
- Record all prior topical, systemic therapies/treatments or interventional treatment for pyoderma gangrenosum
- Serum HCG for all female subjects of child-bearing potential to confirm subject is not pregnant.
- Complete blood count (CBC) with differential, Comprehensive metabolic panel (CMP), C-reactive protein (CRP), QuantiFERON-TB Gold test or PPD, HIV, Hepatitis B (Core, Surface Antigen, Surface Antibody), Hepatitis C Antibody.
- PG clinical assessments (including number/location/measurements of PG lesions, GPG score for target lesion)

*If more than 28 days has lapsed between screening and Baseline/Visit 2, then all procedures should be repeated except for re-obtaining informed consent.

Baseline

Visit 2 – Baseline (Week 0)

- Confirm all inclusion and exclusion criteria have been met
- Record concomitant medications (including use of pain medication) and adverse events
- Patient Pyoderma Gangrenosum Questionnaires and DLQI
- Obtain vital signs

- Perform limited physical exam
- Standardized clinical photography of target lesion and other PG lesions
- PG clinical assessments (including number/location/measurements of PG lesions, GPG score of target lesion)
- Assess status of associated co-morbidities such as IBD or RA. Categorize co-morbid condition status as “improved, no change, worsening”.
- Urine pregnancy test for all female subjects of child-bearing potential to confirm subject is not pregnant
- Collect blood samples for CBC with differential, CMP, and C-reactive protein (CRP), ,serum cytokine profiling (O-link® inflammatory cytokine panel, IL-1ß, and IL-36 subtypes), Nab, ADA, and Pre- and post dose pharmacokinetics.
- Administer study drug

Spesolimab Treatment Phase

Visits 3 thru 9 (subjects that dose every 4 weeks) **or** Visits 3 thru 11 (subjects that are switched to every 3 week dosing at Week 8)

- Record concomitant medications (including use of pain medication) and adverse events
- Urine pregnancy test for all female subjects of child-bearing potential to confirm subject is not pregnant
- Patient Pyoderma Gangrenosum Questionnaires and DLQI
- Obtain vital signs
- Standardized clinical photography of target lesion and other PG lesions
- PG clinical assessments (including number/location/measurements of PG lesions and GPG score for target lesion)
- Assess status of associated comorbid conditions (improved, no change, worse)
- Collect blood samples for CBC with differential, CMP, and C-reactive protein (CRP)
- **Only at Week 8 and Week 28 (subjects dosed every 4 weeks) or Week 26 (subjects switched to dosing every 3 weeks)**: Nab, ADA, and pre dose pharmacokinetics.
- **Only at Week 16:** serum cytokine profiling (O-link® inflammatory cytokine panel, IL-1ß, and IL-36 subtypes), Nab, ADA, and pre dose pharmacokinetics.
- Administer study drug

Post-Spesolimab Follow-up Phase

Visits 10 thru 13 (subjects dosed every 4 weeks) **or** Visits 12-15 (subjects switched to dosing every 3 weeks)
Follow-Up Visits at 1 Month, 2 Months, 3 Months and 4 Months Post-Spesolimab Treatment Cessation

- Record concomitant medications (including use of pain medication) and adverse events
- Patient Pyoderma Gangrenosum Questionnaires and DLQI
- Assess status of associated comorbid conditions (improved, same, worse)
- Standardized clinical photography of target lesion and other PG lesions

- PG clinical assessments (including number/location/measurements of PG lesions, and GPG score of target lesion)
- Collect blood for serum cytokine profiling (O-link® inflammatory cytokine panel, IL-1ß, and IL-36 subtypes)
- If subject worsens or sees progression of their PG during the 4- month follow-up period (defined as 1 or more increase in GPG score of target lesion), then patient will be discontinued from the study and started on available, standard PG therapies.

Early Termination Visit (if applicable)

- Record concomitant medications (including use of pain medication) and adverse events
- Urine pregnancy test for all female subjects of child-bearing potential to confirm subject is not pregnant
- Patient Pyoderma Gangrenosum Questionnaires and DLQI.
- Assess status of associated comorbid conditions (improved, same, worse)
- Obtain vital signs
- Standardized clinical photography of target lesion and other PG lesions
- PG clinical assessments (including number/location/measurements of PG lesions and GPG score of target lesion)
- Collect blood samples for CBC with differential, CMP, and C-reactive protein (CRP), and serum cytokine profiling (O-link® inflammatory cytokine panel, IL-1ß, and IL-36 subtypes)

SAFETY MONITORING:

The study will be conducted in accordance with our department's Standard Operating Procedures, which are based on US FDA Title 21 Code of Federal Regulations and ICH Good Clinical Practice guidelines. An investigator will review all laboratory results and assess for adverse events. The principal investigator will be informed of all adverse events. In the event that a subject's safety is compromised, the investigator will discontinue the subject immediately.

ADVERSE EVENT REPORTING:

Definitions of adverse events

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The following should also be recorded as an AE in the CRF and BI SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions

- Changes in vital signs, physical examination and laboratory test results, if they are judged clinically relevant by the investigator.

Serious adverse event

A serious adverse event (SAE) is defined as any AE, which fulfils at least one of the following criteria:
- results in death,
-is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity,
- is a congenital anomaly / birth defect,
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

Adverse events of Special Interest (AESIs)

The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for Aes based on knowledge from other compounds in the same class. AESIs need to be reported to the Pharmacovigilance Department of Boehringer Ingelheim within the same timeframe that applies to SAEs.

Patients with AESIs need to be followed up appropriately, regardless of the origin of the laboratory data (e.g. central, local etc.). The Investigator should consider which, if any, concomitant therapies should not be taken during evaluation. Discontinued treatments can be reintroduced per Investigator discretion.

