Extension Period: at Week 20 (Day 141) (HiSCR responders) or at Week 18 (Day 127) (HiSCR non-responders), subjects will receive the first administration of IMP during the 28-week Extension Period, as shown in Table 3.

Subjects who are HiSCR responders at Week 16 (response on the basis of HiSCR is defined in Section 8.2.2.2) will receive IFX-1 at a dose of 800 mg q4w during the Extension Period, starting at Week 20 through Week 40 (Day 141 to Day 281). If they have a loss of response (see Definitions of Terms) during the Extension Period, they will have an optional visit 2 weeks later. Subjects who still have a loss of response at the subsequent (planned) visit will be discontinued from the study and will not switch to the non-responder schedule.

Subjects who are HiSCR non-responders at Week 16 (response on the basis of HiSCR is defined in Section 8.2.2.2) will receive IFX-1 at a dose of 800 mg during an Induction Phase at Weeks 18 and 19 (Day 127 and Day 130), followed by IFX-1 at a dose of 800 mg q2w during the remaining Extension Period starting from Week 20 through Week 40. The additional infusions will be administered during interim visits to the study site, starting at Week 22. Subjects who experience WOAI (see Definitions of Terms) at 2 consecutive visits during the Extension Period will be discontinued from the study.

	Induction Phase (Double-Blind)			Maintenance Phase (Open-Label from Week 20 Onwards)									
HiSCR-Non-Responders at Week 16 (800 mg q2w)													
Visit	**V1NR**	**V2NR**	**V3NR**	**V4NR**	**V5NR**	**V6NR**	**V7NR**	**V8NR**	**V9NR**	**V10NR**	**V11NR**	**V12NR**	**V13NR**	**V14NR**
Week	**18**		**19**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**
Day	**127**	**130**	**134**	**141**	**155**	**169**	**183**	**197**	**211**	**225**	**239**	**253**	**267**	**281**
Cohort 1	800	800	800	800	800	800	800	800	800	800	800	800	800	800
Cohort 2	800	P	800	800	800	800	800	800	800	800	800	800	800	800
Cohort 3	800	P	P	800	800	800	800	800	800	800	800	800	800	800
Cohort 4	800	P	P	800	800	800	800	800	800	800	800	800	800	800
Cohort 5	800	P	P	800	800	800	800	800	800	800	800	800	800	800

HiSCR = Hidradenitis Suppurativa Clinical Response; V = scheduled visit for all subjects; VxNR = scheduled visit for HiSCR non-responders at Week 16; VxR = scheduled visit for HiSCR responders at Week 16.
800 = infusion of 800 mg IFX-1, P = infusion of placebo.

IRT	Interactive Response Technology
iv	Intravenous
LPS	Lipopolysaccharide
MAC	Membrane attack complex
MCP-Mod	Multiple comparisons procedure-modelling
MED	Minimum effective dose
MedDRA	Medical Dictionary for Regulatory Activities
mSS	Modified Sartorius Score
NRS	Numeric Rating Scale
NYHA	New York Heart Association
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PPS	Per protocol set
q2w	every two weeks
q4w	every four weeks
SAE	Serious adverse event
SAS	Safety analysis set
SF-36v2	36-Item Short Form Survey (version 2)
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TNF	Tumor necrosis factor
USV	Unscheduled visit
UVA	Ultra-violet A
UVB	Ultra-violet B
VAS	Visual analog scale
WBC	White blood cell count
WOAI	Worsening or Absence of Improvement

	• Stable HS for at least 2 months before Screening, as determined by the investigator through subject interview and review of medical history • Inadequate response to at least 3 months of oral antibiotics, or intolerance to antibiotics • Total abscess and inflammatory nodule (AN) count of ≥ 3 Key exclusion criteria at Screening: • Body weight < 60 or > 130 kg • Any other skin disease that may interfere with assessment of HS • More than 20 draining fistulas • Prior treatment with adalimumab or another biologic product during the 24 weeks before Screening • Prior treatment with IFX-1 • Subjects on permitted oral antibiotic treatment for HS (doxycycline or minocycline only) who have not been on a stable dose during the 28 days before Screening • Subject received systemic non-biologic therapy for HS with potential therapeutic impact for HS during the 28 days before Screening (other than permitted oral antibiotics) • Prior treatment with any of the following medications during the 28 days before Screening: o Any other systemic therapy for HS o Any iv anti-infective therapy o Phototherapy (ultra-violet B [UVB] or psoralen and ultra-violet A [UVA]) • Prior treatment with any of the following medications during the 14 days prior to IMP administration: o Analgesics (including opioids) for HS-related pain o Prescription-only topical therapies for HS o Oral anti-infectives for infections other than HS • History of moderate to severe heart failure (New York Heart Association [NYHA] Class III or IV), cerebrovascular accident during the 24 weeks before Screening, history of malignancy except for successfully treated non-metastatic basal cell or squamous cell carcinoma or in situ carcinoma of the cervix • One of the following abnormal laboratory findings: o White blood cell count (WBC) < 2500/mm^3 o Neutrophil count < 1000/mm^3 o Serum creatinine > 3 × UNL

Schedule of Assessments - Screening and Main Period (All Subjects)

	Screening	Main Period											
		Induction Phase				Maintenance Phase							
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	USV
	Week -4 to Week -2	Week 0		Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	Unsch-eduled Visit
	Day -28 to Day -10	Day 1	Day 4	Day 8	Day 15	Day 29	Day 43	Day 57	Day 71	Day 85	Day 99	Day 113	
Accepted time window			±1 Day	±1 Day	±1 Day	±1 Day	±1 Day	±1 Day	±1 Day	±1 Day	±1 Day	±1 Day	
Informed Consent Procedure	X												
Inclusion/Exclusion Criteria	X	X (a)											
Pregnancy Test	X (serum)	X (a) (urine)				X (j) (urine)		X (j) (urine)		X (j) (urine)		X (urine)	
Medical and Surgical History	X	X (a)											
Demographics and Baseline Characteristics	X												
HS Medical and Surgical History	X	X (a)											
Prior Therapy	X												
Physical Examination	X	X (a)										X	
ECG	X											X	
Vital Signs	X (f)	X (a)	X	X	X	X	X	X	X	X	X	X	X
HS Clinical Parameters	X	X (a)			X	X	X	X	X	X	X	X	X
Erythema Assessment	X	X			X	X	X	X	X	X	X	X	X
Patient's Global Assessment Skin Pain (NRS) (Daily)	←												
Analgesic Therapy (Daily)	←												
Patient's Assessment of Drainage (Daily)	←												
DLQI, HADS, SF-36v2, EQ-5D-5L		X										X	
Photography		X				X						X	
Randomization	X (l)												
Administration of IMP (d)		X	X	X	X	X	X	X	X	X	X	X	
Laboratory Parameters													
Safety Laboratory (c)	X					X		X (j)		X (j)		X	
HIV-1 or 2 / HBV / HCV Test	X												
Plasma													
C3a (c)		X			X							X	
C5a (c)		X	X		X		X					X	
Serum and plasma biomarkers (i)		X			X							X	
Citrate plasma													
IFX-1 (c)			X (g)	X	X (e, g)	X	X	X	X	X	X	X (e)	
Serum													
CH50 (c)		X			X							X	
CRP (c)		X			X	X (j)		X (j)		X (j)		X	
Anti-drug Antibodies (c)		X				X						X	
Continuous Documentation													
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Therapy	X	X (a)	X	X	X	X	X	X	X	X	X	X	X

PK Substudy in Main Period

A PK substudy will be conducted in approximately 50 of the 175 subjects participating in the Main Period. The subjects in Cohorts 1 to 5 will be sequentially included for participation in the PK substudy if consent for participation was given. The PK substudy assessments will be made on 2 visits during the Main Period, at Weeks 2 and 16.

