CLINICAL STUDY PROTOCOL

OPEN LABEL EXPLORATORY PHASE IIA TRIAL TO INVESTIGATE THE SAFETY AND EFFICACY OF IFX-1 IN TREATING SUBJECTS WITH PYODERMA GANGRENOSUM (OPTIMA)

Protocol Number:	IFX-1-P2.7
Compound:	IFX-1
Short Title:	Exploratory study of IFX-1 in Pyoderma Gangrenosum
Phase:	II
Indication:	Treatment of pyoderma gangrenosum
IND Number:	136470
Sponsor Name and Address:	InflaRx Winzerlaer Strasse 2 07745 Jena, Germany
Version and Date:	Version 4.0 Including Amendment 02, 14 May 2020

PROTOCOL SIGNATURES

Confirmation of the Final Protocol

We hereby certify that this is the final version of the protocol:

Protocol Number:	IFX-1-P2.7 including Amendment 01
Title:	Open label exploratory phase IIa trial to investigate the safety and efficacy of IFX-1 in treating subjects with Pyoderma Gangrenosum (OPTIMA).

Sponsor Signatory:

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Signature of Coordinating Investigator:

Protocol Number: IFX-1-P2.7 including Amendment 01

Title: Open label exploratory phase IIa trial to investigate the safety and efficacy of IFX-1 in treating subjects with Pyoderma Gangrenosum.

Herewith I declare that I have read and understood the present protocol and agree to honor each part of it. By signing this study protocol, I agree to conduct the clinical study, following approval by an Ethics Committee, in accordance with the study protocol, the current International Council for Harmonization Guidelines for Good Clinical Practice (GCP), and applicable regulatory requirements. I will ensure that all the subjects enrolled in the study by my site will be treated, observed, and documented in accordance with this protocol. I will ensure that all persons assisting with the study under my supervision are adequately informed about the protocol, the investigational product, and their duties.

[redacted] Date

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ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ANCOVA	Analysis of covariance
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case report form
ECG	Electrocardiogram
EOT	End of treatment
GCP	Good clinical practice
GDPR	General Data Protection Regulation (European Union)
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed consent form
IFN	Interferon
IL	Interleukin
IMP	Investigational medicinal product
IRB	Institutional review board
NRS	Numeric rating scale
Ob(x)	Observation visit x
PPS	Per protocol set
Q2W	Every 2 weeks
SAE	Serious adverse event
SAF	Safety set
SUSAR	Suspected unexpected serious adverse reactions
TEAE	Treatment emergent adverse events
TNF	Tumor necrosis factor
V(x)	Visit x

Definitions of Terms

Term	Definition
Investigational medicinal product (IMP):	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study.
Enrolled:	A subject is considered to be enrolled in a study as soon as he/she signed informed consent (i.e., at screening).
Measurement:	Recording the value of a variable, e.g., recording of blood pressure.
Procedure:	Specific test performed on the subject, e.g., sphygmomanometry after 10 minutes in supine position.
Assessment or evaluation:	Systematic judgment of the recorded variable, e.g., clinical relevance of abnormal blood pressure.
Variable:	A measurable attribute or event that have either qualitative or quantitative values which may be expected to vary over time and within or between subjects, e.g.: diastolic blood pressure at baseline (mmHg); diastolic blood pressure at Week 4 (mmHg)
Endpoint:	A variable that pertains to an objective of a study, e.g., mean change in diastolic blood pressure from baseline to Week 4 or percentage of responders at Week 4.
Baseline value:	The last measurement of a variable before the first dose of IMP.

1 SYNOPSIS OF STUDY

Protocol Number:	IFX-1-P2.7
Protocol Title:	Open label exploratory phase IIa trial to investigate the safety and efficacy of IFX-1 in treating subjects with Pyoderma Gangrenosum (OPTIMA).
Short Title:	Exploratory study of IFX-1 in Pyoderma Gangrenosum
Phase:	II

Indication:	Treatment of pyoderma gangrenosum
IND Number:	136470
Study sites:	Multiple
Sponsor:	InflaRx Winzerlaer Strasse 2 07745 Jena, Germany
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Rationale:

IFX-1 is a monoclonal antibody (which specifically binds to the soluble human complement split product C5a) that is being developed for the treatment of various diseases in which complement activation plays a role.

Neutrophilic dermatoses are a spectrum of inflammatory disorders characterized by skin lesions resulting from a neutrophil-rich inflammatory infiltrate in the absence of infection. Pyoderma gangrenosum is associated with a neutrophilic leukocytosis, which is likely to be triggered by C5a. Pyoderma gangrenosum lesions have pronounced neutrophilic infiltration and the expression of interleukin (IL)-1β, IL-17, tumor necrosis factor (TNF)-alpha, and their receptors is significantly elevated, indicating an auto-inflammatory condition. C5a represents a promising target for blocking and modulating acute or chronic inflammation. Several animal models have demonstrated a positive impact of a blockade of the C5a/C5aR signaling axis on acute and chronic inflammatory diseases. A recent open label study deploying IFX-1 in 12 subjects suffering from hidradenitis suppurativa revealed early evidence of disease modifying activity of IFX-1 in this neutrophil driven skin disorder, with a sustained clinical response even after only 8 weeks of treatment. Given the neutrophil driven nature of pyoderma gangrenosum, the current study is designed to investigate whether IFX-1 could also be a treatment option for this autoimmune type dermatosis.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• Explore the safety of IFX-1 for the treatment of subjects with pyoderma gangrenosum	• Occurrence, nature and intensity of treatment emergent adverse events (TEAEs), related TEAEs, serious TEAEs, and adverse events of special interest
Key Secondary	
• Explore the efficacy of IFX-1 for the treatment of pyoderma gangrenosum	• Responder rate defined as Physician's Global Assessment ≤3 of target ulcer at Visits V4, V6, V10, and V16 (End of Treatment [EOT]) • Time to complete closure of pyoderma gangrenosum target ulcer (investigator assessment)
• Explore additional clinical outcome parameters in subjects with pyoderma gangrenosum under the treatment with IFX-1	• Percentage change in wound area and wound volume (wound healing) of target ulcer between Visits V1-V4, V1-V6, V6-V10; V10-V16, and V1-V16 (photographic assessment) • Rate of change per day in area of target ulcer (photographic assessment) • Number of subjects with a decrease in area of target ulcer of 50% or more at Visit V16 (EOT) compared to baseline (photographic assessment) • Number of subjects with a decrease in area of target ulcer of 100% at Visit V16 (EOT) compared to baseline (remission) (photographic assessment) • Degree of erythema and border elevation of the target ulcer compared to baseline at Visits V4, V6, V10, and V16 (EOT) (investigator assessment) • Mean change from baseline in pain assessed by Numeric Rating Scale (NRS) at Visits V4, V6, V10, and V16 (EOT) • Mean change from baseline in Dermatology Life Quality Index (DLQI) at Visits V4, V6, V10, and V16 (EOT)

Scientific exploratory parameters

The following will be collected at the time points given in the Schedule of Assessments (Section 2).

Blood for the analysis of:

- [redacted]

Fluid draining from the target ulcer, if available, for the analysis of:

- Immunology:
  - [redacted]
- Bacteria using a bacterial culture and polymerase chain reaction

Biopsy from the target ulcer border tissue for immunostaining for:

- [redacted]

Stool samples for the analysis of:

- [redacted]

Absolute values and changes from the baseline value will be evaluated for the above parameters.

In addition, routine safety laboratory tests will be performed. Blood will also be analyzed for antineutrophil cytoplasmic antibody (ANCA) and antinuclear antibody (ANA) formation.

Overall Design:

This is an open-label explorative study in subjects with pyoderma gangrenosum. Subjects will be examined according to the Schedule of Assessments (Section 2) at each visit. All subjects will receive IFX-1 (IMP). The IMP will be administered exclusively at site visits (Visit V1 to Visit V15). Examinations are defined in the Schedule of Assessments (Section 2). At the end of treatment with IMP, subjects should complete an End of Treatment (EOT; [redacted]. Thereafter, subjects receive treatment for their pyoderma

gangrenosum at the discretion of the investigator. Subjects will be followed up for an additional [redacted] after EOT for safety reason, with two observation visits (Visit Ob1 after 30 days and Visit Ob 2 after 60 days). Visit Ob2 is the final visit in the study.

Number of Subjects:

This is planned to be a multi-center study with about 18 subjects treated with IMP (IFX-1).

Subjects discontinuing treatment will not be replaced. It is expected that approximately 15 subjects will undergo at least [redacted] months treatment.

Treatment Groups and Duration:

The estimated recruitment period is approximately 6 to 12 months.

The study duration for an individual subject includes screening ([redacted]), the treatment period ([redacted]), and the observational follow up [redacted]).

If a subject discontinues the trial prematurely for any reason, they should have a termination visit (Visit V16 = EOT) and should be followed up at Visit Ob1 and Visit Ob2.

All subjects will receive IFX-1 at a maximum of 15 dosing visits.

There will be 3 dosing groups (Group 1, Group 2, and Group 3) of 6 subjects each. Each group of subjects is recruited sequentially. The next dose group will be initiated if the previous dose was considered safe and well tolerated. If dosing in Group 2 cannot be initiated, then a further 6 patients will be recruited in Group 1.

Study Population Inclusion Criteria:

Informed Consent

1. Capable of giving signed informed consent as described in Regulatory and Ethical Considerations (63), which includes compliance with the requirements and restrictions listed in the informed consent form and in this protocol, and approval for photographic documentation

Age

2. Subjects must be18 years or older, at the time of signing the informed consent

Sex

3. Male or female

Type of Subject and Disease Characteristics

4. Diagnosis of an ulcerative form of pyoderma gangrenosum confirmed by the investigator
5. In addition, the subject must fulfill at least 3 of the following 6 criteria at screening:

   History of

   - Pathergy (ulcer occurring at the sites of trauma)
   - Personal history of inflammatory bowel disease or inflammatory arthritis
   - History of papule, pustule or vesicle that rapidly ulcerated

   Clinical examination (or photographic evidence) of

   - Peripheral erythema, undermining border, and tenderness at site of ulceration
   - Multiple ulcerations
   - Cribriform or “wrinkled paper” scar(s) at sites of healed ulcers

6. Subject has a minimum of 1 evaluable ulcer (≥2 cm^2) at screening

Study Population Exclusion Criteria:

Subjects are excluded from the study if any of the following criteria apply:

Related to Presenting Medical Condition

1. Pyoderma gangrenosum target ulcer for more than 3 years before screening
2. Surgical wound debridement within the previous 2 weeks before screening

Other Medical Conditions

3. Any comorbidity such as psychiatric or general illness that may put the subject at risk as determined by investigator

4. Poor general condition that might affect wound healing, as determined by the investigator
5. One of the following abnormal laboratory findings at screening:

- White blood cell count <3500/mm^3
- Platelet count <100,000/mm^3
- Hemoglobin <7 g/dL
- Total bilirubin >1.5 times the upper limit of normal and/or alanine aminotransferase or aspartate aminotransferase >2.5 times upper limit of normal

6. Human immunodeficiency virus, hepatitis B or hepatitis C viral screening test showing evidence of active or chronic viral infection at screening or a documented history of the human immunodeficiency virus, hepatitis B, or hepatitis C
7. Evidence of active or latent tuberculosis
8. History of malignancy in the previous 5 years (except for non-melanoma skin cancer and cancer in-situ of the cervix)
9. Subjects with ulceration due to medical causes other than pyoderma gangrenosum (e.g. diabetic ulceration)

Prior/Concomitant Therapy

10. Infection requiring suppressive anti-infective therapy (such as latent tuberculosis, pneumocystis, aspergillosis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria)
11. Use of intravenous antibacterial, antiviral, anti-fungal, or anti-parasitic agents within 30 days before screening
12. Any drug treatment for pyoderma gangrenosum including corticosteroids (>10 mg prednisone or prednisone equivalent), intralesional steroids, cyclosporine A, biologicals and immunosuppressives (with the exception of antibiotics for wound superinfection) used within a time of 5 half-lives of the drug before screening (see 81)
13. Received live attenuated vaccine within the previous 3 months before screening
14. Major surgery planned during the time of foreseen study participation

Prior/Concurrent Clinical Study Experience

15. The subject has participated in an interventional clinical study during the 3 months before screening, or plans to participate in a clinical study
16. Previous exposure to IFX-1 in this or another study
17. Known hypersensitivity to polysorbate 80 (excipient of the IMP)

Other Exclusion Criteria

18. Prior exposure to anticomplement 5a before screening
19. History of sever anaphylactic reaction to any components of C5a before screening
20. Known or suspected active drug and/or alcohol abuse at screening

21. Breast feeding or pregnant woman at screening
22. Male and female subjects of childbearing potential unwilling to follow the contraceptive guidance in 77 during the treatment period and for at least 30 days after the last dose of IMP
23. Pregnancy or positive pregnancy test at screening
24. The subject is imprisoned or lawfully kept in an institution at screening
25. Evidence or suspicion that the subject might not comply with the requirements of the study protocol
26. The subject is an employee or direct relative of an employee at the study site or sponsor
27. Any other factor which, in the investigator's opinion, is likely to compromise the subject's ability to participate in the study

Investigational medical product (IMP), dose, and mode of administration

The IMP (IFX-1) will be provided in [redacted] glass vials at a concentration of [redacted] vial) for reconstitution and intravenous administration. For each dose, the required amount of IFX-1 will be diluted with [redacted] sodium chloride to a total volume of approximately [redacted] mL and given to the subject as a single intravenous dose over 30 to 60 minutes during a site visit.

All subjects will receive IFX-1 800 mg three times during the first week (Days [redacted]).

Starting at Day [redacted]:

- Subjects in Group 1 will continue to receive IFX-1 800 mg at 2 weekly intervals.
- Subjects in Group 2 will receive IFX-1 1600 mg at 2 weekly intervals.
- Subjects in Group 3 will receive IFX-1 2400 at 2 weekly intervals.

At Day [redacted] (Visit V7), subjects in Groups 1 and 2 may have their dose increased to IFX-1 1600 mg or 2400 mg, respectively, if there are no safety concerns and the Physician Global Assessment (main efficacy parameter) is ≥4.

Subjects will receive a total of [redacted] doses of IFX-1. The first 3 doses will be given in the first week on Day [redacted], Day [redacted], and Day [redacted]. The remaining doses will be given thereafter every 2 weeks starting from Day 15.

Statistical methods

No sample size calculation has been performed for this explorative study. The sample size is based on practical considerations in this orphan disease. Interim analyses will be performed after each initial dosing group of 6 subjects has completed Visit V10. The interim analysis will comprise adverse events, Physician's Global Assessment, and photographic documentation of area and volume.

The final analysis will be performed after all subjects have completed the trial including the EOT visit and the 2 observation visits, Visit Ob1 and Visit Ob2.

To evaluate the primary objective of this study, TEAEs, related TEAEs and serious TEAEs will be analyzed according to the number and percentage of subjects who had an adverse event (of the respective category) as well as the number of adverse events by MedDRA System Organ Class and Preferred Term. Related TEAEs and serious TEAEs will be further grouped by severity and relationship.

All other endpoints including efficacy, safety, pain and quality of life parameters will be analyzed descriptively by time point and change from baseline, as applicable. Continuous variables will be analyzed by absolute values and changes from baseline, if applicable. Basic descriptive statistics (e.g., number of observations (n), mean, standard deviation, minimum, median, maximum, lower quartile, upper quartile) will be displayed by visit or time point.

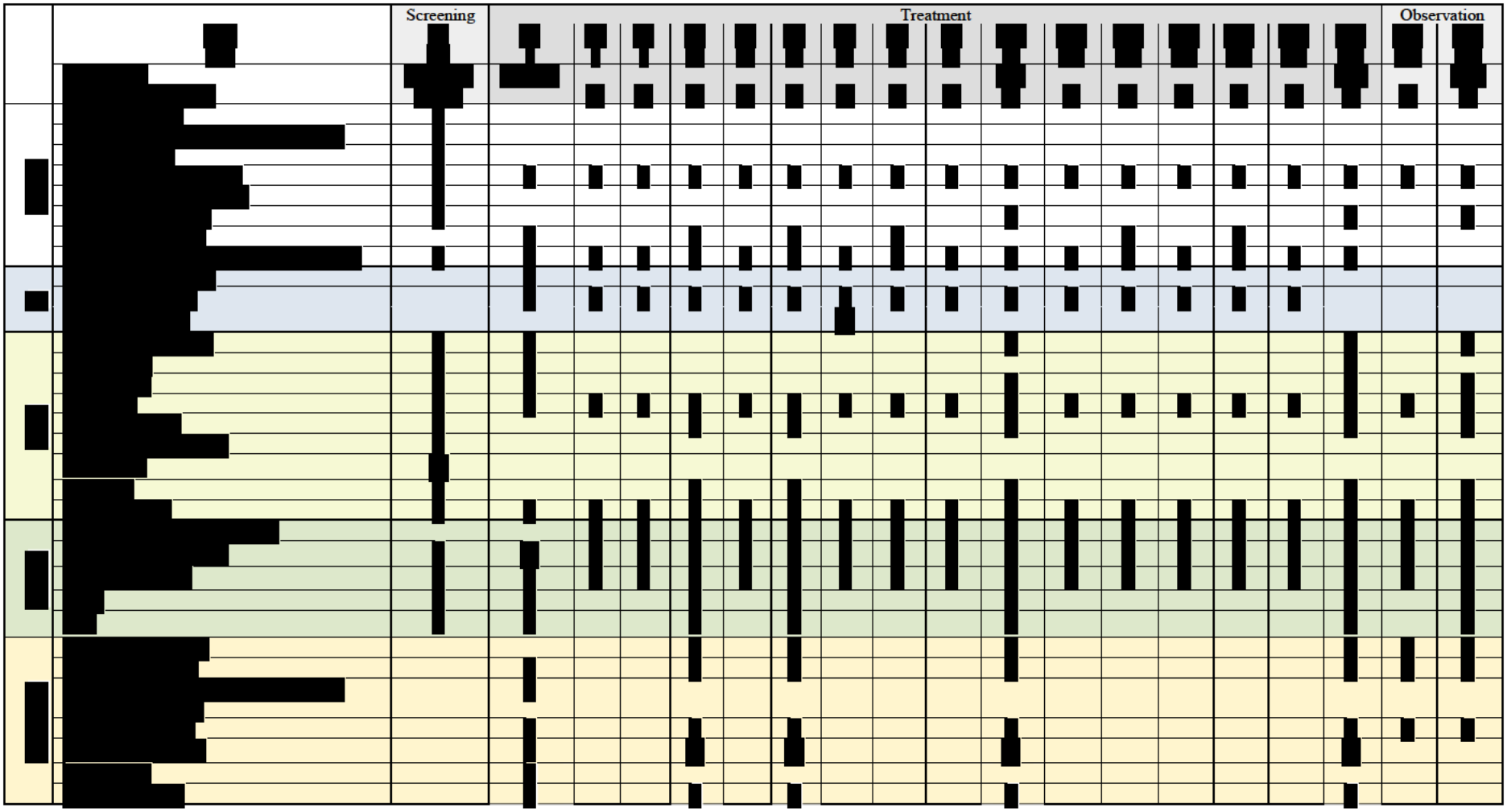
The number and percentage of subjects in each category will be displayed by visit or time point for categorical or binary variables.