The following are considered as AESIs:

(1) Potential Severe Drug-Induced Liver Injury (DILI)

A hepatic injury is defined by the following alterations of hepatic laboratory parameters after randomisation:

- an elevation of AST (Aspartate Aminotransferase) and/or ALT (Alanine Aminotransferase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood draw sample, or in samples drawn within 30 days of each other, or,
- aminotransferase (ALT, and/or AST) elevations ≥10-fold ULN.

These laboratory findings constitute a hepatic injury alert and the patients showing these abnormalities need to be followed up according to medical judgement.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without laboratory results (ALT, AST, total bilirubin) available, the Investigator should make sure these parameters are analysed, if necessary, in an unscheduled blood test.

(2) Systemic hypersensitivity reactions including infusion reaction and anaphylactic reaction

Includes any suspicion of severe systemic hypersensitivity including infusion reactions and any anaphylactic reaction should be defined and assessed using the criteria discussed in the statement paper from Sampson et al. – Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. Journal of Allergy and Clinical Immunology. 2006 Feb 1;117(2):391–7.

(3) Severe infections (according to RCTC/CTCAE version 5.0 grading)

(4) Opportunistic and Mycobacterium tuberculosis infections

Includes pneumocystis jirovecii, BK virus disease including PVAN, CMV, posttransplant lymphoproliferative disorder (EBV), progressive multifocal leucoencephalopathy, bartonellosis (disseminated only), blastomycosis, toxoplasmosis, coccidioidomycosis, histoplasmosis, aspergillosis (invasive only), candidiasis (invasive or pharyngeal), cryptococcosis, other invasive fungi (mucormycosis (zygomycosis, rhizopus, mucor, lichtheimia), scedosporium/pseudallescheria boydii, fusarium), legionellosis, listeria monocytogenes (invasive only), tuberculosis, nocardiosis, non-tuberculous mycobacterium, salmonellosis (invasive only), HBV reactivation, herpes simplex (invasive only), herpes zoster, strongyloides (hyperinfection syndrome and disseminated forms only), paracoccidioides, penicillium marneffei, sporothrix schenckii, cryptosporidium species (chronic only), microsporidiosis, leishmaniasis (visceral only), trypanosoma cruzi infection (Chagas' disease) (disseminated only), campylobacteriosis (invasive only), shigellosis (invasive only), vibriosis (invasive due to vibrio vulnificus), HCV progression.

(5) Peripheral Neuropathy

Any event suspected or diagnosed as peripheral neuropathy would be considered as an AESI. For the treatment interruption rules, please see Section DISCONTINUATION OF TREATMENT AND WITHDRAWAL OF SUBJECTS

Intensity of adverse event

The intensity of the AE should be judged based on the following:

Mild: Awareness of sign(s) or symptom(s) that is/are easily tolerated.
Moderate: Sufficient discomfort to cause interference with usual activity.
Severe: Incapacitating or causing inability to work or to perform usual activities.

Causal relationship of adverse event

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship should be recorded in the case report forms.

Yes (related): There is a reasonable causal relationship between the investigational product administered and the AE.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug.
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced.
- No medically sound alternative etiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is reduced).

No (not related): There is no reasonable causal relationship between the investigational product administered and the AE.

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned).
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

Responsibilities for SAE reporting to Boehringer-Ingelheim (BI)

The Sponsor shall report (i.e., from signing the informed consent onwards through the protocol specified follow-up period after discontinuing spesolimab) all SAEs and non-serious Aes which are relevant for a reported SAE and Adverse Events of Special Interest (AESI) by fax or other secure method using BI IIS SAE form to the BI Unique Entry Point in accordance with timeline specified in the Safety Data Exchange Agreement.

BI Unique Entry point for SAE/AESI reporting:

Fax: 1-203-837-4329

SAE/AESI reporting timelines
- within five (5) calendar days upon receipt of initial and follow-up SAEs containing at least one fatal or immediately life-threatening event;
- within ten (10) calendar days upon receipt of any other initial and follow-up SAEs and AESIs.

For each adverse event, the investigator will provide the onset date, end date, intensity, treatment required, outcome, seriousness, causality and action taken with the BI study drug. The investigator will determine the expectedness of the investigational drug to the Aes as defined in the Listed Adverse Events section of the Boehringer Ingelheim's (BI's) Investigator Brochure for the Product or Product Information (PI) for the authorized Study Drug provided by BI.

The investigator does not need to actively monitor patients for adverse events once the clinical trial has ended. However, if the investigator becomes aware of an SAE(s) that occurred after the patient has completed the clinical trial (including any protocol specified follow-up period), it should be reported to BI if investigator considers it as relevant to the BI study drug.

Pregnancy

In the rare case that a female subject participating in this clinical trial becomes pregnant after having taken trial medication, the Investigator must report immediately (within 24 hours) the drug exposure during pregnancy (DEDP) to the Sponsor's unique entry point. The Pregnancy Monitoring Form for Studies (Part A) should be used.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the Sponsor's unique entry point on the Pregnancy Monitoring Form for Studies (Part B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Studies and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

STUDY WITHDRAWAL:

In the event a study subject wants to withdraw early from the study for any reason, the subject will be asked to return for an Early Termination visit (see above for procedures).

Table 2: TOTAL VOLUME OF BLOOD COLLECTED DURING THE STUDY:

		Treatment				Follow-Up
Visit	**1 Screening**	**2 Baseline**	**3, 5, 7, 8, 9**	**4**	**6**	**10-13**

Blood + Serum	23	32	15	20	23	23
Total volume	**23**	**23**	**15**	**20**	**23**	**23**

The total estimated blood volume is between 15 and 23 mL per month during treatment, and 23 mL per month during Follow-Up period. Additional volumes may be required for repeat testing or as part of unscheduled visits.