Extension Period (28 Weeks) – HiSCR Responders

Subjects from all cohorts who are HiSCR responders at Week 16 (response on the basis of HiSCR is defined in Section 8.2.2.2) will receive IFX-1 at a dose of 800 mg q4w, starting at Week 20 through Week 40. Subjects who have a loss of response (see Definitions of Terms) during the Extension Period will have an optional visit 2 weeks later. Subjects who then have a loss of response at the subsequent (planned) visit will be discontinued from the study.

A final visit at the study site for efficacy, PK, PD, and safety assessments will occur at Week 44. For subjects who discontinue early, a Post-Treatment Follow-Up visit will occur 3 months after the early discontinuation or when another HS therapy has been started, whichever occurs first. At the Post-Treatment Follow-Up visit the same parameters for efficacy, PK, PD and safety as at Week 44 or the early discontinuation visit will be assessed.

Extension Period (28 Weeks) – HiSCR Non-Responders

Subjects from all cohorts who are HiSCR non-responders at Week 16 (response on the basis of HiSCR is defined in Section 8.2.2.2) will receive IMP during an Induction Phase (Weeks 18 and 19), followed by IFX-1 at a dose of 800 mg q2w during the Maintenance Phase from Week 20 through Week 40 (see also Table 3). Subjects who experience WOAI (see Definitions of Terms) at 2 consecutive visits during the Extension Period will be discontinued from the study.

A final visit at the study site for efficacy, PK, PD, and safety assessments will occur at Week 44. For subjects who discontinue early, a Post-Treatment FUV will occur 3 months after the early discontinuation or when another HS therapy has been started, whichever occurs first. At the Post-Treatment Follow-Up visit the same parameters for efficacy, PK, PD and safety as at Week 44 or the early discontinuation visit will be assessed.

3.2 Study Sites and Number of Subjects

This multicenter study is planned to be conducted at approximately 50 sites in approximately 8 countries.

According to the sample size calculation (Section 10.2), 175 subjects are planned to be enrolled and randomized at Screening to 1 of 5 cohorts in the Main Period to ensure that approximately 145 subjects complete treatment with IFX-1 or placebo.

3.3 Expected Duration of the Study

The study start is defined as the date of the first visit of the first subject enrolled in the Main Period, and the end of the study is defined as the date of the last visit of the last subject participating in the Extension Period (Week 44), as recorded in the electronic Case Report Form (eCRF).

The estimated recruitment period is approximately 9 months.

The study duration for an individual subject will be up to 48 weeks and will include the following study periods:

- Screening Period: up to 18 days before first administration of IMP (Week −4 to Week −2 [Days -28 to Day -10])

- Initiate documentation of patient-reported outcomes:
    - Patient's Global Assessment of Skin Pain (NRS) (*daily documentation in e-diary*)
    - Analgesic therapy (*daily documentation in e-diary*)
    - Patient's Assessment of Drainage (*daily documentation in e-diary*)
    - DLQI (*documentation at prespecified visits*)
    - Hospital Anxiety and Depression Scale (HADS [*documentation at prespecified visits]*)
    - 36-Item Short Form Survey (version 2; SF-36v2 [*documentation at prespecified visits]*)
    - EuroQol-5 Dimensions survey (EQ-5D-5L [*documentation at prespecified visits]*)
- Initiate documentation of AEs
- Initiate documentation of concomitant medications

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 randomized to 1 of the 5 cohorts. The maximum time between signing informed consent at Screening and randomization should be 3 weeks, and the maximum time between randomization and first administration of IMP should be 3 weeks. The maximum time between Screening and first administration of IMP should be 4 weeks. Because it may take up to 10 days for the IMP to reach the study site, at least 10 days should be allowed for between Screening and first administration of IMP.

Subjects who give informed consent for participation in the PK substudy will be sequentially included in the PK substudy.

Subjects will further be asked to consent to a photographical documentation of affected areas at prespecified visits.

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.

7.2 Main Period (16 Weeks)

The following section describes all study assessments and procedures that have to be performed in the Main Period (double-blind). For each cohort, the Main Period starts at Week 0 (Day 1, immediately before first administration of IMP) and consists of a 2-week Induction Phase (ends immediately after administration of IMP at Week 2) followed by a 14-week Maintenance Phase through Week 16 (ends immediately after administration of IMP at Week 16). An overview of the visit schedule is available in the Schedule of Assessments - Screening and Main Period **(All Subjects)**.

Before administration of IMP, the following assessments and procedures will be performed at the visits to the study site, as indicated:

- Review all relevant inclusion and exclusion criteria (see Section 4.1 and 4.2) to confirm eligibility for participation in the study *(Week 0 [Day 1])*
- Review and record concomitant therapy, as specified in the exclusion criteria (Section 4.2), to confirm eligibility for participation in the study *(Week 0 [Day 1])*

- Erythema assessment
- Continue documentation of patient-reported outcomes:
    - Patient's Global Assessment of Skin Pain (NRS) (*e-diary*)
    - Analgesic therapy (*e-diary*)
    - Patient's Assessment of Drainage (*e-diary*)
- Documentation of AEs
- Documentation of concomitant therapy

8 STUDY VARIABLES AND METHODS OF ASSESSMENT

8.1 Study Subjects

8.1.1 Demographic Data and Baseline Characteristics

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

- Age
- Sex
- Race and ethnicity
- Body weight
- Height
- Smoking status
- Prior HS-related surgeries (i.e., if prior surgeries have been performed and number and type of prior surgeries). Subjects with prior HS-related surgery will be identified during a medical review before database lock

8.1.2 Medical and Surgical History

A complete medical history (including non-HS-related surgical history), with details of tobacco and alcohol use, will be obtained from each subject at Screening. The medical history will be reviewed and updated on Day 1 to ensure that the subject remains qualified for the study.

8.1.3 Hidradenitis Suppurativa Medical and Surgical History

The diagnosis of HS is based on the following criteria, set by the 2nd Conference of the HS Foundation in San Francisco [13]:

- Disease onset after puberty
- Involvement of at least 2 areas of skin rich in apocrine glands
- History of recurrent drainage of pus from the affected areas

The HS medical history will be documented in terms of:

- Duration of HS (years)
- Family history of HS

8.3.2.2 Physical Examination

A physical examination will be performed at Screening and during the study at prespecified times through Week 44 (as outlined in the Schedules of Assessments) or an early discontinuation visit and the 3-month Post-Treatment Follow-Up visit if the subject discontinues before Week 44. Physical examination findings that are related to the medical history will be recorded in the source documentation and in the eCRF.