Time to event endpoints which will be analyzed using Kaplan-Meier methods.

Concentrations of IFX-1 will be summarized by time point.

Statistical analyses will generally be performed for the entire study population as well as the 3 dosing groups separately. Additional stratifications based on actual dosing and IMP compliance will be defined in the statistical analysis plan.

2 SCHEDULE OF ASSESSMENTS



DLQI = Dermatology Life Quality Index; NRS = numeric rating scale; Tx= Therapy; IMP = Investigational medicinal product; EOT = End of Treatment; ECG = Electrocardiogram.

a Only if wound still open
b An historical X ray may be used if taken within 6 months prior to screening
c This photograph is the Baseline for subsequent Physician's Global Assessments
d Only for subjects in Group 1 and Group 2

3 INTRODUCTION

3.1 Study Rationale

Neutrophilic dermatoses are a spectrum of inflammatory disorders characterized by skin lesions resulting from a neutrophil-rich inflammatory infiltrate in the absence of infection. Neutrophil-rich cutaneous inflammation is also a cardinal feature of several auto-inflammatory diseases with skin involvement, the latter being caused by aberrant innate immune responses. Over-activation of the innate immune system leading to increased production of IL-1 family members and 'sterile' neutrophil-rich cutaneous inflammation are features of both inherited auto-inflammatory syndromes with skin involvement and an increasing number of neutrophilic dermatoses. Therefore, auto-inflammation may be a cause of neutrophilic dermatoses (Satoh 2016).

There are no data available on complement activation and C5a in patients with pyoderma gangrenosum. However, the disease is associated with a neutrophilic leukocytosis (Del Giacco 2011, Noblett 2009), which is likely to be triggered by C5a.

Biopsies of pyoderma gangrenosum lesions also indicated pronounced neutrophilic infiltration (Tay 2014). In addition, in skin samples, the expression of IL-1β, IL-17, TNF-alpha, and their receptors were significantly higher in pyoderma gangrenosum patients than in controls indicating that auto-inflammatory condition (Marzano 2017).

IL-1b and its known target genes IL6, CXCL8, and IL36A were significantly increased in pyoderma gangrenosum skin lesions. Under IL1-beta therapy with canakinumab therapy, 4 of 5 subjects showed a decrease in target-lesion size, Physician's Global Assessment, and Dermatology Life Quality Index, and 3 of 5 achieved complete remission, supporting the auto-inflammatory hypothesis of the pathogenesis of pyoderma gangrenosum (Kolios 2015).

The concept of blocking C5a-induced effects has been substantially reviewed in the literature and discussed as a potential new therapeutic approach in human dermatologic inflammatory diseases (Kanni 2018).

C5a represents a promising target for blocking and modulating acute or chronic inflammation. Several animal models have demonstrated a positive impact on acute inflammation. Because increased plasma levels of C5a also occur during chronic inflammation, a positive effect may also be expected in chronic inflammatory diseases. Therefore IFX-1 could be a treatment option in the auto-inflammatory disease of pyoderma gangrenosum.

3.2 Background

3.2.1 IFX-1

IFX-1 is a monoclonal antibody (which specifically binds to the soluble human complement split product C5a) that is being developed for the treatment of various diseases in which complement activation plays a role.

Nonclinical studies have demonstrated that IFX-1 binds to its target rapidly and is capable of a nearly complete blockade of C5a-induced biological effects while not affecting cleavage of C5 and formation of the complement membrane attack complex.

Single and repeated intravenous (iv) administration of IFX-1 at doses of up to 50 mg/kg over 6 months in cynomolgus monkeys resulted in no related or relevant toxicological adverse findings within an extended core battery of safety pharmacology assessments.

Various nonclinical studies have been conducted to assess pharmacological and toxicological aspects of IFX-1, none of which revealed any obvious toxicological or safety concerns for IFX-1. IFX-1 was well tolerated and did not show any toxicity with any of the doses tested. Therefore, the No Observed Adverse Effect Level was defined as the highest administered dose of 50 mg/kg (corresponding to a human equivalent dose of 16.13 mg/kg).

IFX-1 is an IMP and is not approved in any country worldwide. To date, IFX-1 has been investigated in 1 Phase I study in healthy subjects and in 4 Phase II studies in subjects with early septic organ dysfunction, in subjects undergoing complex cardiac surgery, and in subjects with moderate to severe hidradenitis suppurativa:

Study IFX-1-P1.1 (healthy subjects): in this Phase I study in 15 healthy subjects, 5 consecutive dose groups (IFX-1 0.02, 0.1, 0.5, 2, and 4 mg/kg) received single iv infusions of IFX-1 or placebo. IFX-1 was safe and well tolerated. The following adverse events were reported by the investigator as at least possibly related to IFX-1: nausea, headache, nasopharyngitis, and C-reactive protein increased.

Study IFX-1-P2.1 (subjects with early septic organ dysfunction): in this Phase II study in subjects with early septic organ dysfunction caused by pulmonary or abdominal infection, the safety, pharmacokinetics, pharmacodynamics, and efficacy of IFX-1 were investigated in 3 different dose groups (IFX-1 2 × 2 mg/kg, 2 × 4 mg/kg, and 3 × 4 mg/kg, each with a placebo control). In total, 48 subjects were treated with IFX-1. IFX-1 was safe and well tolerated. The following adverse events were reported by the investigator as at least possibly related to IFX-1: acute hepatic failure, hepatocellular injury, pulmonary embolism, hypertension, atrial fibrillation, and impaired healing.

Study IFX-1-P2.2 (subjects undergoing complex cardiac surgery): in this Phase II study in subjects undergoing complex cardiac surgery, the efficacy, pharmacokinetics,

pharmacodynamics, and safety of single doses of IFX-1 were investigated in 4 different dose groups (IFX-1 1, 2, 4, and 8 mg/kg, each with a placebo control). In total, 82 subjects were treated with IFX-1. IFX-1 was safe and well tolerated. The following adverse events were reported by the investigator as at least possibly related to IFX-1: leukocytosis, impaired healing, blood pressure decreased, and heart rate decreased.

Study IFX-1-P2.3 (subjects with moderate to severe hidradenitis suppurativa): in this Phase II study in subjects with moderate to severe hidradenitis suppurativa, the safety, pharmacokinetics, pharmacodynamics, and efficacy of IFX-1 were investigated after 9 weekly infusions of 800 mg. In total, 12 subjects were treated with IFX-1. IFX-1 was safe and well tolerated. There were no adverse events reported by the investigator as at least possibly related to IFX-1.

Study IFX-1-P2.4 (subjects with moderate to severe hidradenitis suppurativa): in this Phase II study, 177 subjects were treated with either placebo or one of 4 different dose regimens of IFX-1 (400 or 800 mg every four weeks and 800 or 1200 mg every two weeks). The IFX-1 treatment was well tolerated and although most subjects experienced TEAEs, these were for the most part non-serious and similar in all treatment groups. IFX-1 treatment was associated with low immunogenicity.

Further details on IFX-1 are given in the investigator's brochure (the current version is available in the investigator site file).

3.2.2 Pyoderma Gangrenosum

Pyoderma gangrenosum has an annual incidence of 3 to 10 per million (Cozzani 2014, Chatzinasiou 2016, Langan 2012) but the exact prevalence is difficult to determine due to missing data (Gameiro 2015). Any age may be affected, but it is most common in young and middle aged adults (Ahronowitz 2012, Wollina 2007, Chatzinasiou 2016, Gameiro 2015). This incidence is possibly higher in women (Chatzinasiou 2016, Langan 2012, Wollina 2007).

The diagnosis is based on clinical and histological findings; there is no pathognomonic clinical, histological, or biomarker finding. It is a diagnosis of exclusion, which even for experts is difficult. A diagnosis is supported by a rapid progression of a painful, necrolytic, cutaneous ulcer with an irregular, violaceous, and undermined border, with clinical findings (cribriform scarring), systemic diseases associated with pyoderma gangrenosum (e.g., ulcerative colitis), histopathologic findings (e.g., sterile dermal neutrophilic infiltration, mixed inflammation, lymphocytic vasculitis), and a history of pathergy (Sanchez 2004, Su 2004).

There are 4 disease types recognized: ulcerative (the classical variant, which is the focus of this trial), bullous (atypical), pustular, and vegetative (superficial, granulomatous). The

ulcerative variant is the most frequent, with lesions on the lower extremities and trunk. The purulent and painful lesions are small, rapidly expanding and ulcerating.

Pyoderma gangrenosum may be associated with inflammatory bowel disease in up to 65% subjects, rheumatoid or poly-arthritis in 10 to 20% of subjects, and hematological disorders in up to 25% of subjects (DeFilippis 2015, Langan 2012, Vacas 2017). In about a quarter of subjects with pyoderma gangrenosum, it may have followed trauma (Cozzani 2014). Other disease associations are: pulmonary disease (Gade 2015), systemic lupus erythematosus (Gonzalez-Moreno 2015), viral and autoimmune hepatitis (Wat 2014, Pourmorteza 2016), Wilson's disease (Freg 2016), primary immunodeficiency (common variable immunodeficiency; Simsek 2015: leucocyte adhesion deficiency; Thakur 2013, Madkaikar 2015, Vahlquist 2015: chronic granulomatous disease; Nanoudis 2017), pregnancy (Steele 2016, Takeshita 2017, Vigl 2016), and drugs (cocaine; Wang 2017: with less evidence for isoretinoin, propyluracil, sunitinib, levamisol; Wang 2017).

There is substantial medical need for effective treatment for pyoderma gangrenosum. Subjects have severe pain, long times to complete healing, and frequent relapses. The risk of death is 3-times higher than controls (Langan 2012), with an inpatient death rate of 10-20% (Adisen 2016, Cabalag 2015, Ye 2014). However, as subjects with pyoderma gangrenosum usually have notable comorbidities, death may be due to these, an underlying associated disorder, or treatment. Response rates in subjects suitable for topical treatment has been reported to be only about 50%, but the response rates with biologicals has been reported to be between 20% and 90%.

There is no "gold standard" for therapy (Gameiro 2015) or product license for use. Treatment comprises wound dressings, and medicinal treatments (e.g., corticosteroids, tacrolimus, sodium cromoglicate, nicotine, 5-aminosalicylic acid, cyclosporine, activated protein C, timolol gel) (Gameiro 2015, Reichrath 2005, Cabalag 2015, Cozzani 2014, Kim 2014, Moreira 2017). The treatment for more aggressive disease includes steroids, cyclosporine, azathioprine, sulfasalazine, dapsone, thalidomide, minocycline, clofazimine, methotrexate, mycophenolate mofetil, tacrolimus, intravenous immunoglobulin, cyclophosphamide, systemic antibiotics with anti-inflammatory activity (tetracyclines, vancomycin, rifampicin, and mezlocillin), and biologicals such as anakinra (anti-Il1 Receptor), especially with PAPA syndrome, anti-TNF alpha, especially with inflammatory bowel disease (etanercept reported not be effective), and ustekinumab (anti IL12, IL-23).

The assessment of the response to therapy is hampered by the small number of study reports; most have been case reports or case series.

3.2.3 Rationale for Dosing Regimen

In study IFX-1-P2.3, IFX-1 was administered in a dose of 800 mg per week for 8 weeks in subjects with hidradenitis suppurativa. As a result, a sustained hidradenitis suppurativa clinical response was observed. This started on Day [redacted] by which time, [redacted] subjects [redacted])

had responded. The response continued throughout the remaining treatment period and the follow-up period. By Day [redacted] (end of the treatment period), [redacted] subjects [redacted]) had responded and by Day [redacted] (end of the follow-up period), [redacted] subjects ([redacted]) had responded. Secondary endpoints also supported the assumption that IFX-1 is effective in this patient population.

Like hidradenitis suppurativa, pyoderma gangrenosum is also considered to be a leukocytosis driven auto-inflammatory disease. As a dose of 800 mg was efficacious in this subject population, it is likely that the same dose could also be efficacious in pyoderma gangrenosum.

Like hidradenitis suppurativa, pyoderma gangrenosum is also considered to be a neutrophil driven auto-inflammatory disease. As a dose of 800 mg was efficacious in the subject population of IFX-1-P2.3, it is likely that the same dose could also be efficacious in pyoderma gangrenosum with the same auto-inflammatory pathology. Therefore, this dose is used as the starting dose in this study.

However, a recently completed Phase II study in moderate to severe hidradenitis suppurativa indicates that higher doses may be necessary to treat leukocytosis in the skin. In this study IFX-1-P2.4 (SHINE), [redacted] patients were treated with either placebo or one of 4 different dose regimens of IFX-1. The study failed to meet its primary endpoint, a dose-dependent drug effect on the HS Clinical Response Score (HiSCR) after 16 weeks of treatment. The percentages of subjects with HiSCR were similar in all dose groups, with [redacted] for placebo, [redacted] for 400 mg every four weeks, [redacted] for 800 mg every four weeks, [redacted] for 800 mg every two weeks, and 45.0% for 1200 mg every two weeks. However, there was a statistically significant reduction of draining fistulas relative to baseline in the high dose IFX-1 group when compared to placebo [redacted] reduction; p=0.0359) at week 16. In addition, the total abscess and inflammatory nodule count was reduced compared to placebo in all IFX-1 treatment groups (26.5% reduction under placebo and [redacted] in the IFX-1 groups). Abscesses ([redacted] reduction under placebo [redacted]) and inflammatory nodule counts ([redacted]) were also reduced over time. Hence, although the primary endpoint was not met, additional post-hoc analyses of the obtained data at week 16 indicate a robust anti-inflammatory activity in the high dose IFX-1 treatment group across numerous efficacy measures.

Therefore, in this study (IFX-1-P2.7), the dose of 800 mg every 2 weeks in Group 1 is lower than the effective dose in IFX-1-P2.3 which was 800 mg every week. It is also lower than effective dose in IFX-1-P2.4, which was 1200 mg every two weeks.

Population/pharmacokinetic analyses and simulations of data from the IFX-1-P2.3 and IFX-1-P2.4 studies showed a well-defined dose exposure relationship across doses of 400, 800, 1200, 1600, 2000, 2400, 2800, and 3200 mg, given every 2 or 4 weeks. These analyses show that after 16 weeks (112 days) of treatment, only 55% of simulated patients were above the critical efficacy exposure when given 800 mg IFX-1 every 2 weeks. In contrast, 99% of

simulated patients were above the critical exposure if treated with 2400 mg IFX-1 every 2 weeks. At this dose, only 0.3% and 0.1% of simulated patients were above the steady state AUC and Cmax NOAEL values, respectively.

The time to ulcer healing in pyoderma gangrenosum varies in different trials of infliximab and other biologicals (Adişen et al. 2008, Foss et al. 2008, Brooklyn et al. 2006, Guenova et al. 2011, Kolios et al. 2015). However, an effect is likely to be seen after 6 to 8 weeks of treatment. The time to healing seems to correlate to ulcer size and is considered to be less than 2 months for ulcers smaller than 6 cm^2.

Therefore, this study will explore IFX-1 doses of 800 mg, 1600 mg, and 2400 mg given every 2 weeks. All doses are covered by the NOAEL of 50 mg/mL.

3.3 Benefit/Risk Assessment

IFX-1 has been investigated in a number of Phase II studies in which complement activation plays a role in the disease. Furthermore, considerations on risk-benefit-related aspects are derived from nonclinical data and clinical Phase I data in healthy subjects.

3.3.1 Expected Benefits

The subjects participating in this study who are treated with IFX-1 may benefit from an improvement in symptoms and wound healing.

3.3.2 Potential Risks

No obvious findings relevant to the safety of IFX-1 were detected during the extensive nonclinical in vitro/ex vivo and in vivo testing. In addition, IFX-1 has been demonstrated to be safe and well tolerated in healthy human subjects administered IFX-1 intravenously at single doses of up to 4 mg/kg.

Furthermore, the safety of IFX-1 has been investigated in 3 Phase II studies. One study was conducted in 48 subjects with early septic organ dysfunction treated with up to 3 doses of 4 mg/kg IFX-1 given over 4 days. A second study was conducted in 82 subjects undergoing complex cardiac surgery treated with single doses of up to 8 mg/kg IFX-1. The third study was conducted in 12 subjects with moderate to severe hidradenitis suppurativa treated with 9 weekly infusions of 800 mg IFX-1. Overall, IFX-1 was safe and well tolerated in all these studies, and no additional risks associated with the administration of IFX-1 were observed.

The potential risks associated with the intravenous administration of IFX-1 due to its mode of action include the following:

Infections: A theoretical risk of infection exists due to the inhibition of C5a, therefore, investigators (and other health care professionals) should be vigilant for signs and symptoms of infections in general.

Meningitis/meningococcal septicemia: current data does not suggest that subjects treated with IFX-1 are at significantly increased risk of infection with N. meningitides and to date, no cases of meningitis or meningococcal septicemia have been reported in clinical studies with IFX-1. Therefore, mandatory vaccination or concomitant broad-spectrum antibiotic treatment is not warranted based on the mode of action for IFX-1. However, until a larger number of subjects have been exposed to IFX-1, investigators should be vigilant for signs of N. meningitides infection.

Anaphylactic reactions and *acute systemic allergic hypersensitivity*: because IFX-1 is an antibody/protein, a general risk for anaphylactic reactions and acute systemic allergic hypersensitivity exists. Subjects who are included in this study are treated with IFX-1 at the study site so that adequate treatment and care is available in case of an anaphylactic reaction. To date, no anaphylactic reactions have been reported after administration of IFX-1 in clinical Phase I and Phase II studies.

3.3.3 Risk Associated with Lack of Efficacy

No deterioration in health status is expected following the administration of IFX-1 in pyoderma gangrenosum. Nevertheless, deterioration can occur due to the fluctuating nature of the disease. In case of a lack of efficacy with IFX-1 treatment, subjects will continue to experience their typical symptoms.

3.3.4 Risk-Benefit Conclusion

It is hypothesized that treatment with IFX-1 could block the C5a-mediated inflammatory effect and support wound healing. Thus, reducing the pain and consequent physical impairment associated with the lesions of pyoderma gangrenosum, and even improving the disease status.

The hypothesized benefit of treatment with IFX-1, therefore, outweighs the potential risks for the subjects participating in this study.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of IFX-1 may be found in the investigator's brochure.

