CLINICAL STUDY PROTOCOL 2.0
GLOBAL AMENDMENT 1.1

Study Title:	A randomized, double-blind, placebo-controlled, multicenter Phase II study to determine efficacy and safety of IFX-1 in subjects with moderate to severe hidradenitis suppurativa
Study Number:	IFX-1-P2.4
Study Product:	IFX-1
IND Number:	136470
EudraCT Number:	2017-004501-40
Sponsor:	InflaRx GmbH Winzerlaer Str. 2 07745 Jena Germany
Version and Date of Study Protocol	Version 2.0 Final 16 November 2018
Global Amendment	Version 1.1

PROTOCOL AMENDMENT SIGNATURES

Confirmation of the Final Protocol Amendment

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

Protocol Number	IFX-1-P2.4
Study Title	A randomized, double-blind, placebo-controlled, multicenter Phase II study to determine efficacy and safety of IFX-1 in subjects with moderate to severe hidradenitis suppurativa

Sponsor

Othmar Zenker, MD
Chief Medical Officer

19/11/2018 (Date)

(Signature)

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Biostatistician

Lisa Hiller, PhD, Metronomia

19-Nov-2018 Lisa Hiller

(Date) (Signature)

SIGNATURE OF COORDINATING INVESTIGATOR

GLOBAL AMENDMENT 1.1

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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 Harmonisation (ICH) Guideline 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.

Coordinating Investigator

Prof. Dr. med. Evangelos J. Giamarellos-Bourboulis
ATTIKON University Hospital, Athens, Greece

19-11-2018

(Date [DD/MM/YYYY])

(Signature)

SIGNATURE OF INVESTIGATOR

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Investigator <<*TBD*>>

_____ _____

(Date [DD/MM/YYYY]) (Signature)

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ABBREVIATIONS

ADA	Antidrug antibody
AE	Adverse event
AESI	Adverse event of special interest
AN	Total abscess and inflammatory nodule count
ANCOVA	Analysis of covariance
BDRM	Blind Data Review Meeting
bw	Body weight
CI	Confidence interval
CRF	Case Report Form
CRO	Clinical Research Organization
CRP	C-reactive protein
CS	Clinically significant
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ED_{50}	Median effective dose
ELISA	Enzyme-linked immunosorbent assay
E_{max}	Maximum possible effect for the agonist
EQ-5D-5L	EuroQol-5 Dimensions survey
FAS	Full analysis set
FUV	Follow-up visit
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
HBsAb	Hepatitis B virus surface antibody
HBV	Hepatitis B virus
HiSCR	Hidradenitis Suppurativa Clinical Response
HIV	Human immunodeficiency virus
HRQL	Health-related quality of life
HS	Hidradenitis suppurativa
HS-PGA	Hidradenitis Suppurativa- Physician's Global Assessment
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgM anti HBc	IgM-antibody against hepatitis B core antigen
IL	Interleukin
IMP	Investigational medicinal product

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

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.

Study start	The time point at which the first subject gives written informed consent; equivalent to first subject's first visit at the first study site which has enrolled a subject into the study.
Worsening or Absence of Improvement (WOAI)	For subjects who do not achieve HiSCR at the end of the Main Period: AN count at 2 consecutive visits ≥ Baseline AN count.

GENERAL INFORMATION

List of Personnel and Organizations Responsible for Conduct of Study

A list of personnel responsible for the conduct of the study will be supplied to study sites as part of the investigator site file. As needed, this list will be updated by the sponsor or delegate and provided to study sites.

Synopsis

Title of study	A randomized, double-blind, placebo-controlled, multicenter Phase II study to determine efficacy and safety of IFX-1 in subjects with moderate to severe hidradenitis suppurativa.
Protocol / study number	IFX-1-P2.4
EudraCT number	2017-004501-40
Type of study	Dose-range finding
Phase of development	II
Indication	Treatment of patients with moderate or severe hidradenitis suppurativa (HS)
Sponsor	InflaRx GmbH Winzerlaer Str. 2 07745 Jena Germany
Coordinating investigator	Prof. Dr. med. Evangelos J. Giamarellos-Bourboulis ATTIKON University Hospital, Athens, Greece
Study site(s)	Planned: approximately 50 sites in approximately 8 countries
Primary objective	To evaluate a dose-response signal of IFX-1 in subjects with HS according to the Hidradenitis Suppurativa Clinical Response (HiSCR) at Week 16
Secondary objectives	• To assess the efficacy of IFX-1 using additional outcome measures • To assess the safety and tolerability of IFX-1 • To generate data for pharmacokinetic (PK) and pharmacodynamic (PD) modelling • To assess patient-reported outcomes • To evaluate the long-term efficacy and safety of IFX-1
Study design	Prospective, randomized, 2-period, double-blind and placebo-controlled (Main Period) and open-label (Maintenance Phase of Extension Period) multicenter study
Sample size	175 subjects (randomized to receive double-blind treatment in 1 of 5 treatment cohorts in a ratio of 1:1:1:1:1)
Study population	Key inclusion criteria at Screening: • Male or female, ≥ 18 years of age • Written informed consent obtained from subject • Diagnosis of HS for at least 1 year • 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