A symptom-directed physical examination should be performed at all other visits, as warranted. An abnormality noted after starting treatment with IMP (Day 1) will be evaluated by the investigator for whether it constitutes an AE.

8.3.2.3 Vital Signs

Vital sign determinations of systolic and diastolic blood pressure, pulse rate (counted for at least 30 seconds after 5 min in a sitting position), respiratory rate, and body temperature will be obtained at each visit to the study site. Blood pressure and pulse rate should be measured before blood draws are performed. Height and body weight will only be measured at Screening.

8.3.2.4 Electrocardiogram

A resting 12-lead ECG will be performed at Screening and during the study at prespecified times through Week 44 (as outlined in the Schedules of Assessments).

Subjects who had a 12-lead ECG with normal findings performed during the 90 days before Screening will not be required to have a repeat ECG at Screening, provided all the relevant documentation specified in the protocol is available. If there are other findings that are clinically significant (CS), the investigator must contact the medical monitor at the CRO before enrolling the subject into the study.

Subjects will have a repeat ECG at Week 44 or at an early discontinuation visit and the 3-month Post-Treatment Follow-Up visit if the subject discontinues before Week 44.

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

An appropriately certified physician will interpret, sign, and date each ECG. Any clinical significant (CS) and non-clinical significant (NCS) findings will be recorded in the source documentation and in the eCRF. Each signed, original ECG will be reviewed by the clinical monitor for correctness (date, time, and clinically relevant abnormal findings, if applicable) and stored with the source documentation at the study site.

8.3.2.5 Laboratory Safety Parameters

Laboratory safety parameters will be assessed at Screening and during the study at prespecified times through Week 44 (as outlined in the Schedules of Assessments) or an early discontinuation visit and the 3-month Post-Treatment Follow-Up visit if the subject discontinues before Week 44.

Blood samples should be obtained after the subjects have provided responses to questionnaires and after vital sign determinations have been completed, but before administration of IMP.

Analyses will be conducted by a certified central laboratory.

Instructions regarding the collection, processing, and shipping of samples for analysis of laboratory safety parameters will be available in the laboratory manual provided by the responsible CRO. Instructions for urine pregnancy testing are also provided in the laboratory manual.

IMP, withholding treatment with the IMP pending some investigational outcome, reduction of IMP dose, or additional concomitant treatment

- Laboratory abnormalities do not need to be listed as separate AEs if they are considered to be part of a clinical syndrome that is being reported as an AE

Laboratory findings do not need to be reported as AEs in the following cases:

- Laboratory parameters already beyond the reference range at baseline
- Abnormal laboratory parameters caused by mechanical or physical influences on the blood sample (e.g., hemolysis) and flagged as such by the laboratory in the laboratory report
- Abnormal parameters that are obviously biologically implausible (e.g., values that are incompatible with life)
- An abnormal laboratory value that cannot be confirmed after repeated analysis, preferably in the same laboratory (i.e., the previous result could be marked as not valid and should not necessarily be reported as an AE)

In addition, at the investigator's discretion, any changes or trends over time in laboratory parameters can be recorded in the eCRF as AEs, if such changes or trends are considered to be clinically relevant, even if the absolute values are within the reference range.

AEs do not include:

- Medical or surgical procedures; the condition that leads to the procedure is an AE
- Untoward medical findings that occur before initial administration of the IMP if they occur in the scope of investigations that are performed for assessing inclusion and exclusion criteria (e.g., results of laboratory tests conducted at Screening)
- Situations where an untoward medical occurrence has not occurred, e.g., planned hospitalization due to a pre-existing condition that has not worsened, hospitalization that occurs for a procedure not associated with an AE (e.g., elective surgery or social admission), or hospitalization for a diagnostic procedure that takes less than 24 h
- Overdose of an IMP or any concomitant therapy that does not result in any adverse signs or symptoms. Details of the dosing (volume, location of infusion, and infusion rate) of the IMP will be recorded in the eCRF

At each visit to the study site, the investigator will determine whether any AEs have occurred. If known, the medical diagnosis of an AE should be recorded in preference to the listing of individual signs and symptoms.

9.1.2 Documentation and Reporting of Adverse Events

The observation period for AEs will start with confirmation of signed informed consent at Screening (i.e., at Day -28 to Day -10) and ends at Week 44.

All AEs reported from the time the subject gives written informed consent to participate in the study until 28 days after the last administration of IMP will be recorded, irrespective of whether they were solicited or reported spontaneously by the subject. AE information will be collected and recorded in the eCRF.

For subjects who discontinue early, a Post-Treatment FUV will occur 3 months after the early discontinuation or when another HS therapy has been started, whichever occurs first.

Any AEs judged by the investigator to be at least possibly related to treatment with the IMP should be reported to the sponsor regardless of the length of time that has passed since the subject has completed the study.

Every attempt should be made to describe AEs in terms of a diagnosis. If appropriate, component symptoms should be listed in addition to the diagnosis. If only nonspecific signs or symptoms are present, then these should be recorded as separate diagnoses in the eCRF.

All subjects who experience AEs, irrespective of whether they are considered by the investigator to be at least possibly related to treatment with the IMP, must be monitored to determine the outcome. The clinical course of each AE will be followed up according to accepted standards of medical practice, even after the subject has completed participation in the study, until a satisfactory explanation is found or the investigator considers it medically justifiable to terminate the follow-up. Should the AE result in death, a full pathologist's report should be provided, if possible.

AEs will be classified according to their severity, causal relationship to the IMPs, and seriousness.

If the AE is serious or of special interest, as defined in Section 9.3, the investigator or other authorized medical personnel at the study site must be notified and complete the paper "SAE form" at the time the SAE is detected. SAE reporting should occur within 24 h (Section 9.2.2).

Severity of Adverse Events

The severity of AEs will be assessed according to the following criteria:

Mild	• Transient or mild discomfort • No limitation in activity • No medical intervention or therapy required
Moderate	• Marked limitation in activity • Some assistance usually required • Medical intervention or therapy required • Hospitalization possible
Severe	• Extreme limitation in activity • Significant assistance required • Significant medical intervention or therapy required • Hospitalization or hospice care probable

Causal Relationship of Adverse Events

The investigator must assess whether or not the AE is causally related to administration of the IMP. Even if the investigator considers that there is no causal relationship to the IMP, the AE must still be reported.

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

Fax: + 353 1 809 9501
QLS_IFX1@iqvia.com

9.3 Adverse Events of Special Interest

An AESI is an AE 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.

For this study, the following AEs are defined as AESIs:

- Acute systemic hypersensitivity reaction
- Meningitis
- Meningococcal septicemia
- Invasive infection

All AESIs will be recorded and reported as SAEs, and subject narratives will be generated.

9.4 Suspected Unexpected Serious Adverse Reactions

9.4.1 Definition of Suspected Unexpected Serious Adverse Reactions

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.