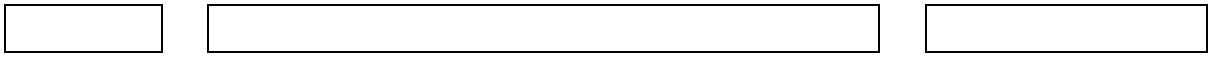
4 OBJECTIVES AND ENDPOINTS

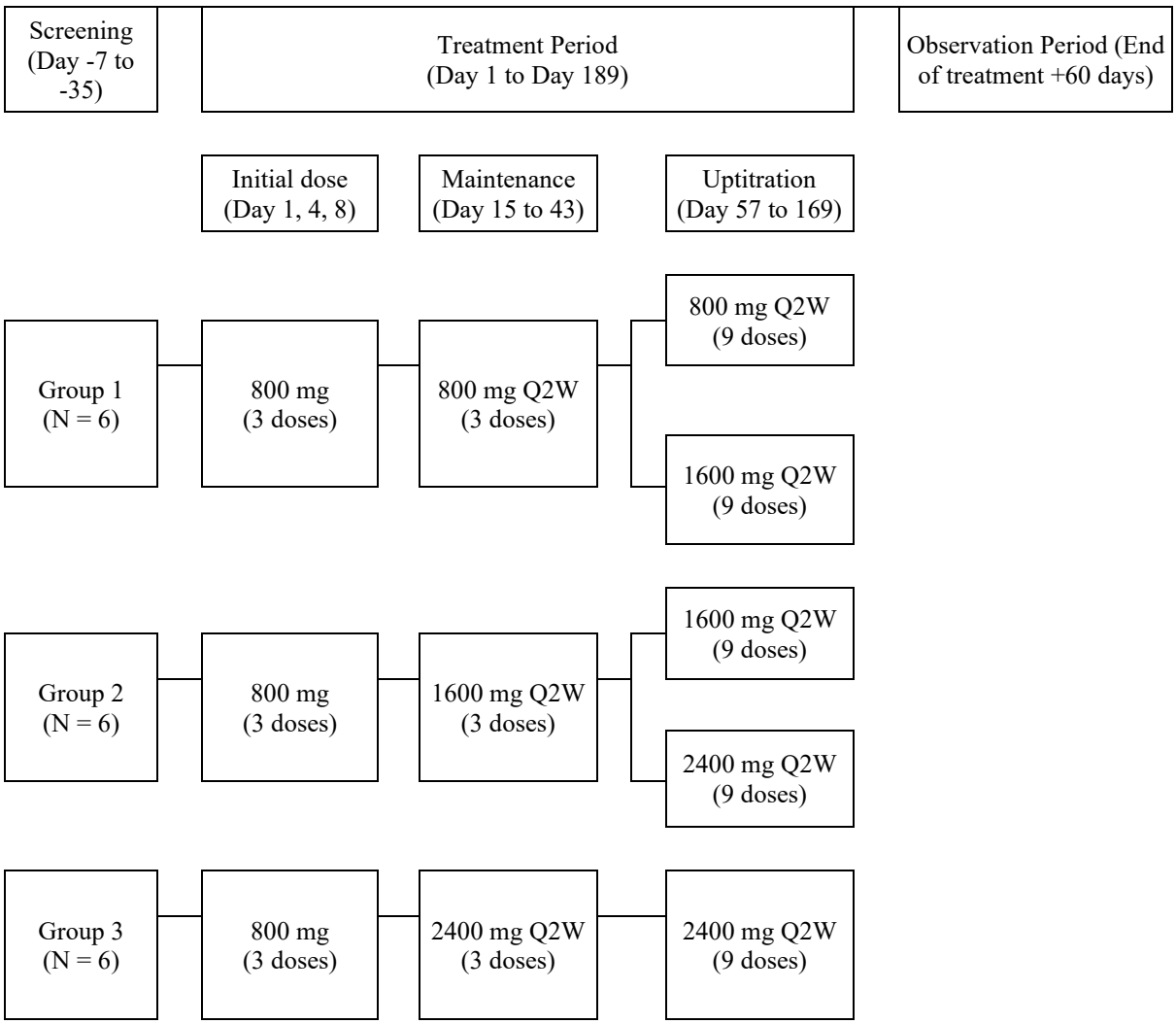
The objectives and endpoints are presented in the Synopsis (Objectives and Endpoints).

5 STUDY DESIGN

5.1 Overall Design

Figure 1 Study Design





Note: last day of dosing of IFX-1 is on Day 169
Q2W = every 2 weeks

This is an open-label explorative study.

Subjects will be examined and receive IMP (IFX-1) according to the Schedule of Assessments (Section 2). IFX-1 will only be administered at a treatment visit.

After completion of treatment with IMP (last IMP is given on Visit V15), subjects should complete an EOT visit at Day [redacted] (Visit V16). Subjects who discontinue early should, if possible, also complete the EOT visit. Thereafter, subjects should receive treatment for pyoderma gangrenosum at the discretion of the investigator.

Subjects will be followed up for an additional [redacted] days after EOT at Visit Ob1 (after [redacted] days) and Visit Ob2 (after 60 days) for safety reason. Visit Ob2 is the final visit in the study.

The allowed time windows for Visits V1 to V6 are ±2 days. All other visits have allowed time windows of ±5 days. There must be at least 48 hours between each dose of IFX-1 (Section 34). Visits should be scheduled appropriately.

5.2 Study Sites, Study Subject, and Expected Duration

This study is planned to be a multi-center study with about 18 subjects treated with IMP (IFX-1).

The study start is defined as the date of the first visit of the first subject enrolled (signature of the informed consent form by the first subject), and the end of the study is defined as the date of the last visit of the last subject participating, as recorded in the Case Report Form (CRF).

The estimated recruitment period is approximately 6 to 12 months.

The study duration for an individual subject includes screening (14 days range 7 to 35 days), the treatment period (189 days ±5 days; the last day of dosing of IFX-1 is Day 169), and the observational follow up (60 days ±5 days).

5.3 End of Study Definition

A subject is considered to have completed the study if all phases of the study have been completed including the last visit.

The end of the study is defined as the date of the last visit of the last subject in the study.

6 STUDY POPULATION

6.1 Inclusion Criteria

The inclusion criteria are presented in the synopsis (Study Population Inclusion Criteria).

6.2 Exclusion Criteria

The exclusion criteria are presented in the synopsis (Study Population Exclusion Criteria).

6.3 Lifestyle Restrictions

6.3.1 Meals and Dietary Restrictions

No restrictions pertaining to meals and dietary restrictions apply during the study.

6.3.2 Caffeine, Alcohol, and Tobacco

No restrictions pertaining to caffeine, alcohol, or tobacco restrictions apply during the study.

6.3.3 Activity

Subjects will abstain from strenuous exercise for 2 hours before each blood collection for safety laboratory tests.

6.4 Screening Failures

Screening failures are defined as subjects who consent to participate in the clinical study but are not subsequently assigned to IMP in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screening failure) may be re-screened once. Re-screened subjects will receive the next available subject number.

6.5 Gender distribution

The incidence of pyoderma gangrenosum is possibly higher in women (Chatzinasiou 2016, Langan 2012, Wollina 2007). It is expected that approximately twice as many women as men will be enrolled in this study.

7 TREATMENT WITH IMP AND CONCOMITANT THERAPY

7.1 Investigational Medicinal Product

Further guidance and information will be provided in a pharmacy manual describing IMP handling, storage and administration.

7.1.1 Treatment Administered

IMP name:	IFX-1
Unit dose strength(s)/ Dosage level(s):	[redacted] mL glass vials at a concentration of [redacted]
Route of administration:	Intravenous
Dosing instructions:	The required dose of IFX-1 will be diluted with [redacted] sodium chloride to a total volume of approximately 250 ml and given as a single intravenous dose over [redacted] minutes
Packaging and labeling:	The vials of IFX-1 [redacted] will be labeled and packed in labeled cardboard cartons. Labeling will be in accordance with all legal requirements. The cartons will be labeled with a unique number (medication or kit number). The vials within a carton will be labeled with the same (medication) number as the carton in which they are packed..
Manufacturer:	Celonics and WuXi on behalf of InflaRx

IFX-1 has the following composition:

Ingredient	Strength
IFX-1	[redacted]
Sodium chloride	[redacted]
Sodium phosphate	[redacted]
Polysorbate 80	[redacted]

7.1.2 Dosing groups

There will be 3 dosing groups (Group 1, Group 2, and Group 3) of 6 subjects each. Each group of subjects is recruited sequentially. The next dose group will be initiated if the previous dose was considered safe and well tolerated. If dosing in Group 2 cannot be initiated, then a further 6 patients will be recruited in Group 1.

All subjects will receive IFX-1 800 mg three times during the first week (Days 1, 4, and 8).

Starting at Day 15:

- Subjects in Group 1 will continue to receive IFX-1 800 mg at 2 weekly intervals.
- Subjects in Group 2 will receive IFX-1 1600 mg at 2 weekly intervals.
- Subjects in Group 3 will receive IFX-1 2400 at 2 weekly intervals.

At Day 57 (Visit V7), subjects in Groups 1 and 2 may have their dose increased to IFX-1 1600 mg or 2400 mg, respectively, if there are no safety concerns and the Physician Global Assessment (main efficacy parameter) is ≥4.

7.1.3 Method of Treatment Assignment

On Day 1, subjects will be allocated with the next available IMP package of IFX-1 at the site. The package number will be recorded in the CRF.

7.1.4 Blinding

This is an open-label study without randomization.

7.1.5 Supply, storage and handling

The IMP will be supplied to study site(s) on behalf of the sponsor by Almac. Almac will provide the initial and all subsequent supplies. The initial shipment will be requested once all required site documentation is in place, including Institutional Review Board (IRB) and Regulatory Authority approvals, as well as the signed site contract(s).

The IMP must be shipped at a temperature of 2°C to 8°C (35.6°F to 46.4°F) and should not be frozen. Each shipment will be controlled by a temperature logger, of which a read-out must be obtained by the site personnel upon receipt of the shipment.

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all IMP received. Any discrepancies must be reported and resolved before use of the IMP.

At each study site, authorized personnel will check the IMP for any loss, damage, or tampering and confirm receipt. Records of the receipt of IMP have to be maintained.

Any technical complaints arising from defects in the quality of the IMP, or defects in the packaging or labeling of the IMP, must be reported to Almac or the sponsor at the earliest opportunity and the IMP should not be used.

The authorized personnel at each site will be responsible for receipt adequate handling, storage, dispensing and preparation of the IMP, and local drug accountability as well as recording of the accurate administration of the IMP (i.e., complete administration of IMP, including flushing of the infusion line) used for each subject.

The IMP must be stored at the site between 2°C and 8°C and should not be frozen. To record the temperature at the site, an established and validated local temperature management system with temperature logs should be used. If this is not possible, the responsible site personnel will maintain temperature records for the entire duration of the study. A template for the temperature records will be provided by the sponsor or sponsor's designee. At a minimum, the daily (working day) minimum and maximum temperatures must be documented.

Only subjects enrolled in the study may receive IMP and only authorized site staff may administer IMP. All IMP must be stored in a secure, temperature controlled, and monitored (manual or automated) area with access limited to the investigator and authorized site staff in accordance with the labeled storage conditions, separated from normal hospital inventories, and in compliance with applicable regulatory requirements.

7.1.6 Preparation and administration

The IFX-1 for infusion will be reconstituted (prepared) under controlled conditions at the study site or at the study site's pharmacy, in accordance with local regulations/requirements for aseptic reconstitution.

The IMP will be diluted in sterile sodium chloride. The total volume in the infusion bag for each infusion should be approximately [redacted] mL.

The reconstituted IFX-1 should be used within 4 hours after dilution when stored at room temperature. Otherwise, the reconstituted IFX-1 has to be stored at [redacted]) and used within 24 hours; if the reconstituted IFX-1 solution is stored in a fridge, it must be left to acclimatize to room temperature prior to administration. Details on reconstituting the IFX-1 will be provided in the Pharmacy Manual.

The number of unused, partially used, and empty vials will be documented accurately, and the vials will be kept at the site until the drug accountability documentation has been checked by the study monitor (Section 33).

The IMP will be infused intravenously over a period of 30 to 60 minutes (± 10 min) via an intravenous line. Sites should use the supplied intravenous lines. The infusion may be briefly (<30 min) interrupted for technical reasons, or for reinsertion of the intravenous line.

At the end of the infusion, the intravenous line will be briefly flushed with approximately 10 mL of sterile sodium chloride to ensure that any IMP remaining in the intravenous line is administered.

After each of the first 2 infusions of IMP administered, subjects must remain at the study site for at least 30 minutes after end of IMP administration; appropriate treatment for potential infusion-related reactions must be available during this time.

Each administration of IMP will be recorded in detail in the source documentation and in the CRF.

7.1.7 Drug Accountability

The investigator/institution is responsible for IMP accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

During the study, all IMP vials will be reconciled against the current inventory and the dispensing records as a component of the monitoring visits.

IMP administration data kept at the site will be monitored throughout the study by the monitor. After completion of the study, copies of all records regarding the IMP will be provided to the sponsor, who will decide on the return or destruction of any unused IMP.

If any unused IMP should be destroyed at the site (according to institutional policies, copies of which must be supplied to the sponsor or sponsor's designee before destruction takes place, and in compliance with the current applicable regulatory requirements) after drug accountability has been assessed by the study monitor, this destruction must be documented. If unused IMP cannot be destroyed at the site, it needs to be returned to the depot.

7.1.8 Treatment Compliance

If a subject misses a visit or a subject appears at the study center for a scheduled infusion but the infusion cannot be administered for any reason, the visit can be repeated within 3 days and the infusion given. Otherwise, the infusion will be considered as omitted and documented accordingly in the CRF.

Subjects who omit more than 2 scheduled (consecutive or non-consecutive) infusions will be discontinued from the study and will undergo the End of Treatment visit (Visit V16) and the 2 observation visits.

7.1.9 Overdose of IMP

At least 48 hours must have elapsed between each dose of IFX-1. Visits should be scheduled appropriately. Any second administration within this time, or any administration that is greater than the scheduled dose will be considered an overdose. The consequences of an overdose with IFX-1 are not known. InflaRx does not recommend specific treatment in case of an overdose.

Overdoses must be recorded as TEAEs.

In the event of an overdose, the investigator/treating physician should:

1. Contact the sponsor or sponsor's designee immediately.
2. Closely monitor the subject for any adverse events or SAEs and laboratory abnormalities for at least 7 days. If more than 130% of the dose is given, the patient should be kept in hospital overnight.
3. Obtain a plasma sample for IFX-1 concentrations if requested by the sponsor or sponsor's designee (determined on a case-by-case basis).
4. Document the quantity of the excess dose of the overdose in the CRF.
5. If there are any symptoms, treatment should be initiated as deemed medically appropriate by the investigator.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the sponsor or sponsor's designee based on the clinical evaluation of the subject.

7.2 Prior and Concomitant Therapy and Procedures

7.2.1 Recording of prior and concomitant therapy and procedures

Any medication or vaccine (including procures such as laser- or photo-therapy, over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject has used in the 3 months, or biologicals (see 81 for Prohibited Biologics) used within 12 months, before screening, is receiving at the time of screening, or receives during the study must be recorded in the source data and CRF along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose, frequency, and route of administration

The sponsor or sponsor's designee should be contacted if there are any questions regarding concomitant or prior therapy.

7.2.2 Allowed Concomitant Therapy

Wound care for pyoderma gangrenosum

Wound care is performed at the scheduled visits, and 2 to 3 times a week depending on necessity according to the standard of care.

Further details of wound care are given in 82.

Concomitant use of wound care dressings on pyoderma gangrenosum ulcers is permitted with absorptive dressings, with or without antiseptics. However, the allowed antiseptics are limited (see 82). No topical therapy is allowed. Standard compression therapy throughout the study is required (Shavit and Alavi 2019).

Antibiotic therapy for pyoderma gangrenosum

Oral antibiotic therapy for treatment of superinfection of pyoderma gangrenosum wounds is permitted.

Analgesic therapy for pyoderma gangrenosum

Short-acting opioid or non-opioid analgesic therapy may be initiated at any time during the study. If possible, analgesic therapy should be avoided on the day of pain assessments until the assessments are made.

Subjects will be required to report any analgesics that are taken. All use of analgesics and any dose adjustments will be recorded in the source documentation and in the CRF.

7.2.3 Prohibited Therapy

The following therapies are prohibited for all subjects from screening until Visit EOT or discontinuation from the study:

- Subject has received a live attenuated vaccine within 3 months prior to screening or plans to receive a live attenuated vaccine during the study or up to 4 weeks after the last study product administration.
- New therapy with biologicals (see 81 for Prohibited Biologics). Biologicals used for an underlying disease at a stable dose may be continued
- Any other systemic medication for pyoderma gangrenosum, including, but not limited to methotrexate, cyclosporine, retinoids, and fumaric acid esters
- Oral or injectable corticosteroids (more than 10 mg prednisone or prednisone equivalent)

- Non-stable, chronic use of high dose oral opioid analgesics
- New prescription topical therapies for pyoderma gangrenosum
- Over-the-counter topical antiseptic washes, creams, ointments, gels, and liquids containing antibacterial agents to treat pyoderma gangrenosum

The following is prohibited for all subjects from screening until Visit Ob2 or discontinuation from the study:

- Any investigational agent

The investigator should contact the sponsor or sponsor's designee if there are any questions regarding prior or concomitant therapy.

7.3 Treatment After the End of the Study

No treatment with IFX-1 is foreseen after Visit EOT. The further treatment of the pyoderma gangrenosum is at the discretion of the investigator.

8 DISCONTINUATION/WITHDRAWAL CRITERIA

Each early discontinuation of individual subject participation, irrespective of the reason for discontinuation, must be documented by the investigator. If possible, the date, circumstances, and reason for discontinuation should be documented.

The investigator will attempt to complete all procedures usually required for Visit EOT for subjects discontinuing. See the Schedule of Assessments (Section 2) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.1 Discontinuation of the Study

The study may be discontinued by the sponsor at any site if any of the following criteria are met:

- The study protocol is not adequately adhered to (protocol violations) despite training of the study site personnel
- The data quality is deficient
- The recruitment is inadequate

Additionally, the entire study can be discontinued at all sites by the sponsor at any time for medical or ethical reasons.

The investigator(s) will be notified in writing, outlining the reasons for discontinuation, and the investigator(s) must promptly inform all participating subjects. Detailed instructions on further assessments will be provided.

All study materials, except documents needed for archiving requirements, will be returned to the sponsor, including all records regarding the IMP, and the sponsor will decide on whether any unused IMP should be returned or destroyed. The sponsor or sponsor's designee will ensure that any outstanding data clarification issues and queries are resolved and that all study records at the study site are complete.

In accordance with applicable regulatory requirements, the sponsor or sponsor's designee will promptly inform the competent regulatory authorities of the discontinuation and its reason(s), and the investigator or sponsor or sponsor's designee will promptly inform the IRB.