DISCONTINUATION OF TREATMENT AND WITHDRAWAL OF SUBJECTS:

The reasons why a subject may discontinue or be withdrawn from the study by the investigator include, but are not limited to the following: subject request, protocol violation, loss to follow up, subject non-compliance, significant worsening of subject's disease, study termination by investigators, and a confirmed grade 3 or higher adverse event (using Common Terminology Criteria for Adverse Events), which is suspected to be related to test article administration. Subjects that elect to withdraw from the trial due to lack of efficacy and/or exacerbation of disease will undergo an Early Termination visit (see Procedure Section and Schedule of Events)

Stopping Rules
Patients will be permanently discontinued from study treatment in the event of:

- Anaphylactic reaction or other severe systemic reaction to study drug injection
- Pregnancy at any time during the study period
- Diagnosis of a malignancy during study, excluding carcinoma in situ of the cervix, or squamous or basal cell carcinoma of the skin
- Treatment with any prohibited concomitant medication or procedure
- Any infection that is opportunistic, whose nature or course may suggest an immunocompromised status

Study drug dosing may be temporarily suspended in the event of:

- Intercurrent illnesses or major surgery
- An infection that requires systemic treatment with antibiotic, antifungal, antiviral, anti-parasitic, or anti-protozoal agents or requires oral treatment with such agents for longer than 2 weeks. Treatment of certain infections such as latent tuberculosis may be treated concurrently with spesolimab treatment

Duration of study drug suspension should be reviewed on a case-by-case basis and can be discussed with the PI.
In case of systemic hypersensitivity including infusion reactions and anaphylactic reaction, emerging during or after infusion/injection of study medication, the investigator should consider in accordance with severity of the reaction and local standard of care to:

- Immediately interrupt the infusion/injection

- Treat with systemic anti-histamines, intravenous steroids, and in case of a severe allergic reaction (e.g., anaphylactic reaction) epinephrine
- Blood draw for plasma sample of IgE and ADA/neutralizing antibody (Nab), serum tryptase, and complement components

In case of systemic hypersensitivity including infusion reactions, based on patient's clinical course and medical judgment, the infusion may be re-initiated in case of mild or moderate infusion reactions at lower speed with gradual increase to complete the infusion as detailed in the label. Regardless, the total duration of infusion should not exceed 180 minutes (3 hours).

Safety Evaluation
This is an open label, proof-of-concept study with an FDA-approved drug. Safety and tolerability will be evaluated from the AEs, limited physical examinations, and vital sign measurements. More frequent safety evaluations may be performed if clinically indicated or at the discretion of the investigator.

Aggregated AEs will be evaluated monthly by the PI/research teams.

Safety data will be reviewed by the investigators who will monitor the study on a regular basis and meet regularly (approximately once a month, depending on the number of subjects enrolled). The local IRBs, FDA, and Boehringer Ingelheim will be notified of adverse events (as required by each institution).

Physical Examination/Vital Signs
Qualified personnel will perform limited physical examinations, blood pressure and heart rate at each visit.

Limited physical examination consists of assessments of general appearance; skin; head, eyes, ears, nose, and throat (HEENT); heart; lungs; abdomen; extremities; neurological function; and lymph nodes.

MEASURES TO MINIMIZE/AVOID BIAS:

Subject Identification
Subjects are numbered sequentially. Each subject screened (total of 25 screened) will be assigned a unique screening number for the duration of the study. Subject screening numbers will also become a subjects treatment number if they are enrolled in the study after providing informed consent and meeting inclusion criteria. Subjects who discontinue or withdraw from the study before receiving a treatment assignment code, but re-enroll at a later time must be assigned a new screening number. The investigator must maintain a master log linking the subject number to the subject's name. The investigator must follow all applicable privacy laws in order to protect a subject's privacy and confidentiality.

INVESTIGATIONAL DRUG SUPPLY :

Eligible participants will receive 900 mg intravenous spesolimab starting at Visit 2/week 0/Baseline. All participants will receive a total of 8 or 9 infusions (depending on dosing frequency) through Week 28 or Week 26 (depending on whether the subject's dosing frequency is increased to every 3 weeks at Week 8), unless there is significant worsening. All subjects should be observed for 30 minutes following the infusion at Baseline to assess safety. Select cases will be offered the opportunity to continue treatment through Week 52 on case-by-case basis if the patient would benefit from continued treatment. All subjects who have not been discontinued will be monitored once a month, for 4 months after treatment cessation.

All study medication will be provided by Boehringer Ingelheim, refrigerated and stored between 2-8˚C in a secure area. Study drug will be administered to subjects at each study visit in office. The investigative site will account for all study drug dispensed and stored during the study.

STATISTICAL CONSIDERATIONS:

Sample Size

This is a proof-of-concept, open-label trial. Twenty patients will be enrolled in the trial to demonstrate efficacy of spesolimab in a population of patients with moderate-severe, refractory PG. Although there is no formal power calculation, a sample size of n=20 subjects allows 81% power at 2.5% significance for a one-sided binomial test to detect at Week 16 a difference of 36.6% in the proportion of GPG success compared to a constant set to be equal to 10%. The choice of the constant was based on data from a randomized clinical trial for efficacy of infliximab where a group of 17 PG placebo-treated patients showed 6% response at Week 2 (Brooklyn et al.,2006).