9.4.2 Reporting of Suspected Unexpected Serious Adverse Reactions

The sponsor will submit all available information on a SUSAR immediately to the applicable Ethics Committee, 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 Ethics Committee, 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.

9.5 Therapeutic Procedures

If a subject requires treatment as a result of an AE, the treatment must meet the recognized standards of medical care in order to restore the subject's health. Appropriate resuscitation devices and medication must be available in order to treat the subject as quickly as possible in the event of an emergency.

The actions taken to treat the AE/SAE must be documented by the investigator either in the appropriate eCRF and/or using additional documents.

9.6 Pregnancy

Pregnancy, by definition, is not considered as an AE unless it results in a complication (such as a maternal complication during pregnancy) that meets the definition of an AE, results in spontaneous abortion or stillbirth, or is associated with a congenital anomaly or birth defect in the fetus. Any such complication must then be reported accordingly as an SAE.

A female subject who becomes pregnant while participating in the study, or up to and including 28 days after the last dose of IMP, must notify the investigator immediately and, if appropriate, discontinue treatment with the IMP. The subject may continue other study procedures at the discretion of the investigator.

The sponsor must be notified within 5 days of the investigator becoming aware of the pregnancy, using the following address.

Fax: + 353 1 809 9501
QLS_IFX1@iqvia.com

Whenever possible, a pregnancy in subjects exposed to IMP should be followed to term so as to assess any potential occurrence of congenital anomalies or birth defects. Any follow-up information, including premature termination and the status of the mother and child after delivery, should be reported by the investigator.

In certain situations, it may be necessary to monitor the development of the child for an appropriate period after birth. If this is the case, details should be included in this section.

Severe side effects and complications during a pregnancy as well as congenital birth defects are SAEs per definition and, therefore, have to be reported additionally as SAEs according to the reporting procedures described above.

10 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

10.1 General Considerations

A detailed statistical analysis plan will be developed and finalized (approved with signatures) before the Blind Data Review Meeting (BDRM), and may be amended after the BDRM and before unblinding the study database if the need arises.

The statistical analysis plan will include the exact definition of endpoints and variables to be analyzed, extensive details of the statistical analysis methods to be used together with the structure of tables and figures to be included as end-of-text tables and figures as well as appended listings for the clinical study report.

All endpoints and variables will be adequately evaluated. Individual data will be listed. Data will be summarized using suitable descriptive statistics; depending on the structure of the data, either sample statistics or frequency tables will be used. Data will be analyzed by cohort and study period (Main Period and Extension Period) and might be further differentiated (e.g., by visit or by study site).

10.2 Determination of Sample Size

The primary efficacy endpoint will be analyzed using the multiple comparisons procedure-modelling (MCP-Mod) procedure [26-28]. A total of 175 subjects are planned to be

- Number of subjects with flares analyzed in terms of ≥ 25% increase in AN count among subjects with a minimum increase of 2 in AN count relative to Day 1
- Absolute values and absolute and relative change in mSS from Day 1 by time point
- Absolute value and absolute and relative change in Patient's Global Assessment of Skin Pain (NRS) from Day 1 by time point
- Percentage of subjects achieving, by time point:
    - At least a 30% reduction and at least 1 unit reduction from Day 1 among subjects with baseline NRS ≥ 3 in Patient's Global Assessment of Skin Pain (NRS30)
    - At least a 50% reduction and at least 2 units reduction from Day 1 among subjects with baseline NRS ≥ 3 in Patient's Global Assessment of Skin Pain (NRS50)
- Absolute values and absolute and relative change in DLQI score from Day 1 by time point

Exploratory efficacy endpoints:

- Percentage of subjects with ≥ 50% reduction in AN count compared to Day 1 by time point
- Percentage of subjects with no increase in number of abscesses compared to Day 1 by time point
- Percentage of subjects with no increase in number of draining fistulas compared to Day 1 by time point
- Percentage of (partial) responders measured by HiSCR and HiSCR25 by time point
- Percentage of subjects with ≥ 25% relative and ≥ 2 absolute increase in counts, using the abscess count, the inflammatory nodule count, and the draining fistula count by time point
- Achievement of clear or minimal severity of HS-PGA among subjects with at least 2 grades of improvement (reduction) from Day 1 to each time point.

The endpoints that are evaluated by time point will be analyzed in a similar way during the Extension Period. Summary tables for the Extension Period will be grouped by HiSCR responders and non-responders.

In addition, the percentage of subjects with loss of response, defined as a loss of at least 50% of the improvement (reduction) in the AN count achieved from baseline to Week 16 [AN > ½ × (Baseline AN count + Week 16 AN count)] based on the number of subjects with HiSCR at Week 16 will be analyzed for the Extension Period.

Descriptive subgroup analyses will be performed on selected efficacy endpoints. Relevant subgroups are defined by subjects with and without previous exposure to adalimumab or other biologic products, and with and without response to adalimumab or other biologic products, Hurley Stage, antibiotic treatment, and baseline demographics. The subgroup analyses will be exploratory. Details on subgroup analyses and further subgroup analyses (if deemed necessary) will be provided in the statistical analysis plan.

Other efficacy endpoints (e.g., erythema assessment, Patient's Assessment of Drainage and analgesic therapy) will be exploratory, as defined in detail in the statistical analysis plan.

Multiple contrast tests, which are part of the MCP-Mod procedure, will be used to test for a dose-response signal using the placebo cohort and the cohorts based on cumulative doses of 2,000 mg, 4,800 mg, 8,000 mg, and 10,800 mg as dose levels.

In the MCP-Mod procedure, dose-response models can be consistently considered as:

$$f(d, \boldsymbol{\theta}) = \theta_0 + \theta_1 \cdot f^0(d, \boldsymbol{\theta}^*),$$

where d denotes the respective dose, and $f^0(d, \boldsymbol{\theta}^*)$ denotes the standardized dose-response model parametrized by the vector $\boldsymbol{\theta}^*$. In this parametrization, θ_0 denotes the location parameter, θ_1 denotes the scale parameter, and $\boldsymbol{\theta}^*$ determines the shape of the model function. For this study, a candidate set of 2 dose-response models are prespecified, $m = 1,2$, which both characterize a monotonically increasing dose-response relationship:

1. E_{max} model
2. Logistic model

For each of the standardized dose-response models $f_m^0(d, \theta^*)$, $(m = 1,2)$ in the candidate set, the null hypothesis H_0^m: $c_m^T \mu = 0$ will be tested against the 1-sided alternative H_1^m: $c_m^T \mu > 0$ using a multiple contrast test with significance level $\alpha/2$ = 0.025, where $c_m = (c_{m1}, \ldots, c_{m5})^T$ is the optimal contrast vector representing model m and $\mu = (\mu_1, \ldots, \mu_5)^T$ denotes the HiSCR at Week 16 for the applied doses.

Single contrast tests will be used to test the null hypotheses that there is no dose-response signal for candidate model m = 1,2. By combining the single test statistics to a multivariate test statistic and comparing this test statistic to a multivariate normal-distribution, the single tests are multiplicity adjusted and the multiple test problem is adequately considered. The maximum of the 2 test statistics will be used as a combined test statistic.