The approval of the study can be rescinded, or the study can be discontinued by a competent authority or a responsible IRB.

8.2 Discontinuation of the IMP

Subjects must be discontinued from treatment with the IMP because of:

- Unacceptable toxicity or TEAE, as determined by the investigator
- Anaphylactic or other serious allergic reaction
- Serious infection, including meningitis and sepsis
- If, in the investigator's opinion, continued administration of IMP could be detrimental to the subject's well-being
- Use of prohibited treatment that in the opinion of the investigator or sponsor or sponsor's designee necessitates the subject being removed
- Biopsy confirmation of any malignancy
- Pregnancy
- Abnormal liver function meeting Hy's Law criteria (62).

8.3 Withdrawal from the Study

A subject may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

Subjects may withdraw their consent at any time without giving reasons. Nevertheless, they should be asked about the reason(s) for discontinuation after being informed that they do not need to do so. Information as to when they withdrew consent must be documented.

If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the source data.

8.4 Lost to Follow-Up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. The date of being lost to follow-up is defined as the last date with any assessment of the subject.

The following actions must be taken if a subject fails to return to the study site for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (e.g., 3 telephone calls at 3 different times on consecutive days or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9 STUDY ASSESSMENTS AND PROCEDURES

9.1 Procedures at visits

Study procedures and their timing are summarized in the Schedule of Assessments (Section 2).

Immediate safety concerns should be discussed with the sponsor or sponsor's designee promptly upon occurrence or awareness to determine if the subject should continue or discontinue IMP.

Adherence to the study design requirements, including those specified in the Schedule of Assessments (Section 2), is essential and required for study conduct.

9.1.1 Screening

Screening is the predetermined series of procedures with which each investigator selects an appropriate and representative sample of subjects for enrollment into the study.

The screening procedures will be conducted within [redacted]) before first administration of IMP.

The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable. Subjects who fail screening may be re-screened once at a later date.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The data for the inclusion and exclusion criteria must be reported in the source data and CRF.

The investigator may pre-screen subjects for study inclusion and exclusion criteria without first obtaining written informed consent for participation in the current study on the basis of either of the following situations:

- Pre-existing data (e.g., for study inclusion and exclusion criteria, as available in medical records held by the investigator)
- Initial contact (e.g., routine visit, phone call) where only routine and/or non-study specific questions are allowed

Procedures conducted as part of the subject's routine clinical management (e.g., blood count) and obtained before signing of the informed consent form may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Assessments (Section 2).

After subjects have provided written informed consent, they will be assessed at the screening visit to determine if all inclusion criteria and no exclusion criteria are met. All subjects must provide written informed consent before any study-specific assessments or procedures are performed.

The following procedures will be conducted and documented at the Screening visit:

- Initiate and complete informed consent procedure and document process
- Record demographic and baseline characteristics
- Record relevant medical and surgical history during the 6 months before Screening
- Initiate documentation of concomitant medications
- Assess target ulcer (degree of erythema and border elevation)
- Record Dermatology Life Quality Index
- Record pain intensity using a numeric rating scale
- Perform a physical examination
- Record body weight
- Record vital signs
- Record a 12 lead ECG
- Perform a chest X-ray. An historical X-ray can be used if taken within 6 months prior to screening
- Take photograph of target ulcer for area and volume measurements
- Take blood for

- Safety laboratory parameters (clinical chemistry and hematology)
- Human immunodeficiency virus, hepatitis B virus, and hepatitis C virus test
- Pregnancy test for women of childbearing potential
- QuantiFERON-TB gold test for the presence of tuberculosis

- Take urine for urinalysis
- Use a standard dressing and compression therapy for the target ulcer
- Record Adverse Events

9.1.2 Start of IMP: Visit V1 (Day 1)

The following will be performed at Visit V1:

- Review all inclusion and exclusion criteria
- Record Dermatology Life Quality Index
- Record pain intensity using a numeric rating scale
- Document concomitant medications
- Record adverse events
- Record body weight
- Record vital signs
- Perform a physical examination
- Assess target ulcer (degree of erythema and border elevation)
- Take photograph of target ulcer for area and volume measurements. This photograph is the baseline for the recording of the Physician's Global Assessment at subsequent visits.
- Record a 12 lead ECG
- Take blood for
  - Immunology
  - Anti-drug antibody, antineutrophil cytoplasmic antibody, and antinuclear antibody
- Take a sample of the target ulcer fluid if wound is open and liquid is available
- Take a biopsy of the target ulcer
- Perform a urine pregnancy test for a woman of childbearing potential
- Take a stool sample for the measurement of calprotectin
- Use a standard dressing and compression therapy for the target ulcer

If the subject fulfills all of the inclusion criteria, does not meet any of the exclusion criteria, and written informed consent is available, the subject will be started on IMP.

- Assign subject to treatment
- Administer IMP
- Update recording of adverse events

Subjects enrolled into the study will be issued a subject card with relevant contact details, including emergency contact details.

If the subject meets an exclusion criterion or another reason for non-inclusion in the study is present after obtaining informed consent, the subject will not be enrolled into the study and will be deemed as screen failure.

9.1.3 Treatment visits (Visits V2, V3, V5, V7, V8, V9, V11 to V15)

The following assessments and procedures will be performed as outlined in the Schedule of Assessments (Section 19):

- Document concomitant medications
- Record adverse events
- Record vital signs
- Record the Physician's Global Assessment
- Assess target ulcer (degree of erythema and border elevation)
- Take photograph of target ulcer for area and volume measurements
- Use a standard dressing and compression therapy for the target ulcer
- Preform urine pregnancy test for a woman of childbearing potential (Visits V8, V12, and V14)
- Administer IMP
- Update recording of adverse events

9.1.3.1 Treatment visit V7

In addition to the assessments and procedures outlined in the Schedule of Assessments (Section 19), the dose of IFX-1 will be assessed and increased in subjects of Group 1 and Group 2 if the dose escalation criteria are met (Section 31).

9.1.4 Treatment visits (Visits V4 and V6)

The following assessments and procedures will be performed as outlined in the Schedule of Assessments (Section 19):

- Record Dermatology Life Quality Index
- Record pain intensity using a numeric rating scale
- Document concomitant medications

- Record adverse events
- Record vital signs
- Record the Physician's Global Assessment
- Take photograph of target ulcer for area and volume measurements
- Assess target ulcer (degree of erythema and border elevation)
- Take a sample of the target ulcer fluid if wound is open and liquid is available
- Use a standard dressing and compression therapy for the target ulcer
- Take blood for
  - Safety laboratory parameters (clinical chemistry and hematology)
  - IFX-1 concentrations
  - Immunology
  - Anti-drug antibody
- Take a urine sample for urinalysis
- Perform a urine pregnancy test for a woman of childbearing potential
- Take a stool sample for the measurement of calprotectin
- Administer IMP
- Update recording of adverse events

9.1.5 Mid visit: Visit V10

The following assessments and procedures will be performed as outlined in the Schedule of Assessments (Section 19):

- Record Dermatology Life Quality Index
- Record pain intensity using a numeric rating scale
- Document concomitant medications
- Record adverse events
- Perform a physical Examination
- Record vital signs
- Record body weight
- Record the Physician's Global Assessment
- Take photograph of target ulcer for area and volume measurements
- Assess target ulcer (degree of erythema and border elevation)
- Take a sample of the target ulcer fluid if wound is open and liquid is available
- Use a standard dressing and compression therapy for the target ulcer

- Take blood for
  - Safety laboratory parameters (clinical chemistry and hematology)
  - Pregnancy test for a woman of childbearing potential
  - IFX-1 concentrations
  - Immunology
  - Anti-drug antibody
- Take a urine sample for urinalysis
- Take a stool sample for the measurement of calprotectin
- Administer IMP
- Update recording of adverse events

9.1.6 End of treatment visit: Visit 16 (Day 189)

The following assessments and procedures will be performed as outlined in the Schedule of Assessments (Section 19):

- Record Dermatology Life Quality Index
- Record pain intensity using a numeric rating scale
- Document concomitant medications
- Perform a physical Examination
- Record vital signs
- Record body weight
- Record 12 lead ECG
- Record the Physician's Global Assessment
- Take photograph of target ulcer for area and volume measurements
- Assess target ulcer (degree of erythema and border elevation)
- Take a sample of the target ulcer fluid if wound is open and liquid is available
- Use a standard dressing and compression therapy for the target ulcer
- Take blood for
  - Safety laboratory parameters (clinical chemistry and hematology)
  - Pregnancy test for a woman of childbearing potential
  - IFX-1 concentrations
  - Immunology
  - Anti-drug antibody
- Take a urine sample for urinalysis

- Take a stool sample for the measurement of calprotectin
- Record adverse events

9.1.7 Observation visits

9.1.7.1 Visit Ob1 (End of treatment +30 days)

The following assessments and procedures will be performed as outlined in the Schedule of Assessments (Section 19):

- Document concomitant medications
- Record vital signs
- Record the Physician's Global Assessment
- Take photograph of target ulcer for area and volume measurements
- Assess target ulcer (degree of erythema and border elevation)
- Take blood for
  - IFX-1 concentrations
  - Immunology
  - Anti-drug antibody
- Record adverse events

9.1.7.2 Final Visit (End of Trial): Visit Ob2 (End of treatment +60 days)

The following assessments and procedures will be performed as outlined in the Schedule of Assessments (Section 19):

- Record Dermatology Life Quality Index
- Record pain intensity using a numeric rating scale
- Document concomitant medications
- Perform a physical Examination
- Record vital signs
- Record body weight
- Record the Physician's Global Assessment
- Take photograph of target ulcer for area and volume measurements
- Assess target ulcer (degree of erythema and border elevation)
- Take blood for
  - Safety laboratory parameters (clinical chemistry and hematology)
  - Pregnancy test for a woman of childbearing potential

- IFX-1 concentrations
- Immunology
- Anti-drug antibody

- Take a urine sample for urinalysis
- Record adverse events

9.1.8 Unscheduled visits

Unscheduled visits to the study site will be arranged as needed for subjects who require additional follow-up assessments (e.g., due to an SAE, abnormal laboratory safety findings, loss of response).

At a minimum, the following assessments and procedures will be performed at each unscheduled visit:

- Vital signs
- Documentation of adverse events
- Documentation of concomitant therapy

9.2 Background characteristics

9.2.1 Demographics and Baseline Characteristics

The following demographic data and baseline characteristics will be documented at screening:

- Age
- Gender
- Race and ethnicity
- Body weight (For weight measurements, the subject is allowed to wear light indoor, daytime clothing with no shoes.)
- Height

9.2.2 Medical History

Relevant medical (and surgical history), including date of diagnosis of pyoderma gangrenosum, in the investigator's opinion will be recorded in the CRF at screening. The medical history will be reviewed and updated on Day 1 to ensure that the subject remains qualified for the study.

9.2.3 Concomitant medications

All prior and concomitant therapy will be documented, as described in Section 34.

9.3 Efficacy Assessments

Efficacy will be assessed on the basis of the following variables:

- Wound assessment (Physician's Global Assessment, erythema, border elevation)
- Photographic documentation
- Dermatology Life Quality Index
- Numeric Rating Scale for pain

9.3.1 Wound Assessments

The investigator will score the degree of wound healing, erythema, border elevation and the presence of remission

Physician's Global Assessment

The following scores will be used to rate overall efficacy (Foss 2008):

Severity score	Description
0	Completely clear: except for possible residual hyperpigmentation
1	Almost clear: very significant clearance (about 90%); however, patchy remnants of dusky erythema and/or very small ulceration
2	Marked improvement: significant improvement (about 75%); however, a small amount of disease remaining (i.e. remaining ulcers, although have decreased in size, minimal erythema and/or barely perceptible border elevation)
3	Moderate improvement: intermediate between slight and marked; representing about 50% improvement
4	Slight improvement: some improvement (about 25%); however, significant disease remaining (i.e. remaining ulcers with only minor decrease in size, erythema or border elevation)
5	No change from baseline
6	Worse

Wound erythema

Wound erythema will be assessed as follows (Foss 2008):

Severity rating (score)	Description
None (0)	No erythema
Slight (1)	Mild pink color
Moderate (2)	Moderate pink color
Severe (3)	Reddish color
Very severe (4)	Dark red or violaceous

Border elevation

Border elevation will be assessed as follows (Foss 2008):

Severity rating (score)	Description
None (0)	Border is flat with ulcer and surrounding skin, no elevation
Slight (1)	Slight elevation of border above ulceration and surrounding skin
Moderate (2)	Noticeable elevation of border above ulceration and surrounding skin
Severe (3)	Significant elevation of border above ulceration and surrounding skin
Very severe (4)	Border rolled high above ulceration and surrounding skin

9.3.2 Photographic documentation

Photographs taken of the affected wound areas will be taken during the study at the times specified in the Schedule of Assessments (Section 19). The photographic documentation will be used to estimate the area and volume of the wound.

9.3.3 Dermatology Life Quality Index

The Dermatology Life Quality Index is an established and widely used patient-reported outcome instrument for assessing the impact on health-related quality of life due to dermatological conditions in clinical studies. The questionnaire will be completed by the subject.

A score is documented for each of the 10 items, ranging from 0 to 3 for each item. Items include, for example:

- Over the last week, how itchy, sore, painful, or stinging has your skin been?
- Over the last week, has your skin prevented you from working or studying?
- 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?

The total score is the sum of the responses to all 10 items, ranging from 0 to 30. A higher score corresponds to worse Health-related quality of life. Guidelines with regard to the scoring of each question and the handling of incorrectly completed questionnaires are taken from the Dermatology Life Quality Index manual (http://sites.cardiff.ac.uk/dermatology/quality-of-life/dermatology-quality-of-life-index-dlqi/dlqi-instructions-for-use-and-scoring/).

To avoid biasing the subject's response, the subject should complete the questionnaire at the study site before any other assessments and before any interaction with the study site personnel has occurred.

9.3.4 Numeric Rating Scale for Pain

The numerical rating scale (NRS) is perhaps the most common pain assessment tool used. It is an 11-point scale (from 0 represent no pain to 10 representing the worst pain the subject can imagine). Subjects are asked to rate the intensity of their pain "right now" verbally with a number. The value is recorded in the CRF. The validity of the NRS has been well established and it has been shown to be easy to use.

9.4 Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Assessments (Section 2).

The following safety variables will be collected:

- Safety laboratory parameters
- Vital signs
- 12-lead electrocardiogram (ECG)
- Physical examination
- QuantiFERON-TB Gold test
- Adverse events
- Pregnancy test
- Chest X-ray

9.4.1 Safety Laboratory Assessments

See 62 for the list of safety laboratory tests to be performed and the Schedule of Assessments (Section 2) for the timing and frequency of the tests.

The safety laboratory assessments will be performed by a central laboratory.

Urinalysis will be centrally performed using a dipstick.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF. The laboratory reports must be filed with the source documents.

All abnormal laboratory values will require a comment in the CRF according to the following classification:

- NCS = not clinically significant
- CS = clinically significant
- Error (e.g., laboratory error, improper sample preparation, hemolysis, or delayed transit to laboratory)

Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of IMP should be repeated until the values return to normal or baseline, or are no longer considered clinically significant by the investigator or sponsor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor or sponsor's designee notified.

All protocol-required laboratory assessments, as defined in 62, must be conducted in accordance with the laboratory manual and the Schedule of Assessments (Section 2).

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the investigator (e.g., SAE or adverse event or stopping IMP), then the results must be recorded in the CRF.

9.4.2 Vital Signs

Vital signs will be measured in a semi-supine position after 5 minutes of rest and will include temperature, systolic and diastolic blood pressure, pulse and respiratory rate. Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if the automated device is not available and will be measured in the following way: Three readings of blood pressure and pulse will be taken. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded in the CRF.

9.4.3 12-lead electrocardiograms

12-lead ECG data will be collected for screening and routine safety monitoring.

A single 12-lead ECG will be obtained as outlined in the Schedule of Assessments (Section 2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc (Bazett) intervals.

Subjects can have a repeat ECG examination at any time during the study if considered necessary by the investigator.

The investigator will interpret each ECG. Any clinically significant and non-clinically significant findings will be recorded in the source documentation. The ECGs will be assessed to decide if changes from baseline represent an adverse event.

9.4.4 Physical Examination

A complete physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

An abnormality noted after starting treatment with IMP (Visit V1) will be evaluated by the investigator for whether it constitutes an adverse event.

9.4.5 QuantiFERON-TB gold test

The QuantiFERON-TB Gold is a simple blood test that aids in the detection of Mycobacterium tuberculosis. It is an IFN-gamma release assay and is unaffected by previous Bacille Calmette-Guerin (BCG) vaccination. It cannot distinguish between active tuberculosis disease and latent tuberculosis infection.

9.4.6 Chest X-ray

A standard chest X-ray will be performed at screening to exclude tuberculosis. An historical X-ray can be used if taken within 6 months prior to screening.

9.4.7 Suicidal Risk Monitoring

No suicidal risk monitoring will be performed as IFX-1 is not centrally active.

9.4.8 Adverse Events

The definitions of an adverse event, adverse event of special interest, and SAE can be found in 69.

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, recording, and reporting (to the sponsor) adverse events, adverse events of special interest, or SAEs. They are also responsible for following up all adverse events until their resolution or until a steady state of the event is reached.

9.4.8.1 Time Period and Frequency for Collecting adverse events and SAE Information

All adverse events and SAEs will be collected from the signing of the informed consent until the final visit at the time points specified in the schedule of assessments (Section 19).

All SAEs will be recorded and reported to the sponsor or sponsor's designee within 24 hours, as indicated in 69. The investigator will submit any updated SAE data to the sponsor or sponsor's designee within 24 hours of it being available.

If the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the IMP or study participation, the investigator must promptly notify the sponsor or sponsor's designee.

The method of recording, evaluating, and assessing causality of adverse events and SAEs and the procedures for completing and transmitting SAE reports are provided in 69.

9.4.8.2 Method of Detecting Adverse Events and SAEs

The investigator must take care not to introduce bias when detecting adverse events or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about adverse event occurrences.

9.4.8.3 Follow-up of adverse events and SAEs

After the initial adverse event or SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up. Further information on follow-up procedures is given in 69.

9.4.8.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor or sponsor's designee of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of an IMP under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an IMP under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary (see 69).

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the investigator's brochure and will notify the IRB, if appropriate according to local requirements.

9.4.8.5 Pregnancy

Details of all pregnancies in female subjects and, if indicated, female partners of male subjects will be collected after the start of IMP and until the final visit.

If a pregnancy is reported, the investigator should inform the sponsor or sponsor's designee within 24 hours of learning of the pregnancy and should follow the procedures outlined in 77.

Pregnancy will not be considered as an adverse event or SAE, but an abnormal outcome (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) is considered an SAE.