Demographics and Other Baseline Characteristics

Descriptive statistics of demographics and other baseline characteristics of patients will be summarized with mean, median, and standard deviation for quantitative outcomes, and frequency and percentage tables for categorical outcomes.. Other baseline characteristics include sex, age, height, weight, vital signs, duration of PG, history of pathergy or PG trigger (if known), concurrent diagnoses from medical history and indications for concomitant medication, concomitant medication, and previous PG treatments.

Target Lesion Measurement and Digital Image Assessments

Size of target PG lesion will be approximated at each visit by measuring the length, width and depth of the lesion. Target lesion will also be analyzed using Image J software to obtain a more precise surface area of each lesion using digital photographs taken at each visit.

Analysis of Primary Endpoint

We will compare the proportion of patients achieving one-point decrease in target lesion GPG score at Week 16 with a constant p=0.10. Clopper-Pearson 90% confidence interval will be estimated.

Analysis of Secondary Endpoints

- One sided Clopper-Pearson 90% confidence intervals will be estimated for the proportion of patients achieving re-epithelization (GPG Severity Score of 0) at Visits 3, 4, 5 , 6, 7, 8, and 9
- We will apply a two-sided paired t-test to evaluate significance of the mean difference of GPG score at Week 16 versus Week 0.
- Mean patient reported scores of pain (Pain VAS) and quality of life (DLQI) at baseline will be compared to those at Week 16 and treatment termination using the student's t- test to compare between subject's pre and post-treatment scores.
- One sided Clopper-Pearson 90% confidence intervals will be estimated for the proportion of patients with recurrence or worsening of PG lesions from point of complete re-epithelization or spesolimab cessation at end of treatment visit (Week 28 or Week 26 depending on dosing frequency).

Interim Analysis
An interim analysis will be performed after the first 10 subjects complete Week 16. We will continue enrollment during this time. Proportion of patients achieving one-point GPG score decrease will be reported. Changes from baseline at Week 16 in the PG lesions (number, size, GPG score) will be evaluated and reported. Enrolled subjects will continue to receive treatments during this time.

Data Transfer and Management
Data including the patient info, demographics, clinical scores will be stored in password-protected files that will be shared only with investigators and a biostatistical team, if necessary. Data will be stored on secure Mount Sinai servers that may only be accessed by investigators listed on this protocol.

Analysis of Safety and Tolerability
Safety will be evaluated by tabulations of adverse events (AEs) and will be presented with descriptive statistics at each visit. AEs will be coded using the CTCAE, Common Terminology Criteria for Adverse Events, V 4.0 and MedDRA. The number and percentage of subjects/lesions experiencing an AE/SAE will be stratified by system organ class, or a preferred term, and/or severity of the adverse event, and recorded and tabulated overall by each sub-strata. Each subject will be counted only once within a system organ class or a preferred term using the adverse events with the highest severity within each category. All information pertaining to adverse events noted during the study will be listed by subject, detailing verbatim given by the investigator, preferred term, system organ class, date of onset, date of resolution, severity, and relationship to treatment. A tabulation of AEs will be provided by subject.

Table 3. Schedule of Events Q4 Week Dosing Through Week 28

Visit Week	(Up to -28 Days before Baseline	0	4	8	12	16	20	24	28	4 wk post-spesoli-mab last dose	8 wk post-spesoli-mab last dose	12 wk post-spesoli= mab last dose	16 wk post-spesoli-mab last dose		
Visit #	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**		
Visit Type	**Screen=ing**	**Baseline**	**TX**	**TX**	**TX**	**TX**	**TX**	**TX**	**TX**	**F/Up**	**F/Up**	**F/Up**	**F/Up**	**Early Term (ET)**	**Additional Treatment Visits**
Informed Consent	X														
Inclusion/ Exclusion Criteria	X	X													
Demographics/ Medical Hx[1]	X														
Limited Physical Exam	X	X													
Vitals[2]	X	X	X	X	X	X	X	X	X					X	X
Serum Preg Test	X														
Urine Preg Test		X	X	X	X	X	X	X	X					X	X
CBC w/differential, CMP and CRP	X	X	X	X	X	X	X	X	X					X	X
Screening for TB (Quantiferon Gold, or PPD), HIV, HepB and HepC	X														
PG Clinical Assessments (including number location and measurements)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Global PG (GPG) Severity Score	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Subject PG [illegible]stionnaire DLQI		X	X	X	X	X	X	X	X	X	X	X	X	X	X

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Visit Week	(Up to -28 Days before Baseline	0	4	8	12	16	20	24	28	4 wk post-spesoli-mab last dose	8 wk post-spesoli-mab last dose	12 wk post-spesoli= mab last dose	16 wk post-spesoli-mab last dose		
Visit #	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**		
Visit Type	**Screen= ing**	**Baseline**	**TX**	**TX**	**TX**	**TX**	**TX**	**TX**	**TX**	**F/Up**	**F/Up**	**F/Up**	**F/Up**	**Early Term (ET)**	**Additional Treatment Visits**
Standardized Photographs		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record and changes related to associated conditions (such as IBD, RA, etc) if applicable		X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum Cytokine Profile O-Link Inflammatory Panel		X				X				X	X	X	X	X	
Pharmaco-kinetics, ADA, NAb		X		X		X			X					X	
Dispense Drug		X	X	X	X	X	X	X	X						
Concomitant Medications	X[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[1] Includes current and past medical conditions in addition to personal and family history of inflammatory bowel disease, rheumatoid arthritis, and autoimmune conditions as well as history of myeloproliferative disorders and malignancy

[2] Includes height and weight (only at screening), blood pressure, and pulse

[3] Pre-dose PK, ADA, NAb samples will be obtained at selected visits (Visit 2, 4, 6, and 9 or ET). At Week 0/Visit 2, a post-dose PK samples will also be obtained approximately 5 mins after end of i.v. infusion.