Only if a dose-response signal can be detected for at least 1 of the candidate models in terms of the multiple contrast tests, the shape of the dose-response curve and the target dose(s) of interest will be estimated.

The estimated dose-response curve will be used to estimate the MED and ED_{50}. The MED is defined as the minimum dose, at which the HiSCR at Week 16 is at least 15% higher than the HiSCR at Week 16 in the placebo group. An improvement of 15% over placebo in HiSCR at Week 16 is considered as clinically relevant [15]. The ED_{50} is defined as the minimum dose that achieves 50% of the maximum achievable effect over placebo. Standard formulas for the estimation of ED_{50} will be used and will be explicitly stated in the statistical analysis plan.

Multiple imputations will be performed for subjects with missing data on HiSCR at Week 16 who did not discontinue before Week 16 because of one of the following reasons:

- Disease relapse
- Progressive disease
- Lack of efficacy

Subjects who discontinued before Week 16 because of one of the above mentioned reasons will be treated as not having achieved HiSCR at Week 16. All further specifications for multiple imputations are based on the assumption that the number of subjects that need to have the HiSCR at Week 16 imputed, will be relatively small.

Multiple imputations will be performed based on the assumption that HiSCR response at Week 16 is missing at random, i.e. missingness will not depend on the HiSCR at Week 16 itself but will only depend on the factors in the imputation model. The factors that will be used in the multiple imputation model for HiSCR at Week 16 are HiSCR at prior visits, cohort, baseline Hurley Stage, baseline AN count, and concomitant use of antibiotics. We anticipate that baseline Hurley Stage, baseline AN count and concomitant use of antibiotics will not be

Table 3 Dosing Schedule by Cohort in Extension Period

	Induction Phase (Double-Blind)			Maintenance Phase (Open-Label from Week 20 Onwards)										
HiSCR Responders at Week 16 (800 mg q4w)														
Visit	**–**	**–**	**–**	**V1R**	**–**	**V2R**	**–**	**V3R**	**–**	**V4R**	**–**	**V5R**	**–**	**V6R**
Week	**18**		**19**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**
Day	**127**	**130**	**134**	**141**	**155**	**169**	**183**	**197**	**211**	**225**	**239**	**253**	**267**	**281**
Cohort 1	–	–	–	800	–	800	–	800	–	800	–	800	–	800
Cohort 2	–	–	–	800	–	800	–	800	–	800	–	800	–	800
Cohort 3	–	–	–	800	–	800	–	800	–	800	–	800	–	800
Cohort 4	–	–	–	800	–	800	–	800	–	800	–	800	–	800
Cohort 5	–	–	–	800	–	800	–	800	–	800	–	800	–	800

During the Main Period and the Extension Period, the IMP (IFX-1 or placebo) will be administered by the responsible personnel at the site:

- The IMP will be infused over a period of 30 to 60 min (± 10 min) via an iv line
- At the end of the infusion, the iv line will be briefly flushed with approximately 10 mL of sterile sodium chloride to ensure that any IMP remaining in the iv line is administered

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

For France: After each infusion of IMP administered in the Induction Phases of the Main and Extension Periods, subjects must remain at the study site for at least 60 min 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 eCRF.

If a subject misses a visit for a scheduled infusion of IMP for any reason, the infusion must be administered as soon as possible after the scheduled time of infusion. If the scheduled infusion cannot be administered within 3 days after the scheduled time of infusion, then that infusion should be omitted and the subsequent infusion must be administered as planned.

If a subject appears at the study center for a scheduled infusion but the infusion cannot be administered due to any reason, the visit can be repeated within 3 days (if the investigator thinks that the IMP can be administered within 3 days). Otherwise, the infusion will be omitted and is documented accordingly in the eCRF.

Subjects who omit more than 2 scheduled (consecutive or non-consecutive) infusions during the Main Period will be discontinued from the study and will have a Post-Treatment FUV 3 months after discontinuation or when another HS therapy has been started (Section 6.2).

The number of unused, partially used, and empty vials will be documented and the vials will be kept until the drug accountability documentation has been checked by the monitor.

5.5 Randomization and Blinding

The randomization can occur at every time point between Screening and Day 1 or at Day 1 after confirmation of the Principal Investigator that the patient fulfills the eligibility criteria.

If the investigator randomizes the patient between Screening Visit and Day 1 and recognizes that the patient did not fulfill the eligibility criteria anymore at Day 1, the patient should not be treated and will be classified as early discontinuation.

For treatment during the double-blind Main Period, subjects will be centrally assigned to randomized IMP in 1 of 5 cohorts in a ratio of 1:1:1:1:1 (Section 3.1) using an Interactive Response Technology (IRT) at Day 1 stratified by Hurley Stage II and III. Complete data from the clinical HS examination must be available before randomization can occur.

The double-blind will be maintained through the Main Period and, for HiSCR non-responders, in the Induction Phase of the Extension Period.

Emergency Identification of Investigational Medicinal Product

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's treatment

DEFINITION OF TERMS

Baseline	A value or quantity that serves as a reference for comparisons over time.
Investigational medicinal product (IMP)	Any drug product that is to be administered in the current study.
Case Report Form (CRF)	A printed or electronic (eCRF) form for recording study participants' data during the study, as required by the protocol.
Central laboratory	A laboratory where all subject-derived samples (e.g., serum, plasma) are centrally analyzed.
Compliance	Adherence to all the study-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements.
Consent	The act of obtaining informed consent for participation in a clinical study from subjects deemed eligible or potentially eligible to participate in the clinical study. Subjects entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
End of study	Overall study completion: the day of the last visit of the last subject enrolled in the study. Individual subject: the time point after which no further study-related procedures are performed.
Endpoint	Key measurement or observation used to measure the effect of experimental variables in a study.
Enrollment	The time point at which a subject formally starts to participate in the study after signing of informed consent form.
Hidradenitis Suppurativa Clinical Response (HiSCR)	• An at least 50% reduction in total abscess and inflammatory nodule count (AN) • No increase in number of abscesses • No increase in number of draining fistulas compared to baseline
Loss of response	For subjects who achieve HiSCR at the end of the Main Period: a loss of at least 50% of the improvement (reduction) in the AN count achieved from baseline to Week 16. AN count > ½ × (Baseline AN count + Week 16 AN count)
Screening	The predetermined series of procedures with which each investigator selects an appropriate and representative sample of subjects for enrollment into the study.