9.4.9 Safety review

An ongoing safety review will also be performed. The decision to go to the next dose group will be made by the sponsor. The decision to start dose Group 2 will be based on safety data from at least 5 patients on IFX-1 800 mg, and to start Group 3 on at least 5 patients on IFX-1 1600 mg for at least 1 month.

9.5 Immunostaining of biopsy

At baseline, a small biopsy of the target pyoderma gangrenosum ulcer will be taken and sent to a central laboratory.

9.6 IFX-1 concentrations

Blood samples will be collected for measurement of plasma concentrations of IFX-1 as specified in the Schedule of Assessments (Section 2). Instructions for the collection and handling of biological samples will be provided by the sponsor or sponsor's designee. The actual date and time (24-hour clock time) of each sample will be recorded.

The plasma concentrations will be used for modeling and simulation.

Each plasma sample will be divided into 2 aliquots (1 sample for concentration measurement, and 1 sample for back-up). Samples collected for analyses of IFX-1 concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

9.7 Immunology and other assessments of blood, ulcer fluid, biopsy and stool samples

Venous blood samples will be collected for the measurement of:

- Anti-drug antibody, antineutrophil cytoplasmic antibody, and antinuclear antibody formation
- Immunology:
  - [redacted]

Fluid draining from the target ulcer, only if wound is open and liquid is available, will be collected for analysis of:

- Immunology:
  - [redacted]

A biopsy will be collected from the border tissue of the target ulcer for analysis for:

- [redacted]

The investigators will be supplied with the necessary sampling tubes [redacted] etc.) and instructed to send the samples to a central laboratory from where they will be forwarded to the analyzing laboratories. Further details are given in a laboratory manual.

Remaining samples will be stored for future research at a suitable storage facility (as documented in the trial master file) and analyses may be performed on biomarker variants that are later identified. Samples may be used for research to develop methods, assays, prognostics and/or companion diagnostics related to the disease process and pathways associated with disease state, and/or mechanism of action of the IFX-1.

9.8 Genetic evaluations

Genetics are not evaluated in this study.

9.9 Health Economics

Health Economics are not evaluated in this study.

9.10 Blood Sampling Volumes

The following table gives an estimation of the blood sampling volumes take during the study. These may vary depending on local sampling requirements and techniques.

Table 1 Estimated Blood Sampling Volumes

Reason for sample	Number of samples	Volume per sample (mL)	Total volume (mL)
Clinical chemistry (including serology and pregnancy test) and hematology	6	11.5 mL at Screening 6.5 mL at other visits	44
IFX-1 concentration	6	3	18
Complement factors	7	6	42
Other immunology	7	3	21
QuantiFERON-TB gold test	1	4	4
Anti-drug antibody	7	7 mL at Basaseline, 5 mL at other visits	37
Antineutrophil cytoplasmic antibody and antinuclear antibody	1	7	7
Total:			**173**

The maximum amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed approximately 200 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

If values are out of range during screening, a single retest is allowed.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

The sample size for this study is not based on statistical consideration and no formal sample size estimation has been performed. In total, 18 subjects will be enrolled in the study. It is expected that at least 15 subjects will undergo 3 months treatment (i.e., evaluable). As the

study is a pilot study in the indication of pyoderma gangrenosum and conducted as an open label study, approximately 5 evaluable subjects per initial dosing group seems to be sufficient to explore the safety and tolerability of IFX-1 administered over 189 days to subjects with pyoderma gangrenosum.

10.2 Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Analysis Set	Description
Enrolled	All subjects who sign the ICF
Safety Set (SAF)	All subjects who received at least 1 dose of IMP.
Per Protocol Set (PPS)	Subjects who completed at least 3 months of treatment and who had no major protocol deviation.

10.3 Statistical Analyses

A statistical analysis plan will be developed and finalized before database lock and will describe the analysis sets to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

10.3.1 Safety Analyses

The primary objective of this study is to explore the safety of IFX-1 administered in subjects with pyoderma gangrenosum. Safety will be described by the following endpoints:

- TEAEs, defined as adverse events that start at or after the first administration of IMP
- Related TEAEs
- Serious TEAEs
- Adverse events of special interest

TEAEs will be analyzed according to the number and percentage of subjects who had an adverse event as well as the number of TEAEs with the respective MedDRA System Organ Class and Preferred Term. Related TEAEs and serious TEAEs will be analyzed in the same way. Additionally, the number and percentage of subjects with adverse events will be further grouped by severity and relationship. The maximum severity/relationship per subject and preferred term will be counted in these summary tables.

All safety analyses will be performed on the SAF. Analyses will generally be performed for the entire SAF as well as the 3 dosing groups separately. Additional stratifications based on actual dosing and IMP compliance will be defined in the statistical analysis plan.

10.3.2 Efficacy Analyses

The efficacy of IFX-1 for the treatment of skin lesions due to pyoderma gangrenosum is one key secondary objective of this study. Further additional clinical outcome measures will also be investigated. The efficacy endpoints include:

- The responder rate based on the Physician's Global Assessment at Visits V4, V6, V10, and V16 (EOT). Response is defined as a Physician's Global Assessment of ≤3 at the target ulcer
- Time to complete closure of pyoderma gangrenosum target ulcer as assessed by the investigator
- Percentage change in wound area and volume assessed by measurement of photographs of the target ulcer between selected visits (i.e., change between Visits V1 and V4, V1 and V6, V6 and V10, V10 and V16, and V1 and V16)
- Rate of change calculated per day in the area of the target ulcer derived from the photographic measurements
- Number of subjects with a decrease in area of the target ulcer of 50% or more at Visit V16 compared to baseline derived from the photographic measurements
- Number of subjects with a decrease in area of the target ulcer of 100% at Visit V16 compared to baseline derived from the photographic measurements
- A wound healing assessment based on the investigators rating of the target ulcer's erythema and border elevation at Visits V4, V6, V10, and V16 (EOT)

Continuous variables, such as the target ulcer area and ulcer volume, will be analyzed by absolute values and changes from baseline, if applicable. Basic descriptive statistics (e.g., number of observations (n), mean, standard deviation, minimum, median, maximum, lower quartile, upper quartile) will be displayed by visit. All efficacy endpoints will be analyzed descriptively only. Therefore, p-values or confidence intervals resulting from possible statistical models or tests will be interpreted descriptively only. No statements concerning statistical significance are valid.

The number and percentage of subjects in each category will be displayed by visit for categorical or binary variables, such as the responder rate based on the Physician's Global Assessment or the number of subjects with remission.

The time to complete closure will be analyzed with Kaplan-Meier methods using the date of first IMP administration as reference time point. The date of complete closure represents the event date. Subjects who do not experience complete closure of the target ulcer will be censored at the date of their last assessment.

All efficacy analyses will be performed on the SAF and on the PPS. Analyses will generally be performed for the entire study SAF and PPS as well as the 3 dosing groups separately. Additional stratifications based on actual dosing and IMP compliance will be defined in the

statistical analysis plan. Additional further details on the statistical analysis will be specified in the SAP.

10.3.3 Pain and Quality of Life Analyses

Pain will be assessed by a:

- NRS at Screening, and Visits V1, V4, V6, V10, V16 (EOT), and Ob2

and quality of life by the:

- Dermatology Life Quality Index score at Screening, and Visits V1, V4, V6, V10, V16 (EOT), and Ob2

Basic descriptive statistics (e.g., number of observations (n), mean, standard deviation, minimum, median, maximum, lower quartile, upper quartile) will be displayed for the absolute values by visit and for the change of baseline at each visit for each scale.

The number and percentage of subjects in each answer category will be displayed for each of the 10 Dermatology life quality index items.

All analyses will be conducted on the SAF. Analyses will generally be performed for the entire SAF as well as the 3 dosing groups separately. Additional stratifications based on actual dosing and IMP compliance will be defined in the statistical analysis plan.

10.3.4 Analyses of Concentrations of IFX-1

Concentrations of IFX-1 will be summarized by time point. Derived parameters will be analyzed by displaying basic statistics (e.g., number of observations (n), mean, standard deviation, coefficient of variation, minimum, median, maximum, geometric mean, geometric coefficient of variation). All concentration parameters will be analyzed on the SAF including all values and subjects that are assessed as evaluable by the pharmacokinetic specialist. Analyses will generally be performed for the entire SAF as well as the 3 dosing groups separately. Additional stratifications based on actual dosing and IMP compliance will be defined in the statistical analysis plan.

10.3.5 Other Analyses

The following parameters will be analyzed descriptively as exploratory endpoints on the SAF.

Safety parameters:

- Safety laboratory parameters will be analyzed by displaying basic summary statistics (e.g., for continuous variables, number of observations (n), mean, standard deviation, minimum, median, maximum, lower quartile, upper quartile) for absolute values and changes from baseline by visit.

- Anti-drug antibody from blood samples at time points described in the Schedule of Assessments will be analyzed by the number and percentage of subjects presenting anti-drug antibody as per time point.
- The number of subjects with abnormal physical examination parameters will be displayed by visit.
- Immunology and other assessments on blood, ulcer fluid, biopsies, and stools will be analyzed by displaying basic summary statistics.

10.3.6 Interim Analyses

Interim analyses will be performed after each initial dosing group of 6 subjects has completed Visit V10. The interim analysis will comprise adverse events, Physician's Global Assessment, and photographic documentation of area and volume.

Statistics for the above parameters will be generated as for the final analysis.

The statistical analysis plan will describe the planned interim analyses in detail.

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12 APPENDICES

Appendix 1 Safety Laboratory Tests

The tests detailed in Table 2 will be performed by a local laboratory. Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 29 of the protocol. Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Investigators must document their review of each laboratory safety report.

Table 2 Protocol-Required Safety Laboratory Assessments

Assessment	**Parameters**	
Hematology	[redacted]	[redacted] eosinophils, basophils)
Clinical chemistry [a]	[redacted]	[redacted]
	[redacted] [b]	
Urinalysis	[redacted])	
Other screening tests	[redacted]	
a) [redacted]		

Appendix 2 Regulatory and Ethical Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation Guidelines for GCP
- Applicable laws and regulations

The protocol, protocol amendments, informed consent form (ICF), investigator's brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB by the investigator and reviewed and approved by the IRB before the study is initiated.

The study can only start after obtaining a positive evaluation by the applicable IRB and approval from the applicable regulatory authority. The written approval of the applicable IRB and the responsible regulatory authority must be filed in the trial master file. Additionally, each study site must receive a copy of these documents to be filed in the investigator site file.

Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
- Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financing and Insurance

The study is financed by the sponsor.

The subjects are covered by an applicable insurance policy for participation in a clinical study. A copy of the insurance policy and the insurance conditions will be filed in the investigator site file.

Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

The investigator or his/her representative will explain the nature of the study, the purposes, the procedures involved, the expected duration, the potential risks and benefits involved, and any discomfort it may entail to each study subject or his/her legally authorized representative and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB and study site.

The informed consent must be given by means of standard written statements, written in non-technical language. The subjects should read the informed consent form and consider their decision before signing and dating the document. A copy of the signed document must be given to the subject. No subject can be involved in the study if he/she is related to the investigator, any member of the team at the study site, or the sponsor.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Subjects must re-consent to the most current version of the ICF during their participation in the study.

A copy of the ICF must be provided to the subject.

Subjects who are rescreened are required to sign a new ICF.

Subjects will need to consent to photographical documentation of affected areas.

Data Protection

Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

The sponsor will ensure that all safeguards are in place to minimize any eventual risk of breaches, and complies otherwise with the requirements of European Union General Data Protection Regulation (GDPR, Regulation (EU) 2016/679). The sponsor will regularly check all procedures relevant to the processing of personal data, as to ensure privacy by design and compliance with GDPR.

Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multisite studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

The sponsor will provide the relevant study protocol information in a public database (e.g., ClinicalTrials.gov, https://clinicaltrials.gov/) before or at commencement of the study. The sponsor may also provide study information for inclusion in national registries according to local regulatory requirements.

If a potential subject contacts the sponsor regarding participation in the study, the investigator agrees that the sponsor may forward the study site and contact details to the subject. Based on the inclusion and exclusion criteria for the study, the investigator will assess the suitability of the subject for enrollment into the study.

Results of this study will be disclosed according to the relevant regulatory requirements. All publications in peer-reviewed medical journals resulting from this study will be listed in the original study protocol registration record (e.g., on ClinicalTrials.gov).

Monitoring

Monitoring of the study sites will be performed by a contract research organization designated by the sponsor and will be based on the contract research organization's monitoring standard operating procedures as well as the study specific monitoring manual.

The clinical monitor, as a representative of the sponsor, has the obligation to follow the study closely. The monitor will visit the study site at periodic intervals in addition to maintaining necessary telephone calls and written contact as appropriate. The monitor will maintain a working knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and study site personnel. Source data verification of the eligibility criteria as described in the monitoring manual will be performed for all subjects.

The monitor will report via the project manager of the sponsor-designated contract research organization to the sponsor who carefully monitors all aspects of the study for compliance with applicable government regulations, with respect to current ICH guidelines for GCP and current standard operating procedures.

Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during

the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Source data comprise data in medical records, ECG assessments, and wound assessment records.

Audits

In order to guarantee that the conduct of the study is in accordance with ICH guidelines for GCP and the national laws, audits may be performed at the study sites to be carried out by an independent auditor. In addition, for-cause audits may be scheduled.

The investigator agrees to give the auditor access to all relevant documents for review.

Inspections

According to the corresponding ICH guidelines for GCP, inspections of the study sites may be performed by the local or federal authorities at any time during or after completion of the study.

The investigator agrees to give the inspectors access to all relevant documents for review.

Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further IMP development

Appendix 3 Adverse Events: Definitions and Procedures for Recording, Evaluation, Follow-up, and Reporting

Definition of an Adverse Event
An adverse event is any untoward medical occurrence in a patient or clinical study subject, whether or not considered related to the IMP. NOTE: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated). Treatment emergent adverse events are adverse events that are temporally associated with the use of IMP.
Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after IMP administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either IMP or a concomitant medication. Overdose per se will not be reported as an adverse event/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an adverse event or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or SAE if they fulfil the definition of an adverse event or SAE.
Events <u>NOT</u> Meeting the Adverse Event Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

• Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital) or planned hospitalizations due to a pre-existing condition that has not worsened (e.g., elective surgery). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of an adverse events of special interest

An adverse event of special interest is an adverse event of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor could be appropriate. Such an event might require further investigation in order to characterize and understand it.

The following are defined as adverse events of special interest:
• Infusion-related reactions, including acute and delayed hypersensitivity and anaphylactic reactions during or after IFX-1 infusion All patients should be observed closely during the IFX-1 administration and for 30 minutes after the first 2 infusions. The IV line should remain open during the observation to allow for administration of IV drugs, if necessary. Medication for infusion-related reactions should be available for immediate use. Medical staff have to be trained in resuscitation and immediate intensive care has to be readily accessible in case of severe life-threatening events. Mild to moderate reactions may be treated by slowing or interruption of the infusion, or with supportive treatment. For any potential infusion-related event, the investigator should check for a potentially developing or existing anaphylactic reaction. If an anaphylactic reaction is possible, appropriate immediate actions should be taken according to the severity or stage of the detected anaphylactic reaction as recommended by existing guidelines for the treatment of anaphylactic reactions or, if established at the study sites, according to available standard operating procedures or other algorithms.
• Meningitis If there are signs of meningitis at any time during the study, the IMP should be discontinued if meningitis is confirmed. The patient must be closely monitored and the guidelines for treatment of meningitis should be followed. This includes lumbar puncture, blood culture testing, immediate start of treatment with dexamethasone and intravenous antibiotics (combination therapy with ampicillin and third generation cephalosporin), and a search made for the focus of the infection (e.g., computed tomography or magnetic resonance tomography).
• Meningococcal septicemia
• Invasive infection

All adverse events of special interest will be recorded and reported as SAEs, and subject narratives will be generated. Further information may be requested from the investigator.

Definition of an SAE

If an event is not an adverse event according to the above definition, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
• Results in death
• Is life-threatening Life-threatening in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.
• Required inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.
• Results in persistent disability or incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
• Is a congenital anomaly or birth defect
• Other situations: – Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to

prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, 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 drug dependency or drug abuse.

Recording of an Adverse Event and/or SAE

Adverse Event and SAE Recording
• When an adverse event/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant adverse event/SAE information in the CRF. • It is **not** acceptable for the investigator to send photocopies of the subject's medical records in lieu of completion of the adverse event/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by, for example, the IRB or regulatory agency. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission. • The will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each adverse event and SAE reported during the study and assign it to 1 of the following categories:

- Mild: an event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: an event that causes sufficiently discomfort and interferes with normal everyday activities.
- Severe: an event that prevents normal everyday activities. An adverse event that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both adverse event and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between IMP and the adverse event/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to IMP administration will be considered and investigated.
- The investigator will also consult the IB in his/her assessment.
- For each adverse event/SAE, the investigator **must** document in the medical notes that he/she has reviewed the adverse event/SAE and has provided an assessment of causality.

The causal relationship of adverse events to administration of the IMP will be assessed according to the following criteria:

- **Not related (must meet at least one criterion listed below)**

This category applies to events that are due to extraneous causes and are not timely related to the administration of the IMP if:

  - Event or laboratory test abnormality with a time to administration of the IMP that makes a relationship impossible
  - Is most likely explained by concurrent disease or other drugs or chemicals (either pathophysiologically or clinically)

- Has occurred before administration of the IMP in comparable severity and/or frequency

- **Unlikely related (must meet at least first two criteria listed below)**

This category applies to events that are unlikely related to the administration of the IMP. The relationship of an event to the sIMP can be considered probably not related if:

- The event does not follow a reasonable temporal sequence from administration of the drug
- The event could readily have been a result of the patient's clinical state or other underlying medical condition environmental or toxic factors, or other modes of therapy administered to the patient
- The event does not follow a known response pattern to the suspected drug
- The event does not reappear or worsen when the IMP is re-administered

- **Possibly related (must meet at least first two criteria listed below)**

This category applies to events that are unlikely to be related to the administration of the IMP, but the possibility cannot be ruled-out with certainty. The relationship of an event to the IMP can be considered possibly related if:

- The event follows a reasonable temporal sequence from administration of the IMP
- The event could readily have been a result of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
- The event follows a known response pattern to the suspected IMP

- **Probably related (must meet at least first three criteria listed below)**

This category applies to events that are considered with a high degree of certainty to be related to the administration of the IMP. The relationship of an event to the IMP drug can be considered probably related if:

- The event follows a reasonable temporal sequence from administration of the IMP
- The event could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
- The event disappears or decreases upon cessation of IMP or reduction in dose
- The event follows a known response pattern to the suspected IMP

- **Definitely related (must meet at least first three criteria listed below)**

This category applies to events that are determined with certainty to be related to the administration of the IMP. The relationship of an event to the IMP can be considered definitely related if:

- The event follows a reasonable temporal sequence from administration of the IMP or IMP levels have been established in body fluids or tissues
- The event could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
- The event disappears or decreases upon cessation of IMP or reduction in dose and, if applicable, appears upon re-challenge
- The event follows a known response pattern to the suspected IMP
- There are exceptions when an event does not disappear upon discontinuation of the IMP, yet IMP relatedness clearly exists; e.g., 1) tardive dyskinesia, 2) fixed drug eruptions

Follow-Up of Adverse Events and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the IRB or regulatory agency to elucidate the nature and/or causality of the adverse event or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide copies of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting to the sponsor and CRO

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the sponsor and contract research organization.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- The sponsor will supply the investigator with the contact details for SAE reporting.