[4] Record all concomitant medications at each visit, and at screening also collect any medications taken within the last 30 days, and previous therapies/treatments for PG (including systemic and topical treatments, and invasive treatment such as surgery, radiation and cryotherapy).

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Table 4. Schedule of Events Q4 Week Dosing through Week 8 Followed by Q3 Week Dosing Through Week 26

Visit Week	(Up to -28 Days before Baseline	0	4	8	11	14	16	17	20	23	26	4 wk post-spesoli-mab last dose	8 wk post-spesoli-mab last dose	12 wk post-spesoli= mab last dose	16 wk post-spesoli-mab last dose		
Visit #	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**		
Visit Type	**Screen= ing**	**Baseline**	**TX**	**TX**	**TX**	**TX**		**TX**	**TX**	**TX**	**TX**	**F/Up**	**F/Up**	**F/Up**	**F/Up**	**Early Term (ET)**	**Additional Treatment Visits**
Informed Consent	**X**																
Inclusion/ Exclusion Criteria	**X**	**X**															
Demographics/ Medical Hx[1]	**X**																
Limited Physical Exam	**X**	**X**															
Vitals[2]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**					**X**	**X**
Serum Preg Test	**X**																
Urine Preg Test		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**					**X**	**X**
CBC w/differential, CMP and CRP	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**					**X**	**X**
Screening for TB (Quantiferon Gold, or PPD), HIV, HepB and HepC	**X**																
PG Clinical Assessments (including number location and measurements)	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Global PG (GPG) Severity Score	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
: PG nnaire QI		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

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Visit Week	(Up to -28 Days before Baseline	0	4	8	11	14	16	17	20	23	26	4 wk post-spesoli-mab last dose	8 wk post-spesoli-mab last dose	12 wk post-spesoli= mab last dose	16 wk post-spesoli-mab last dose		
Visit #	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**		
Visit Type	**Screen= ing**	**Baseline**	**TX**	**TX**	**TX**	**TX**		**TX**	**TX**	**TX**	**TX**	**F/Up**	**F/Up**	**F/Up**	**F/Up**	**Early Term (ET)**	**Additional Treatment Visits**
Standardized Photographs		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Record and changes related to associated conditions (such as IBD, RA, etc) if applicable		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Serum Cytokine Profile O-Link Inflammatory Panel		**X**					**X**					**X**	**X**	**X**	**X**	**X**	
Pharmaco-kinetics, ADA, NAb [3]		**X**		**X**			**X**				**X**					**X**	
Dispense Drug		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**						
Concomitant Medications	**X [4]**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Adverse Events	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

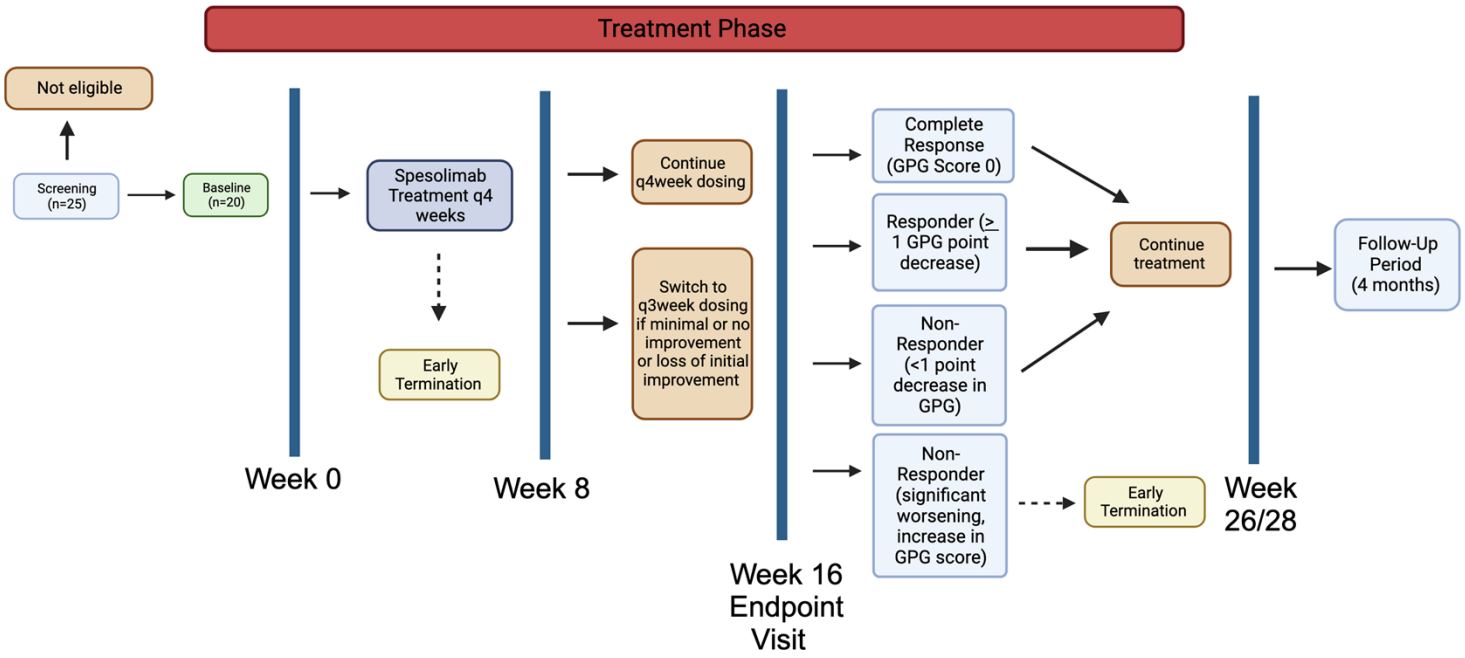
[1] Includes current and past medical conditions in addition to personal and family history of inflammatory bowel disease, rheumatoid arthritis, and autoimmune conditions as well as history of myeloproliferative disorders and malignancy

[2] Includes height and weight (only at screening), blood pressure, and pulse

[3] Pre-dose PK, ADA, NAb samples will be obtained at selected visits (Visit 2, 4, 7 and 11, or ET). At Week 0/Visit 2, a post-dose PK samples will also be obtained approximately 5 mins after end of i.v. infusion.