	○ Total bilirubin > 3 × UNL ○ Alanine aminotransferase > 5 × UNL ○ Aspartate aminotransferase > 5 × UNL ○ Positive Screening test for human immunodeficiency virus (HIV)-1 or 2, or hepatitis B or C virus For Canada only: One of the following abnormal laboratory findings: ○ WBC < 2500/mm^3 ○ Neutrophil count < 1000/mm^3 ○ Serum creatinine > 3 × UNL ○ Total bilirubin > 1.5 × UNL ○ Alanine aminotransferase > 2.5 × UNL ○ Aspartate aminotransferase > 2.5 × UNL ○ Positive Screening test for HIV-1 or 2, or hepatitis B or C virus • Chronic and/or recurring systemic infections, history of invasive infections with atypical pathogens (i.e., which normally do not cause invasive infection, such as listeriosis), or known primary immunodeficiency • Subject is judged to be in poor general health, as determined by the investigator based upon medical history, physical examination, laboratory safety, and a 12-lead electrocardiogram (ECG) • Female subjects of childbearing potential unwilling or unable to use a highly effective method of contraception (pearl index < 1%) such as complete sexual abstinence, combined oral contraceptive, vaginal hormone ring, transdermal contraceptive patch, contraceptive implant, or depot contraceptive injection in combination with a second method of contraception such as condom, cervical cap, or diaphragm with spermicide during the study and for at least 1 month after last administration of investigational medicinal product (IMP). For France only: the methods of contraception are applicable during the study and for at least 3 months after last administration of IMP. • History of drug or alcohol abuse during the 24 weeks before Screening • Pregnancy, as verified by a positive pregnancy test, or nursing woman • Evidence or suspicion that the subject might not comply with the requirements of the study protocol

Schedule of Assessments - Extension Period (HiSCR Responders at Week 16)

	Extension Period								
	Maintenance Phase								
	V1R	V2R	V3R	V4R	V5R	V6R	FUV	OVx	USV
	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44 (b)	Optional Visit	Unsch-eduled Visit
	Day 141	Day 169	Day 197	Day 225	Day 253	Day 281	Day 309		
Accepted time window	± 1 Day	± 2 Days	± 2 Days	± 2 Days	± 2 Days	± 2 Days	+ 2 Days		
Informed Consent Procedure									
Inclusion/Exclusion Criteria									
Pregnancy Test	X (j) (urine)	X (j) (urine)	X (j) (urine)	X (j) (urine)	X (j) (urine)	X (j) (urine)	X (serum)		
Medical and Surgical History									
Demographics and Baseline Characteristics									
HS Medical and Surgical History									
Prior Therapy									
Physical Examination				X			X		
ECG				X			X (h)		
Vital Signs	X	X	X	X	X	X	X	X	X
HS Clinical Parameters	X	X	X	X	X	X	X	X	X
Erythema Assessment	X	X	X	X	X	X	X	X	X
Patient's Global Assessment Skin Pain (NRS) (Daily)	→	→	→	→	→	→	→	→	→
Analgesic Therapy (Daily)	→	→	→	→	→	→	→	→	→
Patient's Assessment of Drainage (Daily)	→	→	→	→	→	→	→	→	→
DLQI, HADS, SF-36v2, EQ-5D-5L				X			X		
Photography		X		X			X		
Randomization									
Administration of IMP (d)	X	X	X	X	X	X			
Laboratory Parameters									
Safety Laboratory (c)	X (j, k)	X (j)	X (j)	X	X (j)	X (j)	X		
HIV-1 or 2 / HBV / HCV Test									
Plasma									
C3a (c)				X			X		
C5a (c)		X		X			X		
Serum and plasma biomarkers (i)				X			X		
Citrate plasma									
IFX-1 (c)	X	X	X	X	X	X	X		
Serum									
CH50 (c)				X			X		
CRP (c)	X (j)	X (j)	X (j)	X	X (j)	X (j)	X		
Anti-drug Antibodies (c)		X		X			X		
Continuous Documentation									
Adverse Events	X	X	X	X	X	X	X	X	X
Concomitant Therapy	X	X	X	X	X	X	X	X	X

- Main Period: starts with the first infusion of IMP on Week 0 (Day 1) and ends at Week 16 (Day 113), after administration of IMP
- Extension Period (open-label from Week 20 onwards): starts after administration of IMP at Week 16 and ends at Week 44

4 STUDY POPULATION

4.1 Inclusion Criteria

Subjects must meet all of the following criteria to be enrolled into the study:

Inclusion Criteria	Rationale	Criteria Checked at	
		Screening	Day 1
1. Male or female, ≥ 18 years of age	Safety concern	X	
2. Written informed consent obtained from subject	Administrative	X	
3. Diagnosis of HS for at least 1 year	Effectiveness	X	
4. Moderate or severe HS, as indicated by HS lesions in at least 2 distinct areas, 1 of which must be at least Hurley Stage II or Stage III (Appendix 17.1)	Effectiveness	X	X
5. Stable HS for at least 2 months before Screening, as determined by the investigator through subject interview and review of medical history	Effectiveness	X	
6. Inadequate response to at least 3 months of oral antibiotics, or intolerance to antibiotics	Effectiveness	X	
7. Total abscess and inflammatory nodule count of ≥ 3	Effectiveness	X	X

HS = hidradenitis suppurativa.

4.2 Exclusion Criteria

Subjects who fulfill any of the following criteria are not eligible to participate in the study:

Exclusion Criteria	Rationale	Criteria Checked at	
		Screening	Day 1
1. Body weight < 60 or > 130 kg	Safety concern	X	
2. Any other skin disease that may interfere with assessment of HS	Effectiveness	X	X
3. More than 20 draining fistulas	Safety concern	X	

- Urine pregnancy test, required for all women of childbearing potential *(Weeks 0 [Day 1], 4 [France only], 8 [France only], 12 [France only], 16)*
- Blood sample for analysis of safety laboratory parameters *(Weeks 4, 8 [France only], 12 [France only], 16)*
- Review medical and surgical history to confirm eligibility for participation in the study *(Week 0 [Day 1])*
- HS medical and surgical history *(Week 0 [Day 1])*
- Physical examination *(Weeks 0 [Day 1], 16)*
- ECG *(Week 16)*
- Vital signs *(Weeks 0 [Days 1 and 4], 1, 2, 4, 6, 8, 10, 12, 14, 16)*
- HS clinical parameters *(Weeks 0 [Day 1], 2, 4, 6, 8, 10, 12, 14, 16)*
- Erythema assessment *(Weeks 0 [Day 1], 2, 4, 6, 8, 10, 12, 14, 16)*
- Continue documentation of patient-reported outcomes:
    - Patient's Global Assessment of Skin Pain (NRS) *(daily in e-diary throughout Main Period)*
    - Analgesic therapy *(daily in e-diary throughout Main Period)*
    - Patient's Assessment of Drainage *(daily in e-diary throughout Main Period)*
    - DLQI *(Weeks 0 [Day 1], 16)*
    - HADS *(Weeks 0 [Day 1], 16)*
    - SF-36v2 *(Weeks 0 [Day 1], 16)*
    - EQ-5D-5L *(Week 0 [Day 1], 16)*
- Citrate plasma sample for analysis of:
    - IFX-1 *(Weeks 0 [Day 4], 1, 2, 4, 6, 8, 10, 12, 14, 16)*
- Plasma sample for analysis of:
    - C3a *(Weeks 0 [Day 1], 2, 16)*
    - C5a *(Weeks 0 [Days 1 and 4], 2, 6, 16)*
- Serum and plasma biomarker sample *(Weeks 0 [Day 1], 2, 16), not applicable for Denmark*
- Serum sample for analysis of:
    - CH50 *(Weeks 0 [Day 1], 2, 16)*
    - CRP *(Weeks 0 [Day 1], 2, 4 [France only], 8 [France only], 12 [France only],16)*
    - Antidrug antibodies (ADAs) *(Weeks 0 [Day 1], 4, 16)*
- Photographic documentation of affected areas *(Weeks 0 [Day 1], 4, 16)*
- Documentation of AEs *(Weeks 0 [Days 1 and 4], 1, 2, 4, 6, 8, 10, 12, 14, 16)*
- Documentation of concomitant therapy *(Weeks 0 [Days 1 and 4], 1, 2, 4, 6, 8, 10, 12, 14, 16)*