Suspected unexpected serious adverse reactions (SUSAR)

SUSAR Reporting to the sponsor and CRO
• Suspected unexpected serious adverse reactions (SUSARs) are side effects whose nature or severity is inconsistent with the information available about the product in the investigator's brochure. • The sponsor will submit all available information on a SUSAR immediately to the applicable IRB, the applicable regulatory authority, and the investigators in this study, at the latest within 15 calendar days after the event becomes known. • For every SUSAR that results in death or a life-threatening condition, the responsible IRB, the applicable regulatory authority, and the investigators in this study must be informed by the sponsor within 7 calendar days after the event becomes known. • Additional information has to be given within 8 further calendar days. • The sponsor will supply the investigator with the contact details for SUSAR reporting.

Appendix 4 Contraceptive Guidance and Collections of Pregnancy Information

Definitions

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered women of child-bearing potential:

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview.

Postmenopausal female:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Note: Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods.

Contraception Guidance

Male subjects

Male subjects who have not had a vasectomy must, during the entire study participation and for at least one month after last administration of study drug:

- either abstain from reproductive sexual intercourse or use a condom during intercourse
- not donate sperm.

Female subjects

Female subjects of childbearing potential must not donate eggs and must agree to use a highly effective method of contraception consistently and correctly as described in Table 3.

Table 3 Highly Effective Contraceptive Methods

Note: Subjects must have been on a stable dose of hormonal contraceptives for at least 4 weeks before Day 1.

Highly Effective Contraceptive Methods That Are User Dependent [a] (failure rate of <1% per year when used consistently and correctly)
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: [b] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent [a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation: [b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomized partner: A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the woman of child-bearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the IMP. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.

a Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. b Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraceptive method. In this case, two highly effective methods of contraception should be utilized during the treatment period and for at least 30 days after the last dose of IMP.

Pregnancy Testing

Women of child-bearing potential should only be included after a confirmed menstrual period and a negative highly sensitive urine pregnancy test.

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Collection of Pregnancy Information

Male Subjects with Partners who Become Pregnant

The investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. This applies only to male subjects who receive IMP.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Subjects who Become Pregnant

The investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a subject's pregnancy. The subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an adverse event or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an adverse event or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as

such. Any post-study pregnancy related SAE considered reasonably related to the IMP by the investigator will be reported to the sponsor as described in Section 52. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating in the study will discontinue IMP.

Appendix 5 Prohibited biologics

Note: Biologicals used for an underlying disease at a stable dose may be continued.

Class	Drug	Time use prohibited before screening
Anti-TNF	Etanercept	1 month
	Infliximab, golimumab, certolizumab pegol, adalimumab	3 months
IL-17	Brodalumab, ixekizumab, secukinumab	3 months
Other biologics	Ustekinumab	6 months
	Alefacept, efalizumab, guselkumab, tocilizumab	3 months
	Tildrakizumab, risankizumab	5 months
	Briakinumab	6 months
	Rituximab, alemtuzumab, abatacept, visilizumab, natlizumab, belimumab	12 months
	Anakinra	1 month
Systemics	Apremilast, tofacitinib, methotrexate, cyclosporin, azathioprine, thioguanine	1 month

Appendix 6 Permitted wound care

Dressings	• Foams • Superabsorbants • Calcium alginate • Gelling fibers (hydrofibers)
Compression therapy	• Coban2 • Profore • Compression stockings • Viscopaste and Easifix
Antiseptics	• Iodine derivatives • Silver dressings • Polyhexamethylene biguanide hydrochloride/polyhexanide/polyaminopropyl biguanide (PHMB) and Dialkylcarbamoylchloride (DACC)

Appendix 7 Amendment 01

Rationale for Amendment 01

Amendment 01 was enacted to:

- Enable the exploration of a dose range of IFX-1 and also to allow the dose to be increased in individual patients during study.
- Increase the number of patients in the study from 12 to a possible 18.
- Allow screening to take 7 to 35 days instead of 9 to 19 days.
- Move laboratory tests from screening to the Baseline visit for tests not required for screen failures.
- Add live attenuated vaccination to the list of prohibited medications.
- Remove analyses of blood and ulcer fluid that will not be performed due to feasibility and analytical hurdles of small volumes.
- Replace incorrect reference to analysis at a local safety laboratory by analysis at a central laboratory.
- Correct the total amount of blood taken.
- Add contraceptive guidance for male subjects.
- Standardize definitions of relationship to IMP.
- Correct inconsistencies in the protocol.

Corrections to spelling and punctuation are not listed.

List of changes

Section	Original text	Amended text
Title page Protocol signatures 10 Synopsis of Study	Open label exploratory phase IIa trial to investigate the safety and efficacy of IFX-1 in treating subjects with Pyoderma Gangrenosum	Open label exploratory phase IIa trial to investigate the safety and efficacy of IFX-1 in treating subjects with Pyoderma Gangrenosum *(OPTIMA)*
Sponsor Signatory:	~~Othmar Zenker, MD~~ ~~Chief Medical Officer~~	*Ronald Rosenburg, MD, PhD* *Program Director Dermatology*
Signature of Coordinating Investigator:	Afsaneh Alavi MD, Msc, FRCPC Coordinating Investigator Assistant Professor of Dermatology York Dermatology Center 250 Harding Blvd. West, Suite ~~312~~, Richmond Hill, Ontario, L4C 9M7, Canada	Afsaneh Alavi MD, Msc, FRCPC Coordinating Investigator Assistant Professor of Dermatology *University of Toronto* *76 Grenville Street* *Toronto, Ontario* *M5S 1B2* York Dermatology Center 250 Harding Blvd. West, Suite *202*, Richmond Hill, Ontario L4C 9M7, Canada
10 Synopsis of Study	Rationale ... Several animal models have demonstrated a positive impact of a blockade of the C5a/C5aR signaling axis on acute and chronic inflammatory disease ~~condition~~s. A recent open label study deploying IFX-1 in 12 subjects suffering from ~~the chronic dermatologic disease~~ hidradenitis suppurativa ~~has~~ revealed early evidence of disease modifying activity of IFX-1 in this neutrophil driven skin disorder~~. In this condition. IFX-1 treatment also leads to~~ a sustained clinical response even after only 8 weeks of treatment.	Rationale … Several animal models have demonstrated a positive impact of a blockade of the C5a/C5aR signaling axis on acute and chronic inflammatory diseases. A recent open label study deploying IFX-1 in 12 subjects suffering from hidradenitis suppurativa revealed early evidence of disease modifying activity of IFX-1 in this neutrophil driven skin disorder*, with* a sustained clinical response even after only 8 weeks of treatment.
10 Synopsis of Study	Objectives and Endpoints: Occurrence, nature and intensity of treatment emergent adverse events (TEAEs), related TEAEs, ~~and~~ serious TEAEs	Objectives and Endpoints: Occurrence, nature and intensity of treatment emergent adverse events (TEAEs), related TEAEs, serious TEAEs*, and adverse events of special interest*
10 Synopsis of Study	Objectives and Endpoints: • Mean change from baseline in pain assessed by Numeric Rating Scale (NRS) at Visits V4, V6, V10, and V16 (EOT) ~~(investigator assessment)~~ • Mean change from baseline in Dermatology Life Quality Index (DLQI) at Visits V4, V6, V10, and V16 (EOT) ~~(investigator assessment)~~	Objectives and Endpoints: • Mean change from baseline in pain assessed by Numeric Rating Scale (NRS) at Visits V4, V6, V10, and V16 (EOT) • Mean change from baseline in Dermatology Life Quality Index (DLQI) at Visits V4, V6, V10, and V16 (EOT)
10 Synopsis of Study	Scientific exploratory parameters	Scientific exploratory parameters

	Fluid draining from the target ulcer, if ~~applicable~~, for analysis of: • ~~Concentrations of IFX-1~~ • Immunology: ◦ ~~Complement factors C3a, C5a~~ ◦ IL-1beta, IL-6, IL-8, IL-12p40, IL-12p19, IL-13, IL-17, IL-36 ◦ IFN-a, TNF-alpha ◦ ~~Elastase, calprotectin, other matrix metalloproteins~~ • Bacteria using a bacterial culture and polymerase chain reaction Biopsies will be collected from the border tissue of the target ulcer for analysis for: • ~~C1q, C3, C5b-9~~ • IL-1beta, IL-6, IL-8, IL-17, IL-36 • TNF-alpha	Fluid draining from the target ulcer, if *available*, for analysis of: • Immunology: ◦ IL-1beta, IL-6, IL-8, IL-12p40, IL-12p19, IL-13, IL-17, IL-36 ◦ IFN-a, TNF-alpha • Bacteria using a bacterial culture and polymerase chain reaction Biopsies will be collected from the border tissue of the target ulcer for analysis for: • IL-1beta, IL-6, IL-8, IL-17, IL-36 • TNF-alpha
10 Synopsis of Study	Scientific exploratory parameters Absolute values and changes from ~~baseline~~ will be evaluated for the above parameters.	Scientific exploratory parameters Absolute values and changes from *the baseline value* will be evaluated for the above parameters.
10 Synopsis of Study	Number of Subjects: This is planned to be a multi-center study with ~~12~~ subjects treated with IMP (IFX-1). Subjects discontinuing treatment will not be replaced. It is expected that approximately ~~10~~ subjects will undergo at least 3 months treatment.	Number of Subjects: This is planned to be a multi-center study with *about 18* subjects treated with IMP (IFX-1). Subjects discontinuing treatment will not be replaced. It is expected that approximately *15* subjects will undergo at least 3 months treatment.
10 Synopsis of Study	Treatment Groups and Duration: The study duration for an individual subject includes screening (14 days ~~±5 days~~), the treatment period (189 days ±5 days), and the observational follow up (60 days ±5 days).	Treatment Groups and Duration: The study duration for an individual subject includes screening (14 days *range 7 to 35* days), the treatment period (189 days ±5 days), and the observational follow up (60 days ±5 days).
10 Synopsis of Study	Treatment Groups and Duration: All subjects will receive ~~800 mg~~ IFX-1 ~~per dose (for~~ a maximum of 15 ~~doses in total)~~.	Treatment Groups and Duration: All subjects will receive IFX-1 *at* a maximum of 15 *dosing visits*. *There will be 3 dosing groups (Group 1, Group 2, and Group 3) of 6 subjects each. Each group of subjects is recruited sequentially. The next dose group will be initiated if the previous dose was considered safe and well tolerated. If dosing in Group 2 cannot be initiated, then a further 6 patients will be recruited in Group 1.*
10 Synopsis of Study Study Population Exclusion Criteria:	5. One of the following abnormal laboratory findings at screening: Hemoglobin <7 g/~~mL~~	5. One of the following abnormal laboratory findings at screening: Hemoglobin <7 g/*dL*

	7. ~~No evidence~~ of active tuberculosis ~~on a chest X-ray taken within 1 year prior to screening or a positive QuantiFERON®-TB gold test at screening~~	7. *Evidence* of active tuberculosis
	9. An ankle brachial index of less than 0.8 or toe pressure of less than 80 mmHg in subjects with a compromised vascular system (e.g., diabetic subjects) at screening	9. An ankle brachial index of less than 0.8 or toe pressure of less than 80 mmHg in subjects with a compromised vascular system (e.g., diabetic subjects) *within previous year or* at screening
	10. ~~Chronic~~ infection requiring suppressive anti-infective therapy (such as latent tuberculosis, pneumocystis, aspergillosis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria)	10. *I*nfection requiring suppressive anti-infective therapy (such as latent tuberculosis, pneumocystis, aspergillosis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria)
	12 Any drug treatment for pyoderma gangrenosum including corticosteroids (>10 mg), intralesional steroids, cyclosporine A, biologicals and immunosuppressives (with the exception of antibiotics for wound superinfection) used within a time of 5 half-lives of the drug before screening (see Appendix 5)	Any drug treatment for pyoderma gangrenosum including corticosteroids (>10 mg *prednisone or prednisone equivalent*), intralesional steroids, cyclosporine A, biologicals and immunosuppressives (with the exception of antibiotics for wound superinfection) used within a time of 5 half-lives of the drug before screening (see Appendix 5)
	22. ~~F~~emale subjects of childbearing potential unwilling to follow the contraceptive guidance in Appendix 4 during the treatment period and for at least 30 days after the last dose of IMP	22. *Male and f*emale subjects of childbearing potential unwilling to follow the contraceptive guidance in Appendix 4 during the treatment period and for at least 30 days after the last dose of IMP
10 Synopsis of Study	Investigational medical product (IMP), dose, and mode of administration The IMP will be provided in 10 mL glass vials ~~containing 100 mg of IFX-1~~. For each dose, ~~800 mg~~ of IFX-1 will be diluted with ~~approximately 250 ml of~~ 0.9% sodium chloride and given to the subject as a single intravenous dose over 30 to 60 minutes during a site visit. Subjects will receive a total of 15 doses of ~~IMP~~ ~~(~~IFX~~-1 800 mg)~~. The first 3 doses will be given in the first week – on Day 1, Day 4, and Day 8. The remaining doses will be given thereafter every 2 weeks starting from Day 15. ~~The starting dose of IFX-1 is 800mg.~~	Investigational medical product (IMP), dose, and mode of administration The IMP *(IFX-1)* will be provided in 10 mL *or 20 mL* glass vials *at a concentration of 10 mg/mL (i.e., 100 mg per 10 mL vial or 200 mg per 20 mL vial) for reconstitution and intravenous administration*. For each dose, *the required amount* of IFX-1 will be diluted with 0.9% sodium chloride *to a total volume of approximately 250 mL* and given to the subject as a single intravenous dose over 30 to 60 minutes during a site visit. *All subjects will receive IFX-1 800 mg three times during the first week (Days 1, 4, and 8).* *Starting at Day 15:* • *Subjects in Group 1 will continue to receive IFX-1 800 mg at 2 weekly intervals.* • *Subjects in Group 2 will receive IFX-1 1600 mg at 2 weekly intervals.* • *Subjects in Group 3 will receive IFX-1 2400 at 2 weekly intervals.*

		At Day 57 (Visit V7), subjects in Groups 1 and 2 may have their dose increased to IFX-1 1600 mg or 2400 mg, respectively, if there are no safety concerns and the Physician Global Assessment (main efficacy parameter) is ≥4. Subjects will receive a total of 15 doses of IFX-1. The first 3 doses will be given in the first week on Day 1, Day 4, and Day 8. The remaining doses will be given thereafter every 2 weeks starting from Day 15.
10 Synopsis of Study	Statistical methods … ~~An~~ interim ~~analysis~~ will be performed ~~on a minimum~~ of 6 subjects ~~who complete~~ Visit V10 ~~at Day 99 to assess the progress of the study~~. ...	Statistical methods ... Interim *analyses* will be performed *after each initial dosing group* of 6 subjects *has completed* Visit V10. *The interim analysis will comprise adverse events, Physician's Global Assessment, and photographic documentation of area and volume.* … *Statistical analyses will generally be performed for the entire study population as well as the 3 dosing groups separately. Additional stratifications based on actual dosing and IMP compliance will be defined in the statistical analysis plan.*
19 Schedule of Assessments	Screening Visit V0 Day -14 ~~±5~~	Screening Visit V0 Day 14 *7 to 35*
	Visit V15 Day ~~179~~	Visit V15 Day *169*
		[Tx: Added dose modification for visit V7] [Safety: Added Chest X-ray at Visit V0] [Moved all biomarkers from Screening to Visit V1] [Deleted measurement of antinuclear antibody from all but Visit V1]
	Footnotes b Subjects with a compromised vascular system (e.g., diabetic subjects)	Footnotes b Subjects with a compromised vascular system (e.g., diabetic subjects)*, within previous year or at screening* [added footnote "d" for Visit V2: *d Only for subjects in Group 1 and Group 2*]
21 Study Rationale	Neutrophilic dermatoses are a spectrum of inflammatory disorders characterized by skin lesions resulting from a neutrophil-rich inflammatory infiltrate in the absence of infection. ~~The exact molecular pathophysiology of the neutrophilic dermatoses has long been poorly understood. Interestingly,~~ ~~n~~eutrophil-rich cutaneous inflammation is also a cardinal feature of several auto-inflammatory diseases with skin	Neutrophilic dermatoses are a spectrum of inflammatory disorders characterized by skin lesions resulting from a neutrophil-rich inflammatory infiltrate in the absence of infection. *N*eutrophil-rich cutaneous inflammation is also a cardinal feature of several auto-inflammatory diseases with skin involvement, the latter being caused by aberrant innate immune responses.

	involvement, the latter being caused by aberrant innate immune responses.	
22 IFX-1	IFX-1 is an IMP and is not approved in any country worldwide. To date, IFX-1 has been investigated in 1 Phase I study in healthy subjects and in ~~3~~ Phase II studies in subjects with early septic organ dysfunction, in subjects undergoing complex cardiac surgery, and in subjects with moderate to severe hidradenitis suppurativa~~.~~ … Further details on IFX-1 are given in the Investigator's Brochure~~,~~ the current version ~~of which~~ is available in the investigator site file.	IFX-1 is an IMP and is not approved in any country worldwide. To date, IFX-1 has been investigated in 1 Phase I study in healthy subjects and in *4* Phase II studies in subjects with early septic organ dysfunction, in subjects undergoing complex cardiac surgery, and in subjects with moderate to severe hidradenitis suppurativa*:* … *Study IFX-1-P2.4 (subjects with moderate to severe hidradenitis suppurativa): in this Phase II study, 177 subjects were treated with either placebo or one of 4 different dose regimens of IFX-1 (400 or 800 mg every four weeks and 800 or 1200 mg every two weeks). The IFX-1 treatment was well tolerated and although most subjects experienced TEAEs, these were for the most part non-serious and similar in all treatment groups. IFX-1 treatment was associated with low immunogenicity.* Further details on IFX-1 are given in the investigator's brochure *(*the current version is available in the investigator site file*)*.
24 Rationale for Dosing Regimen	Like hidradenitis suppurativa, pyoderma gangrenosum is also considered to be a ~~leukocytosis~~ driven auto-inflammatory disease. As a dose of 800 mg was efficacious in ~~this~~ subject population, it is likely that the same dose could also be efficacious in pyoderma gangrenosum with the same auto-inflammatory pathology. Therefore this dose ~~will be~~ used in this study.	Like hidradenitis suppurativa, pyoderma gangrenosum is also considered to be a *neutrophil* driven auto-inflammatory disease. As a dose of 800 mg was efficacious in *the* subject population *of IFX-1-P2.3*, it is likely that the same dose could also be efficacious in pyoderma gangrenosum with the same auto-inflammatory pathology. Therefore, this dose *is* used *as the starting dose* in this study. *However, a recently completed Phase II study in moderate to severe hidradenitis suppurativa indicates that higher doses may be necessary to treat leukocytosis in the skin. In this study IFX-1-P2.4 (SHINE), 177 patients were treated with either placebo or one of 4 different dose regimens of IFX-1. The study failed to meet its primary endpoint, a dose-dependent drug effect on the HS Clinical Response Score (HiSCR) after 16 weeks of treatment. The percentages of subjects with HiSCR were similar in all dose groups, with 46.0% for placebo, 38.1% for 400 mg every four weeks, 48.6% for 800 mg every four weeks, 35.9% for 800 mg every two weeks, and 45.0% for 1200 mg every two weeks.*