[4] Record all concomitant medications at each visit, and at screening also collect any medications taken within the last 30 days, and previous therapies/treatments for PG (including systemic and topical treatments, and invasive treatment such as surgery, radiation and cryotherapy).

Figure 3. Flow Diagram for Participants



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Appendix 1. Clinician Assessment of Pyoderma Gangrenosum

At each visit, the following assessments will be performed:

1. Photographs of target PG ulcer (and other PG ulcers present)
2. Measure length, width, and depth target lesion

The following tools/questions have been adapted from various clinical studies for pyoderma gangrenosum and other dermatological conditions[22-24].

Global Pyoderma Gangrenosum (GPG) Severity Score

Assess subject GPG severity of target lesion at each visit by using below categories

I. INFLAMMATION (adapted from Foss, C. et al 2008)[1]

Ulcer Border Erythema	Point Value
None; possible residual hyperpigmentation	0
Slight: Pink to red color	1
Mild: Red color	2
Moderate: Deep red color	3
Severe: Violaceous/Grey	4

Ulcer Border Elevation	Point Value
None; flat border in plane with surrounding skin	0
Slight: border slightly elevated, <1 mm above ulcer base	1
Mild: Border noticeably elevated (1-2 mm) above ulcer base and surrounding skin	2
Moderate: Border significantly elevated above ulcer base (2-5mm)	3
Severe: Significant, rolled border >5 mm in any part of ulcer	4

Ulcer Purulence	Point Value
None: dry ulcer base	0
Slight Purulence • minimal to no purulent drainage • dressing is dry at presentation and dabbing lesion with 4x4 gauze does not appreciably wet the gauze. • No drops of purulence appreciated.	1

Mild Purulence • Few drops purulence appreciated upon examination. • Dressings are damp at presentation and dabbing the wound with a 4x4 gauze wets the first layer of the gauze.	2
Moderate Purulence • Ulcer bed covered with purulent drainage • Dressings are wet at presentation and ulcer bed significantly wets a 4x4 gauze upon presentation.	3
Severe Purulence • Necrotic tissue may be present • Extensive purulent drops present on ulcer bed • Dressings soaked at presentation and soaks 4x4 gauze when cleaned (can wet multiple 4x4 gauzes).	4

II. RE-EPITHELIZATION

% Active Ulcer Base	Point Value
0% Active Ulcer	0
1%-25% Active Ulcer	1
26-50 % Active Ulcer	2
51-75% Active Ulcer	3
76-100% Active Ulcer	4

% Granulation Tissue	Point Value
Re-epithelization evident with cribiform scarring	0
More than 90% granulation tissue with some re-epithelization of skin evident	1
Mostly granulation tissue without any evidence of re-epithelization	2
Some evidence of granulation tissue; mostly purulent ulcer	3
No evidence of granulation tissue	4

III. PG ULCER Diameter

PG Ulcer Size	Point Value
No ulcer	0
Lesion measures greater than 0 cm and less than or equal to 2 cm	1
Lesion measures greater than 2 cm and less than or equal to 4 cm	2
Lesion measures greater than 4 cm and less than or equal to 6 cm	3
Lesion measures greater than 6 cm and less than or equal to 8 cm	4
Lesion measures greater than 8 cm and less than or equal to 10 cm	5
Lesion measures greater than 10 cm	6

Final Calculation

Sum of Points	Target Lesion GPG Severity Score & Ulcer Description
0-5	Completely Clear: 0 • evidence of cribriform scarring, re-epithelization and possible residual hyperpigmentation. 0% ulceration apparent and lesion is dry
6-10	Almost Clear: 1 • <25% of active ulceration present; more than 90% granulation tissue present with mild pink, slightly elevated borders. Some evidence of re-epithelization. Minimal to no purulent drainage at presentation; dressing is dry at presentation and dabbing lesion with 4x4 gauze does not appreciably wet the gauze. No drops of purulence appreciated.
11-15	Mild: 2 • <50% of active ulceration with perceptible border elevation with mild red border. Evidence of granulation tissue without any re-epithelization of skin. Few drops purulence appreciated upon examination. Dressings are damp at presentation and dabbing the wound with a 4x4 gauze wets the first layer of the gauze.
16-20	Moderate: 3 • <75% active ulceration with marked red, rolled borders and significant purulence. Some evidence of granulation tissue with multiple purulent drops and significant purulence on ulcer bed at presentation. Dressings are wet at presentation and ulcer bed significantly wets a 4x4 gauze upon presentation.
21-26	Severe: 4 • 100% active ulcer with violaceous, raised rolled borders. Necrotic tissue may be present. No evidence of granulation tissue. Extensive purulent drops present on ulcer bed. Dressings soaked at presentation and soaks 4x4 gauze when cleaned (can wet multiple 4x4 gauzes).

Effective Date: 2/27/2024
End Date:8/14/2024

Appendix 2. Patient Pyoderma Gangrenosum Questionnaires

The following tools/questions have been adapted from various clinical studies for pyoderma gangrenosum and other dermatological conditions[22].