After the assessments and procedures listed above have been completed:

- Allocation of affected areas to the Hurley Stage gradation of disease severity [13]. Subjects with Hurley Stage II and III, indicating moderate and severe HS, will be enrolled into the study (Appendix 17.1)

All surgical interventions for HS before Screening will be documented in the eCRF

8.1.4 Prior and Concomitant Therapy

All prior therapy taken during the 3 months before Screening and all concomitant therapy will be documented. For details, refer to Section 5.8.

8.2 Efficacy Variables

8.2.1 Overview of Variables

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

- HS clinical parameters
- HiSCR, based on HS clinical parameters
- HS-PGA, based on HS clinical parameters
- Modified Sartorius Score (mSS), based on HS clinical parameters
- Lesions, based on HS clinical parameters
- Erythema assessment
- Patient's Assessment of Drainage
- Use of analgesic therapy
- Patient's Global Assessment of Skin Pain (NRS)
- DLQI
- HADS
- SF-36v2
- EQ-5D-5L
- Photographic documentation of affected areas

8.2.2 Methods of Assessment

8.2.2.1 Hidradenitis Suppurativa Clinical Parameters

To evaluate the severity of illness, the following HS clinical parameters will be assessed and documented at Screening, at Week 0 (Day 1), and at prespecified times during the study, as outlined in the Schedules of Assessments through Week 44 or an early discontinuation visit and the 3-month Post-Treatment Follow-Up visit, if the subject discontinues before Week 44:

- Affected area (i.e., left and right axilla, left and right sub/inframammary area, intermammary area, left and right buttock, left and right inguino-crural fold, perianal, perineal area, other [to be specified]), as described in guidance provided to the investigator

  NOTE: lesions in each affected area will be counted. The identification of lesions will be performed according to standard definitions of elementary cutaneous lesions.

The following parameters will be assessed using standard validated methods:

Clinical chemistry:	serum creatinine, urea, alanine transaminase, aspartate transaminase, gamma-glutamyltransferase, total bilirubin, lactate dehydrogenase, alkaline phosphatase, sodium, potassium, calcium, albumin
Hematology:	red blood cells (erythrocytes), platelets, hemoglobin, white blood cells (including differential blood count)
Coagulation:	partial thromboplastin time, international normalized rate

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

- Not CS
- CS
- Error (e.g., laboratory error, improper sample preparation, hemolysis, or delayed transit to laboratory)

At Screening, any laboratory value that deviates from the reference range and is considered by the investigator to be CS, or considered as a result of a disease noted in the medical history, must be documented on the medical history page of the eCRF. Any deviation outside of the reference range considered by the investigator as CS at any later visit must be documented in the eCRF as an AE if not previously documented as an ongoing medical condition or as an ongoing AE. Follow-up laboratory investigations due to an AE will be performed at a local laboratory at the discretion of the investigator.

8.3.2.6 Pregnancy Testing

Pregnancy testing will be conducted in all women of childbearing potential.

A serum pregnancy test will be performed at Screening, at Week 44 or an early discontinuation visit and the 3-month Post-Treatment Follow-Up visit if the subject discontinues before Week 44.

An urine pregnancy test will be performed at Weeks 0 (Day 1) and 16.

For France: an urine pregnancy test will be performed in addition at Weeks 4, 8, 12, 20, 24, 28, 32, 36, 40).

If any pregnancy test is positive, the subject will not be eligible for participation or continuation in the study.

Lactating women will not be eligible for participation or continuation in the study.

8.3.2.7 Human Immunodeficiency Virus (HIV) and Hepatitis Virus (HBV or HCV) Testing

Tests for HIV-1 or 2 and HBV or HCV will be conducted at Screening.

Analyses for HIV-1 or 2 antibodies will be conducted by the central laboratory. Subjects will not be eligible for participation in the study if they test positive for HIV infection.

Analyses for the presence of HBV surface antigen (HBsAg) will be conducted by a central laboratory. Subjects will not be eligible for participation in the study if they test positive for HBsAg. Subjects who test negative for HBsAg will be tested for the presence of HBV surface antibody (HBsAb) and IgM-antibody against hepatitis B core antigen (IgM anti HBc). If test results are positive for HBsAb or IgM anti HBc, then an HBV DNA PCR test will be conducted. If "target is not detected" for the DNA PCR, the patient is eligible to enter the study. If test results are negative for HBsAB and IgM anti HBcA, patient is eligible to enter the study.

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 • 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

All AEs classified as “possibly”, “probably”, or “certainly” related will be considered as “at least possibly related to the IMP”. All AEs classified as “not related” or “unlikely related” will be considered as “not related” to the IMP.

The degree of certainty with which an AE is attributed to administration of the IMP or an alternative cause (e.g., natural history of the underlying disease, concomitant therapy, etc.) must be determined on the basis of how well the AE can be understood in terms of:

- Known pharmacology of the IMP
- Clinically and/or pathophysiologically plausible context
- Reaction of a similar nature previously observed with similar products, or reported in the literature for similar products as being product-related (e.g., headache, facial flushing, pallor)
- Plausibility supported by the temporal relationship (e.g., the event being related by time to administration or termination of treatment with the IMP, drug withdrawal, or reproduced on rechallenge)

enrolled into the study (i.e., 35 subjects per cohort) to achieve at least 29 subjects per cohort available for the primary analysis of the primary efficacy endpoint.

The sample size is selected in a way that the multiple contrast test exceeds a power of 90%. With the planned sample size, the power criterion of the multiple contrast test is fulfilled because 29 subjects per cohort would yield a power of at least 90% to detect a dose-response signal if present. In this context, the HiSCR at Week 16 is assumed to be 25% in the placebo group, as shown in earlier HS studies [15], and 30%, 45%, 55%, and 60% in the active cohorts (Cohorts 2 to 5), with cumulative doses of 2000 mg, 4800 mg, 8000 mg, and 10,800 mg, respectively. A 1-sided significance level of α = 0.025 will be used.

Additionally, simulations were conducted to investigate the expected length of the 2-sided 90% confidence intervals (CIs) for the minimum effective dose (MED) and the median effective dose (ED_{50}). Definitions of MED and ED_{50} can be found in Section 10.5. Based on the planned sample size of at least 29 evaluable subjects per cohort, wide 90% CIs can be expected for the MED and the ED_{50}. The expected length of the 90% CIs was determined by simulations of the modelling step of the MCP-Mod procedure. To determine the true HiSCR at Week 16, a maximum possible effect for the agonist (E_{max}) model and a logistic model were selected, which are the same models that will be used as candidate models in the MCP-Mod procedure. A guesstimate of ED_{50} = 3000 was used for the E_{max} model and guesstimates of ED_{50} = 3500 and δ = 1100 was used for the logistic model.