		However, there was a statistically significant reduction of draining fistulas relative to baseline in the high dose IFX-1 group when compared to placebo (63.2% vs 18.0% reduction; p=0.0359) at week 16. In addition, the total abscess and inflammatory nodule count was reduced compared to placebo in all IFX-1 treatment groups (26.5% reduction under placebo and 32.7%, 54.6%, 44.9%, 47.7% respectively in the IFX-1 groups). Abscesses (20.4% reduction under placebo vs 31.1% reduction under high dose at week 16) and inflammatory nodule counts (30.7% reduction under placebo vs 40.7% reduction under high dose at week 16) were also reduced over time. Hence, although the primary endpoint was not met, additional post-hoc analyses of the obtained data at week 16 indicate a robust anti-inflammatory activity in the high dose IFX-1 treatment group across numerous efficacy measures. *Therefore, in this study (IFX-1-P2.7), the dose of 800 mg every 2 weeks in Group 1 is lower than the effective dose in IFX-1-P2.3 which was 800 mg every week. It is also lower than effective dose in IFX-1-P2.4, which was 1200 mg every two weeks. Population/pharmacokinetic analyses and simulations of data from the IFX-1-P2.3 and* *IFX-1-P2.4 studies showed a well-defined dose exposure relationship across doses of 400, 800, 1200, 1600, 2000, 2400, 2800, and 3200 mg, given every 2 or 4 weeks. These analyses show that after 16 weeks (112 days) of treatment, only 55% of simulated patients were above the critical efficacy exposure when given 800 mg IFX-1 every 2 weeks. In contrast, 99% of simulated patients were above the critical exposure if treated with 2400 mg IFX-1 every 2 weeks. At this dose, only 0.3% and 0.1% of simulated patients were above the steady state AUC and Cmax NOAEL values, respectively.* *The time to ulcer healing in pyoderma gangrenosum varies in different trials of infliximab and other biologicals (Foss et al. 2008, Adişen et al. 2008, Foss et al. 2008, Brooklyn et al. 2006, Guenova et al. 2011, Kolios et al. 2015). However, an effect is likely to be seen after 6 to 8 weeks of treatment. The time to healing seems to correlate to ulcer size and is considered to*

		be less than 2 months for ulcers smaller than 6 cm2. *Therefore, this study will explore IFX-1 doses of 800 mg, 1600 mg, and 2400 mg given every 2 weeks. All doses are covered by the NOAEL of 50 mg/mL*
27 Overall Design	Figure 1 Study Design	Figure 1 Study Design [New flow chart inserted to include dose groups and dose modification]
27 Overall Design	The allowed time windows for Visits V1 to V6 are ±2 days. All other visits have allowed time windows of ±5 days.	The allowed time windows for Visits V1 to V6 are ±2 days. All other visits have allowed time windows of ±5 days. *There must be at least 48 hours between each dose of IFX-1 (Section 7.1.9). Visits should be scheduled appropriately.*
29 Study Sites, Study Subject, and Expected Duration	This study is planned to be a multi-center study with ~~12~~ subjects treated with IMP (IFX-1). ... The study duration for an individual subject includes screening (14 days ~~±5~~ days), the treatment period (189 days ±5 days), and the observational follow up (60 days ±5 days).	This study is planned to be a multi-center study with *about 18* subjects treated with IMP (IFX-1). … The study duration for an individual subject includes screening (14 days *range 7 to 35* days), the treatment period (189 days ±5 days*; the last day of dosing of IFX-1 is Day 169*), and the observational follow up (60 days ±5 days).
30 Screening Failures	Re-screened subjects will ~~be reported with the same~~ subject number ~~as for the initial screening~~.	Re-screened subjects will *receive the next available* subject number.
30 Treatment Administered	Unit dose strength(s)/ Dosage level(s): 10 mL glass vials at a concentration of 10 mg/mL ~~(total 100 mg per vial)~~ Dosing instructions: IFX-1 ~~800 mg~~ will be diluted with ~~approximately 250 ml of~~ 0.9% sodium chloride and given as a single intravenous dose over 30 to 60 minutes Packaging and labeling: The cartons will be labeled with a unique (medication) *number ("medcode")*. The vials within a carton will be labeled with the same (medication) number as the carton in which they are packed. ~~The labels are part of the Clinical Trial Application documentation.~~ Manufacturer: Celonics on behalf of InflaRx	Unit dose strength(s)/ Dosage level(s): 10 mL *and 20 mL* glass vials at a concentration of 10 mg/mL Dosing instructions: *The required dose of* IFX-1 will be diluted with 0.9% sodium chloride *to a total volume of approximately 250 ml* and given as a single intravenous dose over 30 to 60 minutes The cartons will be labeled with a unique *number* (medication *or kit number*). The vials within a carton will be labeled with the same (medication) number as the carton in which they are packed. Manufacturer: Celonics *and WuXi* on behalf of InflaRx
31 Dosing groups	~~No dose modification of IFX-1 is foreseen in this study.~~	*There will be 3 dosing groups (Group 1, Group 2, and Group 3) of 6 subjects each. Each group of subjects is recruited sequentially. The next dose group will be*

		initiated if the previous dose was considered safe and well tolerated. If dosing in Group 2 cannot be initiated, then a further 6 patients will be recruited in Group 1. *All subjects will receive IFX-1 800 mg three times during the first week (Days 1, 4, and 8).* *Starting at Day 15:* *• Subjects in Group 1 will continue to receive IFX-1 800 mg at 2 weekly intervals.* *• Subjects in Group 2 will receive IFX-1 1600 mg at 2 weekly intervals.* *• Subjects in Group 3 will receive IFX-1 2400 at 2 weekly intervals.* *At Day 57 (Visit V7), subjects in Groups 1 and 2 may have their dose increased to IFX-1 1600 mg or 2400 mg, respectively, if there are no safety concerns and the Physician Global Assessment (main efficacy parameter) is ≥4.*
32 Preparation and administration	~~The IMP will be prepared at the study site or site pharmacy~~ under controlled conditions and in compliance with rules governing preparations. ~~The amount of IMP for a single infusion is 800 mg IFX-1.~~ The IMP will be diluted in sterile sodium chloride. The total volume in the infusion bag for each infusion should be approximately 250 mL. ~~Details of IMP preparation and application will be outlined in the pharmacy manual.~~	*The IFX-1 for infusion will be reconstituted (prepared) under controlled conditions at the study site or at the study site's pharmacy, in accordance with local regulations/ requirements for aseptic reconstitution.* The IMP will be diluted in sterile sodium chloride. The total volume in the infusion bag for each infusion should be approximately 250 mL. *The reconstituted IFX-1 should be used within 4 hours after dilution when stored at room temperature. Otherwise, the reconstituted IFX-1 has to be stored at 2°C to 8°C (35.6°F to 46.4°F) and used within 24 hours; if the reconstituted IFX-1 solution is stored in a fridge, it must be left to acclimatize to room temperature prior to administration. Details on reconstituting the IFX-1 will be provided in the Pharmacy Manual.* *The number of unused, partially used, and empty vials will be documented accurately, and the vials will be kept at the site until the drug accountability documentation has been checked by the study monitor (Section 7.1.7).*
32 Preparation and administration	The IMP will be infused over a period of 30 to ~~60~~ minutes ~~(± 10 min)~~ via an intravenous line. Sites ~~may~~ use ~~their own~~ intravenous lines.	The IMP will be infused *intravenously* over a period of 30 to *70* minutes via an intravenous line. Sites *should* use t*he supplied* intravenous lines.
34 Overdose of IMP	~~For this study, any dose of IFX-1 greater than 800 mg within a 2-day time period~~	*At least 48 hours must have elapsed between each dose of IFX-1. Visits should*

	will be considered an overdose. The consequences of an overdose with IFX-1 are not known. InflaRx does not recommend specific treatment ~~for~~ an overdose. … 2. Closely monitor the subject for any adverse events or SAEs and laboratory abnormalities for at least 7 days.	*be scheduled appropriately. Any second administration within this time, or any administration that is greater than the scheduled dose* will be considered an overdose. The consequences of an overdose with IFX-1 are not known. InflaRx does not recommend specific treatment *in case of* an overdose. … 2. Closely monitor the subject for any adverse events or SAEs and laboratory abnormalities for at least 7 days. *If more than 130% of the dose is given, the patient should be kept in hospital overnight.*
35 Allowed Concomitant Therapy	Wound care for pyoderma gangrenosum Further details of wound care are given in Appendix 6. … Standard compression therapy throughout the study is required.	Wound care for pyoderma gangrenosum *Wound care is performed at the scheduled visits, and 2 to 3 times a week depending on necessity according to the standard of care.* Further details of wound care are given in Appendix 6. … Standard compression therapy throughout the study is required *(Shavit and Alavi 2019)*.
35 Prohibited Therapy	The following therapies are prohibited for all subjects from screening until Visit EOT or discontinuation from the study: … Oral or injectable corticosteroids … Over-the-counter topical antiseptic washes, creams, ~~soaps,~~ ointments, gels, and liquids containing antibacterial agents to treat pyoderma gangrenosum	The following therapies are prohibited for all subjects from screening until Visit EOT or discontinuation from the study: *Subject has received a live attenuated vaccine within 3 months prior to screening or plans to receive a live attenuated vaccine during the study or up to 4 weeks after the last study product administration.* … Oral or injectable corticosteroids *(more than 10 mg prednisone or prednisone equivalent)* … Over-the-counter topical antiseptic washes, creams, ointments, gels, and liquids containing antibacterial agents to treat pyoderma gangrenosum
38 Screening	The screening procedures will be conducted within 14 days (~~±5~~ days) before first administration of IMP.	The screening procedures will be conducted within 14 days (*range 7 to 35* days) before first administration of IMP.
38 Screening	The following procedures will be conducted and documented at the Screening visit: … • Measure ankle brachial index/toe pressure in subjects with a compromized cardiovascular system • Record a 12 lead ECG	The following procedures will be conducted and documented at the Screening visit: … • Measure ankle brachial index/toe pressure in subjects with a compromized cardiovascular system *(unless performed in the previous year)*

	• Take blood for ◦ Safety laboratory parameters (clinical chemistry and hematology) ◦ Human immunodeficiency virus, hepatitis B virus, and hepatitis C virus test ◦ Pregnancy test for women of childbearing potential ◦ QuantiFERON-TB gold test for the presence of tuberculosis ◦ ~~Immunology~~ ~~◦ Anti-drug antibody, antineutrophil cytoplasmic antibody, and antinuclear antibody~~ ~~• Take a sample of the target ulcer fluid, if applicable~~ ~~• Take a biopsy of the target ulcer~~ • Take urine for urinalysis	• Record a 12 lead ECG • *Chest X-ray* • Take blood for ◦ Safety laboratory parameters (clinical chemistry and hematology) ◦ Human immunodeficiency virus, hepatitis B virus, and hepatitis C virus test ◦ Pregnancy test for women of childbearing potential ◦ QuantiFERON-TB gold test for the presence of tuberculosis • Take urine for urinalysis
40 Start of IMP: Visit V1 (Day 1)	The following will be performed at Visit V1: … • Record a 12 lead ECG • Perform a urine pregnancy test for a woman of childbearing potential	The following will be performed at Visit V1: … • Record a 12 lead ECG • *Take blood for* ◦ *Immunology* ◦ *Anti-drug antibody, antineutrophil cytoplasmic antibody, and antinuclear antibody* • *Take a sample of the target ulcer fluid if wound is open and liquid is available* • *Take a biopsy of the target ulcer* • Perform a urine pregnancy test for a woman of childbearing potential
41 Treatment visit V7	[New section]	*9.1.3.1 Treatment visit V7* *In addition to the assessments and procedures outlined in the Schedule of Assessments (Section 2), the dose of IFX-1 will be assessed and increased in subjects of Group 1 and Group 2 if the dose escalation criteria are met (Section 7.1.2).*
41 Treatment visits (Visits V4 and V6) 42 Mid visit: Visit V10 43 End of treatment visit: Visit 16 (Day 189)	Take a sample of the target ulcer fluid, if ~~applicable~~	Take a sample of the target ulcer fluid if *wound is open and liquid is available*
43 End of treatment visit: Visit 16 (Day 189)	~~Take a biopsy of the target ulcer~~ Use a standard dressing and compression therapy for the target ulcer	Use a standard dressing and compression therapy for the target ulcer
41 Treatment visits (Visits V4 and V6)	• Take blood for ...	• Take blood for ... ◦ Anti-drug antibody

42 Mid visit: Visit V10 43 End of treatment visit: Visit 16 (Day 189) 44 Visit Ob1 (End of treatment +30 days) 44 Final Visit (End of Trial): Visit Ob2 (End of treatment +60 days)	◦ Anti-drug antibody~~, antineutrophil cytoplasmic antibody, and antinuclear antibody~~	
47 Dermatology Life Quality Index	To avoid biasing the subject's response, the subject should complete the questionnaire ~~in the diary~~ at the study site before study site personnel perform any other assessments and before any interaction with the study site personnel has occurred.	To avoid biasing the subject's response, the subject should complete the questionnaire at the study site before study site personnel perform any other assessments and before any interaction with the study site personnel has occurred.
48 Numeric Rating Scale for Pain	It is an 11-point scale (from 0 represent no pain to 10 representing the worst pain the subject can imagine). Subjects are asked to rate the intensity of their pain "right now" verbally with a number ~~or by pointing to the number that represents their pain intensity~~.	It is an 11-point scale (from 0 represent no pain to 10 representing the worst pain the subject can imagine). Subjects are asked to rate the intensity of their pain "right now" verbally with a number.
48 Safety Assessments	~~S~~afety ~~will be assessed on the basis of the following~~ variables:	*The following s*afety variables *will be collected*: … *Chest X-ray*
48 Safety Laboratory Assessments	The safety laboratory assessments will be performed by a ~~local~~ laboratory. Urinalysis will be ~~locally~~ performed using a dipstick.	The safety laboratory assessments will be performed by a *central* laboratory. Urinalysis will be *centrally* performed using a dipstick.
50 12-lead electrocardiograms	~~Digital ECG wave forms will be centrally archived.~~	
50 Physical Examination	~~A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).~~	
50 Adverse events	The definitions of an adverse event ~~or~~ SAE can be found in Appendix 3. … The investigator and any designees are responsible for detecting, documenting, ~~and~~ recording events ~~that meet the definition of an adverse events~~ or SAE. They are responsible for following up adverse events ~~that are serious, considered related to the IMP or study procedures, or that caused the subject to discontinue the IMP or study~~.	The definitions of an adverse event*, adverse event of special interest, and* SAE can be found in Appendix 3. … The investigator and any designees are responsible for detecting, documenting, recording*, and reporting (to the sponsor) adverse* events*, adverse events of special interest,* or SAEs. They are *also* responsible for following up *all* adverse events *until their resolution or until a steady state of the event is reached*.

51 Time Period and Frequency for Collecting adverse events and SAE Information	~~Investigators are not obligated to actively seek adverse event or SAE information from former study subjects. However, if~~ the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the IMP or study participation, the investigator must promptly notify the sponsor or sponsor's designee.	*If* the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the IMP or study participation, the investigator must promptly notify the sponsor or sponsor's designee.
[9.4.8] Chest X-ray	[New section]	*A standard chest X-ray will be performed at screening.*
52 Safety review	[New section]	*An ongoing safety review will also be performed. The decision to go to the next dose group will be made by the sponsor. The decision to start dose Group 2 will be based on safety data from at least 5 patients on IFX-1 800 mg, and to start Group 3 on at least 5 patients on IFX-1 1600 mg for at least 1 month.*
52 Immunostaining of biopsy	At ~~screening~~, a small biopsy of the target pyoderma gangrenosum ulcer will be taken and sent to a central laboratory ~~for immunostaining~~.	At *baseline*, a small biopsy of the target pyoderma gangrenosum ulcer will be taken and sent to a central laboratory.
53 Immunology and other assessments of blood, ulcer fluid, biopsies and stool samples	Venous blood samples will be collected for the measurement of: ... Fluid draining from the target ulcer, ~~if applicable~~, will be collected for analysis of: • Immunology: ~~◦ Complement factors C3a, C5a~~ ◦ IL-1beta, IL-6, IL-8, IL-12p40, IL-12p19, IL-13, IL-17, IL-36 ◦ IFN-a, TNF-alpha ~~◦ Elastase, calprotectin, other matrix metalloproteins~~ • Bacteria using a bacterial culture and polymerase chain reaction ~~Biopsies~~ will be collected from the border tissue of the target ulcer for analysis for: ~~• C1q, C3, C5b-9~~ • IL-1beta, IL-6, IL-8, IL-17, IL-36 • TNF-alpha	Venous blood samples will be collected for the measurement of: … Fluid draining from the target ulcer, *only if wound is open and liquid is available*, will be collected for analysis of: • Immunology: ◦ IL-1beta, IL-6, IL-8, IL-12p40, IL-12p19, IL-13, IL-17, IL-36 ◦ IFN-a, TNF-alpha • Bacteria using a bacterial culture and polymerase chain reaction *A biopsy* will be collected from the border tissue of the target ulcer for analysis for: • IL-1beta, IL-6, IL-8, IL-17, IL-36 • TNF-alpha
53 Immunology and other assessments of blood, ulcer fluid, biopsies and stool samples	~~Complement factors C3a and C5a will be analyzed at InflaRx with an ELISA test system. All other analyses will be performed by a specialized laboratory.~~ ~~S~~amples will be stored and analyses may be performed on biomarker variants that are later identified.	*The investigators will be supplied with the necessary sampling tubes (citrate, EDTA etc.) and instructed to send the samples to a central laboratory from where they will be forwarded to the analyzing laboratories. Further details are given in a laboratory manual.*