Patient Reported- "Ooze" or Purulence Measure [24]

1. How often do you need to change your wound dressings in the past 4 weeks (circle the response that best applies to you)?
    a. Multiple times per day
        i. How many times? _____
    b. Daily
    c. Every other day
    d. Every 3 days
    e. Once a week
    f. I do not use dressings
        i. If you no longer require dressings, how many days after treatment did you stop placing dressings on your lesion (in days)? _____
        ii. I have never used dressings for the ulcers

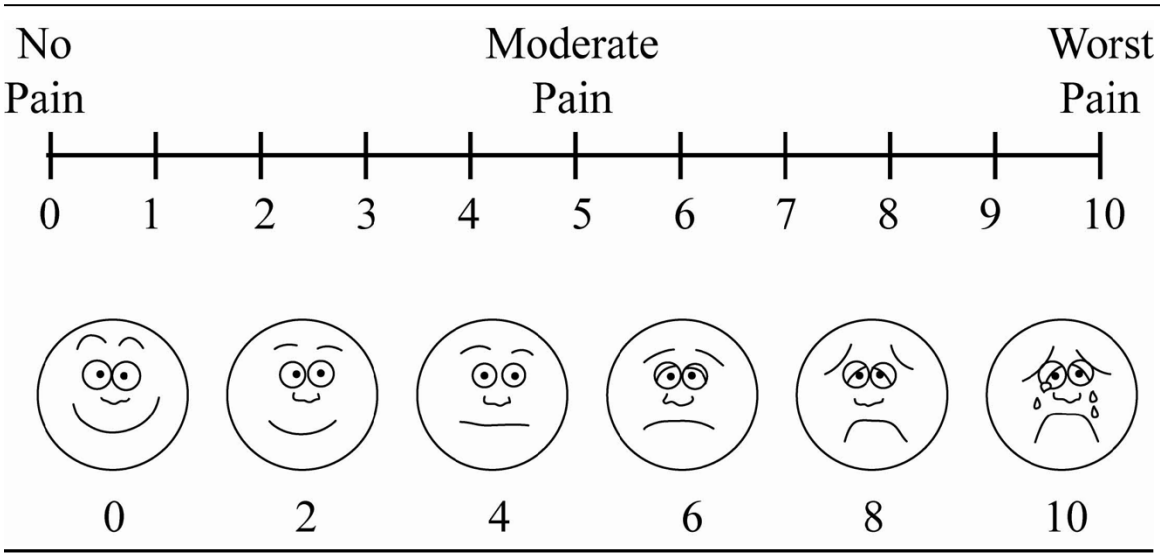
    g. Other: _____

Patient Pain Visual Analogue Scale (VAS) [22]

Patients will be asked to report pain scores at each visit. Patients will report scores on a scale of 0 to 10.

0 signifies no pain and 10 signifies the worst pain imaginable. Choose an integer whole number.

Effective Date: 2/27/2024
End Date:8/14/2024



https://assessment-module.yale.edu/im-palliative/visual-analogue-scale

DLQI (Dermatology Life Quality Index)

The DLQI is a validated questionnaire consisting of 10 questions that has been used in many randomized controlled trials in dermatology. [22,22]

Scoring
The scoring of each question is as follows:

Very much	scored 3
A lot	scored 2
A little	scored 1
Not at all	scored 0
Not relevant	scored 0
Question unanswered	scored 0

The DLQI is calculated by summing the score of each question. The maximum score is 30 and minimum score is 0. Higher score represents a quality of life that is more impaired.

Definition of DLQI Scores
0-1 = no effect at all on patient's life
2-5 = small effect on patient's life
·10 = moderate effect on patient's life
1-20 = very large effect on patient's life

21-30 = extremely large effect on patient's life

A change in DLQI score of at least 4 points is considered clinically important [22]. Such change suggests that there has actually been a meaningful change in that patient's quality of life since the previous measurement of his/her/their DLQI scores.

Dermatology Life Quality Index

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please check one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **yard?**	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐

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7.	Over the last week, has your skin prevented you from **working** or **studying**?	yes no	☐ ☐	Not relevant ☐
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐

Appendix 3 – Amendments

Amendment #1 August 10, 2023
Page 1-Amendment 1 June 13, 2023 added.

Page 2 – Table of Contents added Appendix 1 Amendments page 31 and revised References to page 33

Page 8 and 9 – Study Design Overview

- Clarified length of dosing period:
  "Subjects will receive 900 mg of spesolimab intravenously (IV) over 90 minutes every 3 weeks until re-epithelization (GPG Severity Score 0) and regression of target lesion, or through Week 15, whichever is sooner. Subjects will receive treatment for a maximum of 15 weeks."
- Clarified which subjects will be monitored during the Follow-Up Period:
  "Subjects who reached GPG score 0 will then be monitored for recurrence of lesions for 4 months subsequent to treatment cessation."

Page 13, 14 and 15 – Procedures

- Clarified length of dosing period:
  "Subjects will receive 900mg IV spesolimab every 3 weeks until re-epithelization of skin and/or GPG severity score 0, or through Week 15, whichever is sooner. Subjects who achieved GPG score 0 will then be monitored once a month, for 4 months after treatment cessation to monitor recurrence of lesions and adverse events."

- Clarified which subjects will be monitored during the Follow-Up Period:
    - If patient has seen full-epithelization of skin (GPG Score 0), patient will continue with follow-up phase of study.
    - If patient has not experienced any improvement or has experienced worsening of condition (rise in GPG score), patient will be considered a non-responder and be discontinued from the study
    - If patient has experienced a decrease in GPG score but not full-epithelization of skin (GPG Score 0), patient will be a partial responder and will be discontinued from the study, however, they may seek additional infusions outside of this study.
- Clarified that Week 16 is Visit 8
- Revised Follow-Up period numbers to Visits 9-12 and added month 3.