10.3 Analysis Sets

Full analysis set (FAS): the FAS will consist of all subjects who will receive at least 1 infusion of IMP. The analysis will be based on the cohort the subjects are randomized to (intention-to-treat principle).

Per protocol set (PPS): the PPS will be a subset of the FAS and will exclude all subjects with major protocol violations that affect the evaluation of the primary endpoint of the study. Subjects who will receive treatment from a cohort that they are not randomized to for the complete treatment course until Week 16 will not be excluded from the PPS and will be analyzed based on the actual treatment they will receive.

Safety analysis set (SAS): the SAS will consist of all subjects who will receive at least 1 infusion of IMP. Subjects will be analyzed according to the treatment they actually received. Actual treatment refers to the individual dosing schedule. The allocation of single subjects to the actual dosing groups will be performed under blinded conditions during the blinded data review.

Safety analyses will be based on the SAS. Efficacy analyses will be provided for the FAS and the PPS.

More detailed specifications of the analysis sets and analyses will be provided in the statistical analysis plan.

10.4 Endpoints

10.4.1 Efficacy Endpoints

The primary efficacy endpoint is the percentage of subjects with a response on the basis of the HiSCR (Section 8.2.2.2) determined at Week 16, before administration of IMP.

The secondary efficacy endpoints are:

- Percentage of subjects with a response on the basis of the HiSCR determined at Week 12, before administration of IMP

10.4.2 Safety Endpoints

The number and percentage of subjects who had a TEAE as well as the number of TEAEs will be assessed for all TEAEs and SAEs.

Furthermore, the number and percentage of subjects who have a TEAE as well as the number of TEAEs will be assessed for all causally related TEAEs, related SAEs, AESIs, TEAEs leading to study discontinuation, related TEAEs leading to study discontinuation, TEAEs leading to IMP discontinuation, and related TEAEs leading to IMP discontinuation.

For the analysis of severity and causal relationship of AEs, the worst severity and the strongest relationship per subject and class of AE will be considered.

Laboratory safety parameters, especially the change in inflammatory markers and differential blood cell counts, will be assessed by time point and changes in routine laboratory parameters from baseline will be determined. Shifts in safety laboratory parameters outside of normal ranges compared with baseline will be investigated.

Immunogenicity will be assessed by determining the number and percentage of subjects with detection of ADAs (before and after administration of IMP).

Other safety endpoints will be exploratory, as defined in detail in the statistical analysis plan.

Non-treatment-emergent AEs will be listed.

10.4.3 Pharmacokinetic Endpoints

The exposure to IFX-1 in all subjects will be measured as the plasma concentration of IFX-1 determined on Day 4 and at all subsequent scheduled visits to the study site through Week 44 before administration of IMP, and at Weeks 0 (Day 4), 2, and 16 after administration of IMP using a separate infusion line. Actual PK sampling times will be determined and the plasma concentration of IFX-1 will be assessed by time point.

A PK substudy will be conducted during the Main Period, at Weeks 2 and 16, in approximately50 of the 175 subjects participating in the Main Period (8 to 10 subjects per cohort). At these times, blood samples will be obtained for the analysis of IFX-1 in citrate plasma before IMP administration (0 h), after end of IMP administration (+ 10 min), and at 2 h (± 10 min), 6 h (± 10 min), 24 h (± 2 h), and 48 h (± 2 h) after start of IMP administration, in all cases using a separate infusion line.

The analysis of derived PK parameters will be described in a separate PK analysis plan.

10.4.4 Pharmacodynamic Endpoints

The PD of IFX-1 are primarily measured by plasma concentration of C5a, which is determined at prespecified times after administration of IFX-1.

Plasma concentrations of C5a and C3a and serum concentrations of CH50 will be assessed by time point and as change from Day 1.

Serum concentrations of CRP will be assessed by time point and as change from Day 1.

10.5 Analysis of Endpoints

10.5.1 Efficacy

The primary efficacy endpoint HiSCR at Week 16 will be analyzed using the MCP-Mod procedure. The MCP-Mod approach will include Hurley Stage at baseline, concomitant use of antibiotic therapy, and AN count at baseline as covariates.

missing for subjects in the intent-to-treat population. The multiple imputation model will be using fully conditional specification logistic regression. We will perform 20 imputations using a random seed of 122007 using SAS PROC MI.

The MCP-Mod approach as outlined above will be applied to all 20 imputed datasets. If the MCP step results in a non-significant dose-response signal for more than one of the 20 datasets, the results will be considered as not robust enough for dose-response estimation. In this case, the Mod step will not be performed. For the estimation of the dose-response curve for each candidate model (Mod step), the individual model parameters (ED_{50} for the E_{max} model and ED_{50} and δ for the logistic model) from the analysis on each imputed dataset will be combined using Rubin's rule.

The percentage of subjects with a response on the basis of the HiSCR (Section 8.2.2.2) determined at Week 12 before administration of IMP will be analyzed in the same way as the primary endpoint.

For all other continuous efficacy endpoints, the absolute values and changes from baseline (absolute and relative) will be summarized by display of basic descriptive statistics (e.g., number of observations (n), mean, standard deviation, minimum, median, maximum, lower quartile, upper quartile, and upper and lower boundary of the 95% CI for the mean) by time point.

Model-based analyses (e.g. analysis of covariance [ANCOVA], Poisson, and logistic regression models) for continuous, count, and binary endpoints will be defined in the statistical analysis plan as deemed necessary and possible.

All categorical efficacy endpoints will be summarized by time point using absolute and relative frequencies including 95% exact CIs based on the binomial distribution.

Sensitivity analyses will be defined for all efficacy endpoints if deemed necessary.

10.5.2 Safety

Treatment-emergent AEs will be analyzed according to the number and percentage of subjects who had a TEAE, as well as the number of TEAEs with the respective MedDRA System Organ Class and Preferred Term. Additionally, the number and percentage of subjects with TEAEs will be further grouped by severity and causal relationship. The number and percentage of subjects with SAEs and AESIs and the number of SAEs and AESIs will be analyzed. Where AEs are grouped by severity or relationship, the maximum severity/relationship per subject and class of AE will be considered. If the number of subjects discontinuing treatment or discontinuing the study is substantial, further analyses taking into account the time of AE onset and cumulative dose may be considered.

Safety laboratory, physical examination, and vital signs parameters will be analyzed by summary statistics (e.g., number of observations, mean, standard deviation, minimum, median, maximum, lower quartile, upper quartile) for absolute values and changes from baseline by visit.

Categorical safety parameters will be summarized by absolute and relative frequencies by time point.

10.5.3 Pharmacokinetics

The analysis of derived PK parameters will be described in a separate PK analysis plan.

10.5.4 Pharmacodynamics

Where applicable, the absolute values and changes from baseline of PD endpoints will be summarized using descriptive statistics (e.g., number of observations (n), mean, standard