		*Remaining s*amples will be stored *for future research at a suitable storage facility (as documented in the trial master file)* and analyses may be performed on biomarker variants that are later identified.
54 Blood Sampling Volumes	Estimated Blood Sampling Volumes Total ~~221~~ The maximum amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed approximately ~~250~~ mL.	[Sample volumes for tests amended] Estimated Blood Sampling Volumes Total *173* The maximum amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed approximately *200* mL.
54 Sample Size Determination	The sample size for this study is not based on statistical consideration and no formal sample size estimation has been performed. In total, ~~12~~ subjects will be enrolled in the study. It is expected that at least ~~10~~ subjects will undergo 3 months treatment (i.e., evaluable). As the study is a pilot study in the indication of pyoderma gangrenosum and conducted as an open label study, approximately ~~10~~ evaluable subjects seems to be sufficient to explore the safety and tolerability of IFX-1 administered over 189 days to subjects with pyoderma gangrenosum.	The sample size for this study is not based on statistical consideration and no formal sample size estimation has been performed. In total, *18* subjects will be enrolled in the study. It is expected that at least *15* subjects will undergo 3 months treatment (i.e., evaluable). As the study is a pilot study in the indication of pyoderma gangrenosum and conducted as an open label study, approximately *5* evaluable subjects *per initial dosing group* seems to be sufficient to explore the safety and tolerability of IFX-1 administered over 189 days to subjects with pyoderma gangrenosum.
55 Safety Analyses	The primary objective of this study is to explore the safety of IFX-1 administered in subjects with pyoderma gangrenosum. Safety will be described by the following endpoints: • TEAEs, defined as adverse events that start at or after the first administration of IMP • Related TEAEs • Serious TEAEs … All safety analyses will be performed on the ~~safety analysis set~~.	The primary objective of this study is to explore the safety of IFX-1 administered in subjects with pyoderma gangrenosum. Safety will be described by the following endpoints: • TEAEs, defined as adverse events that start at or after the first administration of IMP • Related TEAEs • Serious TEAEs • *Adverse events of special interest* *…* All safety analyses will be performed on the *SAF. Analyses will generally be performed for the entire SAF as well as the 3 dosing groups separately. Additional stratifications based on actual dosing and IMP compliance will be defined in the statistical analysis plan.*
56 Efficacy Analyses	All efficacy analyses will be performed on the SAF and on the PPS. ~~F~~urther details on the statistical analysis will be specified in the SAP.	All efficacy analyses will be performed on the SAF and on the PPS. *Analyses will generally be performed for the entire study SAF and PPS as well as the 3 dosing groups separately. Additional stratifications based on actual dosing and IMP compliance will be defined in the*

		*statistical analysis plan. Additional f*urther details on the statistical analysis will be specified in the SAP.
57 Pain and Quality of Life Analyses	All analyses will be conducted on the SAF.	All analyses will be conducted on the SAF. *Analyses will generally be performed for the entire SAF as well as the 3 dosing groups separately. Additional stratifications based on actual dosing and IMP compliance will be defined in the statistical analysis plan.*
57 Analyses of Concentrations of IFX-1	All concentration parameters will be analyzed on the SAF including all values and subjects that are assessed as evaluable by the pharmacokinetic specialist.	All concentration parameters will be analyzed on the SAF including all values and subjects that are assessed as evaluable by the pharmacokinetic specialist. *Analyses will generally be performed for the entire SAF as well as the 3 dosing groups separately. Additional stratifications based on actual dosing and IMP compliance will be defined in the statistical analysis plan.*
58 Interim Analyses	~~An~~ interim ~~analysis~~ will be performed ~~on a minimum~~ of 6 subjects ~~on their data up to~~ Visit 10. The interim analysis will comprise adverse events, ~~p~~hysicians ~~g~~lobal ~~a~~ssessment, and photographic documentation of area and volume.	Interim *analyses* will be performed *after each initial dosing group* of 6 subjects *has completed* Visit V10. The interim analysis will comprise adverse events, *P*hysician's *G*lobal *A*ssessment, and photographic documentation of area and volume.
58 References	[References added]	*Adişen E, Oztaş M, Gürer MA. Treatment of idiopathic pyoderma gangrenosum with infliximab: induction dosing regimen or on-demand therapy? Dermatology (Basel) 2008; 216(2): 163–5.* *Brooklyn TN, Dunnill MGS, Shetty A, Bowden JJ, Williams JDL, Griffiths CEM, et al. Infliximab for the treatment of pyoderma gangrenosum: a randomised, double blind, placebo controlled trial. Gut 2006; 55(4): 505–9.* *Guenova E, Teske A, Fehrenbacher B, Hoerber S, Adamczyk A, Schaller M, et al. Interleukin 23 expression in pyoderma gangrenosum and targeted therapy with ustekinumab. Arch Dermatol 2011; 147(10): 1203–5.* *Shavit E, Alavi A. Compression therapy for non-venous leg ulcers: Current viewpoint. Int Wound J 2019.*
69 Adverse Events: Definitions and Procedures for Recording, Evaluation,	Definition of an Adverse Event An adverse event is any untoward medical occurrence in a patient or clinical study subject, ~~temporally~~	Definition of an Adverse Event An adverse event is any untoward medical occurrence in a patient or clinical study subject, whether or not considered related to the IMP.

Follow-up, and Reporting	~~associated with the use of IMP,~~ whether or not considered related to the IMP. NOTE: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) ~~temporally associated with the use of IMP~~.	NOTE: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated). *Treatment emergent adverse events are adverse events that are temporally associated with the use of IMP.*
69 Adverse Events: Definitions and Procedures for Recording, Evaluation, Follow-up, and Reporting	Appendix 3 Adverse Events: Definitions and Procedures for Recording, Evaluation, Follow-up, and Reporting Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).	Appendix 3 Adverse Events: Definitions and Procedures for Recording, Evaluation, Follow-up, and Reporting Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital) *or planned hospitalizations due to a pre-existing condition that has not worsened (e.g., elective surgery).*
69 Adverse Events: Definitions and Procedures for Recording, Evaluation, Follow-up, and Reporting	[New section]	*Definition of an adverse events of special interest* *An adverse event of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor could be appropriate. Such an event might require further investigation in order to characterize and understand it.* *• Infusion-related reactions, including acute and delayed hypersensitivity and anaphylactic reactions during or after IFX-1 infusion* *All patients should be observed closely during the IFX-1 administration and for 30 minutes after the first 2 infusions. The IV line should remain open during the observation to allow for administration of IV drugs, if necessary. Medication for infusion-related reactions should be available for immediate use. Medical staff have to be trained in resuscitation and immediate intensive care has to be readily accessible in case of severe life-threatening events. Mild to moderate reactions may be treated by slowing or interruption of the infusion, or with supportive treatment.* *For any potential infusion-related event, the investigator should check for a potentially developing or existing anaphylactic reaction. If an anaphylactic reaction is possible, appropriate immediate actions should be taken according to the severity or stage of the detected anaphylactic reaction as recommended by*

		existing guidelines for the treatment of anaphylactic reactions or, if established at the study sites, according to available standard operating procedures or other algorithms. *• Meningitis* *If there are signs of meningitis at any time during the study, the IMP should be discontinued if meningitis is confirmed. The patient must be closely monitored and the guidelines for treatment of meningitis should be followed. This includes lumbar puncture, blood culture testing, immediate start of treatment with dexamethasone and intravenous antibiotics (combination therapy with ampicillin and third generation cephalosporin), and a search made for the focus of the infection (e.g., computed tomography or magnetic resonance tomography).* *• Meningococcal septicemia* *• Invasive infection* *All adverse events of special interest will be recorded and reported as SAEs, and subject narratives will be generated. Further information may be requested from the investigator.*
	Assessment of Causality • The investigator is obligated to assess the relationship between IMP and ~~each occurrence of each~~ adverse event/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to IMP administration will be considered and investigated. • The investigator will also consult the IB in his/her assessment. • For each adverse event/SAE, the investigator must document in the medical notes that he/she has reviewed the adverse event/SAE and has provided an assessment of causality. ~~• There may be situations in which an SAE has occurred and the investigator has minimal information to include in~~	Assessment of Causality • The investigator is obligated to assess the relationship between IMP *the* adverse event/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to IMP administration will be considered and investigated. • The investigator will also consult the IB in his/her assessment. • For each adverse event/SAE, the investigator must document in the medical notes that he/she has reviewed the adverse event/SAE and has provided an assessment of causality.

	~~the initial report to, for example, a regulatory agency. However, it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data.~~ ~~• The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.~~ ~~• The causality assessment is one of the criteria used when determining regulatory reporting requirements.~~ The causal relationship of adverse events to administration of the IMP will be assessed according to the following criteria: • Not related ◦ Event or laboratory test abnormality with a time to administration of the IMP that makes a relationship impossible ◦ Is most likely explained by concurrent disease or other drugs or chemicals (either pathophysiologically or clinically) ◦ Has occurred before administration of the IMP in comparable severity and/or frequency • Unlikely related ◦ Event ~~or laboratory test abnormality with a time to administration of the IMP that makes a relationship improbable (but not impossible)~~ ~~◦ Disease or other drugs provide plausible explanations~~ • Possibly related ◦ Event ~~or laboratory test abnormality with~~ reasonable *time relationship to* administration of the IMP	The causal relationship of adverse events to administration of the IMP will be assessed according to the following criteria: • Not Related *(must meet at least one criterion listed below)* *This category applies to events that are due to extraneous causes and are not timely related to the administration of the IMP if:* ◦ Event or laboratory test abnormality with a time to administration of the IMP that makes a relationship impossible ◦ Is most likely explained by concurrent disease or other drugs or chemicals (either pathophysiologically or clinically) ◦ Has occurred before administration of the IMP in comparable severity and/or frequency • Unlikely Related *(must meet at least first two criteria listed below)* *This category applies to events that are unlikely related to the administration of the IMP. The relationship of an event to the sIMP can be considered probably not related if:* ◦ *The* event *does not follow a reasonable temporal sequence from administration of the drug* ◦ *The event could readily have been a result of the patient's clinical state or other underlying medical condition environmental or toxic factors, or other modes of therapy administered to the patient* ◦ *The event does not follow a known response pattern to the suspected drug* ◦ *The event does not reappear or worsen when the IMP is re-administered* • Possibly Related *(must meet at least first two criteria listed below)* *This category applies to events that are unlikely to be related to the administration of the IMP, but the possibility cannot be ruled-out with certainty. The relationship*

	◦ ~~Could also be explained by disease or other drugs~~ ◦ ~~Information on IMP withdrawal may be lacking or unclear~~ • Probably related ◦ Event ~~or laboratory test abnormality with~~ reasonable ~~time relationship to~~ administration of the IMP ◦ ~~Unlikely to be attributed to disease or other drugs~~ ◦ Response to withdrawal clinically reasonable ◦ Rechallenge not required • ~~Certainly~~ related ◦ Event ~~or laboratory test abnormality with plausible time relationship to~~ administration of the IMP ◦ ~~Cannot be explained by disease or other drugs~~ ◦ ~~Response to withdrawal plausible (pharmacologically or pathologically)~~ ◦ ~~Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon)~~ ◦ ~~Rechallenge satisfactory, if necessary~~	*of an event to the IMP can be considered possibly related if:* ◦ The event *follows a* reasonable *temporal sequence from* administration of the IMP ◦ *The event could readily have been a result of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient* ◦ *The event follows a known response pattern to the suspected IMP* • Probably Related *(must meet at least first three criteria listed below)* *This category applies to events that are considered with a high degree of certainty to be related to the administration of the IMP. The relationship of an event to the IMP drug can be considered probably related if*: ◦ The event follows a reasonable *temporal sequence from* administration of the IMP ◦ *The event could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient* ◦ *The event disappears or decreases upon cessation of IMP or reduction in dose* ◦ *The event follows a known response pattern to the suspected IMP* • *Definitely* Related *(must meet at least first three criteria listed below)* This category applies to events that are determined with certainty to be related to the administration of the IMP. The relationship of an event to the IMP can be considered definitely related if: ◦ The event *follows a reasonable temporal sequence from* administration of the IMP *or IMP levels have been established in body fluids or tissues* ◦ The event could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient ◦ The event disappears or decreases upon cessation of IMP or reduction in dose and, if applicable, appears upon re-challenge ◦ The event follows a known response pattern to the suspected IMP ◦ There are exceptions when an event does not disappear upon discontinuation of

		the IMP, yet IMP relatedness clearly exists; e.g., 1) tardive dyskinesia, 2) fixed drug eruptions
77 Contraceptive Guidance and Collections of Pregnancy Information	Definitions ~~1.~~ Postmenopausal female: • A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. ~~•~~ Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods.	Definitions Postmenopausal female: • A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. *Note:* Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods.
77 Contraceptive Guidance and Collections of Pregnancy Information	Contraception Guidance ... Female subjects Female subjects of childbearing potential ~~are eligible to participate if they~~ agree to use a highly effective method of contraception consistently and correctly as described in Table 3.	Contraception Guidance *Male subjects* *Male subjects who have not had a vasectomy must, during the entire study participation and for at least one month after last administration of study drug:* • *either abstain from reproductive sexual intercourse or use a condom during intercourse* • *not donate sperm.* *Female subjects* Female subjects of childbearing potential *must not donate eggs and must* agree to use a highly effective method of contraception consistently and correctly as described in Table 3.
77 Contraceptive Guidance and Collections of Pregnancy Information	Table 3 Highly Effective Contraceptive Methods	Table 3 Highly Effective Contraceptive Methods *Note: Subjects must have been on a stable dose of hormonal contraceptives for at least 4 weeks before Day 1.*
81 Prohibited biologics		*Note: Biologicals used for an underlying disease at a stable dose may be continued.*

Appendix 8 Amendment 02

Rationale for Amendment 02

Amendment 02 was enacted to:

- Allow subjects with lesions on other parts of the body than the legs to enter the trial. Pyoderma Gangrenosum is a rare disease, and focusing on lesions of the lower extremity adversely limits the potential size of the subject population.
- To allow the use of stable chronic opioid medication. Ulceration in the patients with Pyoderma Gangrenosum causes debilitating pain, and these patients are in need of strong pain relief.
- Correct inconsistencies in the protocol.

Corrections to spelling and punctuation are not listed.

List of changes

Section	Original text	Amended text
Protocol signatures Sponsor Signatory:	Ronald Rosenburg, MD, PhD# ... 07745 Jena, Germany	Ronald Rosenburg, MD, PhD# … 07745 Jena, Germany telephone: 0049 89 414 189 7825
Abbreviations and Definitions of Terms		*Q2W Every 2 weeks*
10 Synopsis of Study Study Population Inclusion Criteria:	5. In addition, the subject must fulfill at least 3 of the following 6 criteria at screening: History of ... Multiple ulcerations ~~(at least 1 occurring on the lower leg)~~ Cribriform or "wrinkled paper" scar(s) at sites of healed ulcers	5. In addition, the subject must fulfill at least 3 of the following 6 criteria at screening: History of ... Multiple ulcerations Cribriform or "wrinkled paper" scar(s) at sites of healed ulcers
	6. Subject has a minimum of 1 evaluable ulcer (≥2 cm^2) ~~on the lower extremity~~ at screening	6. Subject has a minimum of 1 evaluable ulcer (≥2 cm^2) at screening
Study Population Exclusion Criteria:	Evidence of active tuberculosis	Evidence of active *or latent* tuberculosis
	9. ~~An ankle brachial index of less than 0.8 or toe pressure of less than 80 mmHg in subjects with a compromised vascular system (e.g., diabetic subjects) within previous year or at screening~~	9. *Subjects with Ulceration due to medical causes other than pyoderma gangrenosum (e.g. diabetic ulceration)*
	17. Known hypersensitivity to ~~any~~ excipient of the IMP	17. Known hypersensitivity to *polysorbate 80 (*excipient of the IMP*)*
19 Schedule of Assessments	[deleted measurement of "Ankle brachial index/toe pressure"]	
		[Added footnote "b" to chest X-ray]
[Footnotes]	a Only if wound still open b ~~Subjects with a compromised vascular system (e.g., diabetic subjects), within previous year or at screening~~ c This photograph is the Baseline for subsequent Physician's Global Assessments d Only for subjects in Group 1 and Group 2	a Only if wound still open b *An historical X ray may be used if taken within 6 months prior to screening* c This photograph is the Baseline for subsequent Physician's Global Assessments d Only for subjects in Group 1 and Group 2
27 Overall Design	Screening Day ~~-14~~	Screening Day *-7 to Day -35*
[Initial dose]	800 mg ~~Q2W~~ (3 doses)	800 mg (3 doses)
34 Recording of prior and concomitant therapy and procedures	Any medication or vaccine (including procures such as laser- or photo-therapy, over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject has	Any medication or vaccine (including procures such as laser- or photo-therapy, over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject has

	used in the 3 months81 before screening, is receiving at the time of screening, or receives during the study must be recorded in the source data and CRF along with	used in the 3 months*, or biologicals (see* 81 *for Prohibited Biologics) used within 12 months,* before screening, is receiving at the time of screening, or receives during the study must be recorded in the source data and CRF along with
35 Allowed Concomitant Therapy	Analgesic therapy for pyoderma gangrenosum Analgesic therapy may be initiated at any time during the study ~~with non-opioid analgesic if a subject's pain worsens after Day 1. All non-opioid analgesics (including tramadol)~~ are ~~allowed at the recommended or prescribed dose~~.	Analgesic therapy for pyoderma gangrenosum *Short-acting opioid or non-opioid* analgesic therapy may be initiated at any time during the study. *If possible, analgesic therapy should be avoided on the day of pain assessments until the assessments* are *made*.
35 Prohibited Therapy	The following therapies are prohibited for all subjects from screening until Visit EOT or discontinuation from the study: ... oral opioid analgesics	The following therapies are prohibited for all subjects from screening until Visit EOT or discontinuation from the study: ... *Non-stable, chronic use of high dose* oral opioid analgesics
38 Screening	The following procedures will be conducted and documented at the Screening visit: ... • Record vital signs • ~~Measure ankle brachial index/toe pressure in subjects with a compromized cardiovascular system (unless performed in the previous year)~~ • Record a 12 lead ECG • Chest X-ray • Take photograph of target ulcer for area and volume measurements	The following procedures will be conducted and documented at the Screening visit: … • Record vital signs • • Record a 12 lead ECG • Perform a chest X-ray. *An historical X-ray can be used if taken within 6 months prior to screening* • Take photograph of target ulcer for area and volume measurements
50 Chest X-ray [moved from section 9.4.8]	A standard chest X-ray will be performed at screening to exclude ~~active~~ tuberculosis.	A standard chest X-ray will be performed at screening to exclude tuberculosis. *An historical X-ray can be used if taken within 6 months prior to screening.*
54 Blood Sampling Volumes	… Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.	… Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. *If values are out of range during screening, a single retest is allowed.*