Page 20 Table 1: Total Volume of Blood Collected During the Study – Updated table with corrected visits and volume amounts.

Page 22 Investigational Drug Supply – added that drug will be supplied for up to a total of 6 infusions.

<u>Amendment #2 December 21, 2023</u>

Throughout document: Replaced “Guenin” with “Global”

Page 1- Amendment 2 October 19, 2023 added; Updated investigators

Page 2- Table of Contents revised paginations

Page 3- Background: corrected PARACELSUS score definition to subject with a score greater than **or equal to** 10 points instead of greater than 10 points

Page 8- Objectives: removed time point of Week 16

Page 8 – Endpoints:

- clarified primary endpoint one point decrease in GPG severity score at Visit 8 – one week post 6th infusion instead of week 16 .
- Removed references to Weeks and added only references to Visits.
- Added secondary endpoint Time to worsening (1 or more GPG point increase) of target PG lesion from spesolimab cessation

Page 9. Study Design Overview:

- Changed spesolimab dosing from every 3 weeks to every 4 weeks. Added a potential dose switch at week 8 if subject does not show improvement. Updated section with only Visits and not Weeks to reflect variable dosing schedules.
- Revised who will be discontinued from treatment: Only if subject significantly worsens while on treatment will they be removed from study and not receive the full 6 infusions.
- Added the collection of Pharmacokinetics, NAb, and ADA

age 9 Inclusion Criteria:

- Corrected inclusion criteria PARACELSUS score must be greater than or equal to 10, instead of greater than 10

Page 13 Procedures:

- Clarified that all subjects will receive infusions of spesolimab every 4 weeks until Visit 4, at which time frequency can be increased to every 3 weeks for the remainder of the treatment period. All subjects will receive 6 infusions regardless of full-reepithelization, unless they experience worsening. Clarified that all responders will enter the 4-month follow-up period. Only patients who experience disease progression will be removed from the study and/or follow-up period to receive standard of care of PG. Clarified that patients benefiting from treatment at week 28 but need more therapy to achieve wound closure may be eligible to continue on treatment (on case-by-case basis) to a maximum of 52 week after discussion with Boehringer Ingelheim trial team.
- Screening: Added review of PARACELSUS criteria and determination of PARACELSUS score in screening Visit 1.
- Screening:Added HIV screening and added an option to perform PPD in lieu of quantiferon gold.
- Visit 2: Added PK, ADA and NAb collections; removed the double entry of “vitals”
- Visit 3 thru 7: removed references to “Weeks”; added urine pregnancy tests for females of child bearing potential; added PK, ADA and NAb collections
- Visit 9: Clarified those that will enter follow-up (anyone who has not worsened)
- Visit 10-13: Added assessment of associated comorbidities; added that subjects who worsen will be discontinued from Follow-Up.
- Early Termination: Added urine pregnancy test for FOCBP; added assessment of associated comorbidities.

Page 20 Table 2 Total Volume of Blood Collected

- Removed references to Week #s; split Visits 3-6 to Visits 3, 5, 7, 8, 9 and Visit 4 and Visit 6; updated the total amount of blood collected at Baseline and Visit 8; updated follow up visits to Visits 10-13.

Page 20 Discontinuation of Treatment:

- Defined subject disease worsening as a reason for discontinuation of treatment.

Page 22 Investigational Drug Supply:

- Added language to include dose frequency switch possibility at week 8 for patients who experience progression of disease.
- Added that drug will be supplied by Boehringer Ingelheim

Page 22-23 Statistical considerations:

- Updated section to match revised endpoints.
- Removed references to Weeks and included only Visits
  Changed secondary endpoint week numbers to reflect dosing frequency change from every 3 to every 4 weeks with potential to switch after week 8 to every 3 week.
  Revised “Patients” to “Subjects”
- Included explanation of power analysis in sample size section
- Updated description of descriptive statistics section

- Updated Primary and Secondary endpoints sections to include description of paired t-test, CI and p-value.

Page 23 Analysis of Secondary Endpoints
- Updated to include Visit #'s

Page 25-28 Schedule of Events Table(s)
- Added second schedule of events table: 'Table 4 Schedule of Events Q4 Week Dosing through Week 8 Followed by Q3 Week Dosing Through Week 26'
- Updated Week #s.
- Added HIV at Screening
- Added option of PPD at screening in lieu of quantiferon gold.
- Removed urine pregnancy tests during follow-up
- Added PK, ADA, and NAb sample collections at Baseline, and Visits 4, 6 and 9 (Table 3) or at Baseline and Visits 4, 7 and 11 (Table 4).
- Replaced "Guenin" with "Global"
- Added footnote regarding PKs, ADA and NAb for Table 3: "Pre-dose PK, ADA, NAb samples will be obtained at selected visits (Visit 2, 4, 6, and 9 or ET). At Week 0/Visit 2, a post-dose PK samples will also be obtained approximately 5 mins after end of i.v. infusion." and for Table 4: "Pre-dose PK, ADA, NAb samples will be obtained at selected visits (Visit 2, 4, 7 and 11, or ET). At Week 0/Visit 2, a post-dose PK samples will also be obtained approximately 5 mins after end of i.v. infusion."

Page 29: Corrected Figure 3 with "Visits" and updated outcome measures

Page 26: updated description of GPG

Page 32 Appendix 1:
- Updated GPG Severity score name from 'Guenin' to 'Global'
- Updated last category of final calculation sum of points