	• 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

	○ 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

	• Any other factor which, in the investigator's opinion, is likely to compromise the subject's ability to participate in the study • The subject is an employee or direct relative of an employee at the study site or sponsor • The subject is imprisoned or lawfully kept in an institution • The subject has participated in a clinical study during the 3 months before Screening, or plans to participate in a clinical study • <u>For Denmark only:</u> Hypersensitivity to any excipients of IFX-1
Investigational medical product(s) [IMP], dose, and mode of administration	IFX-1 is provided in 10 mL vials containing 100 mg IFX-1 and will be infused over a period of 30 to 60 minutes (min) via an intravenous (iv) line. Placebo is provided in 10 mL vials containing sodium chloride, sodium phosphate, and Polysorbate 80. The placebo vials and content have the same appearance as the IFX-1 vials and additives. <u>Main Period (16 weeks):</u> 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). *Cohort 1 (placebo):* • Induction Phase: placebo at Weeks 0 (Days 1 and 4), 1, and 2 • Maintenance Phase: placebo at Week 4 and every other week through Week 16 *Cohort 2 (IFX-1 400 mg q4w):* • Induction Phase: IFX-1 400 mg at Week 0 (Days 1 and 4), followed by placebo at Weeks 1 and 2 • Maintenance Phase: IFX-1 400 mg at Week 4, followed by alternating infusions every other week of placebo or 400 mg IFX-1 through Week 16 *Cohort 3 (IFX-1 800 mg q4w):* • Induction Phase: IFX-1 800 mg at Weeks 0 (Days 1 and 4) and 1, followed by placebo at Week 2 • Maintenance Phase: IFX-1 800 mg at Week 4 followed by alternating infusions every other week of placebo or IFX-1 800 mg through Week 16 *Cohort 4 (IFX-1 800 mg q2w):* • Induction Phase: IFX-1 800 mg at Weeks 0 (Days 1 and 4), 1, and 2 • Maintenance Phase: IFX-1 800 mg at Week 4 followed by IFX-1 800 mg every other week through Week 16

	Cohort 5 (IFX-1 1200 mg q2w): • Induction Phase: IFX-1 800 mg at Weeks 0 (Days 1 and 4) and 1, followed by IFX-1 1200 mg at Week 2 • Maintenance Phase: IFX-1 1200 mg at Week 4 followed by IFX-1 1200 mg every other week through Week 16 <u>PK substudy in Main Period:</u> 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 included in the PK substudy, only after giving consent to participation. The PK substudy assessments will be made on 2 visits during the Main Period, at Weeks 2 and 16.
	<u>Extension Period (28 weeks) – HiSCR responders</u> Subjects from all cohorts who are HiSCR responders at Week 16 will receive IFX-1 at a dose of 800 mg q4w, starting at Week 20 through Week 40. 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 then 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. <u>Extension Period (28 weeks) – HiSCR non-responders</u> Subjects from all cohorts who are HiSCR non-responders at Week 16 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. *Cohort 1:* • Induction Phase: infusion of IFX-1 800 mg at Weeks 18 (Days 127 and 130) and 19 • Maintenance Phase: IFX-1 800 mg at Week 20 and every other week through Week 40 *Cohort 2:* • Induction Phase: infusion of IFX-1 800 mg at Week 18 (Day 127), placebo at Week 18 (Day 130), and IFX-1 800 mg at Week 19 • Maintenance Phase: IFX-1 800 mg at Week 20 and every other week through Week 40 *Cohorts 3, 4, and 5:* • Induction Phase: infusion of IFX-1 800 mg at Week 18 (Day 127), and placebo at Week 18 (Day 130) and Week 19 • Maintenance Phase: IFX-1 800 mg at Week 20 and every other week through Week 40 Subjects who experience Worsening or Absence of Improvement (WOAI) (see Definitions of Terms) at 2 consecutive visits during the Maintenance Period of the Extension Period will be discontinued from the study.

Study duration	The study duration for an individual subject will be up to 48 weeks and includes the following study periods: • Screening Period: up to 18 days before first administration of IMP (Week −4 to Week −2 [Day -28 to Day -10) • 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: starts after administration of IMP at Week 16 and ends at Week 44
Criteria for evaluation	Efficacy: The primary efficacy endpoint is the percentage of subjects with a response on the basis of the HiSCR determined at Week 16, before administration of IMP. The secondary efficacy endpoints include: • Percentage of subjects with a response on the basis of the HiSCR determined at Week 12, before administration of IMP • 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 modified Sartorius Score (mSS) from Day 1 by time point • Absolute value and absolute and relative change in Patient's Global Assessment of Skin Pain (Numeric Rating Scale [NRS]) from Day 1 by time point • Percentage of subjects achieving, by time point: o 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) o 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 Dermatology Life Quality Index (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 Hidradenitis Suppurativa- Physician's Global Assessment (HS-PGA) among subjects with at least 2 grades improvement (reduction) from Day 1 to each time point. All other efficacy endpoints will be exploratory. Safety endpoints: • The number and percentage of subjects who had a treatment-emergent adverse event (TEAE) as well as the number of TEAEs will be assessed for all TEAEs and serious adverse events (SAEs). Exploratory safety endpoints: • 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, adverse events of special interest (AESIs), TEAEs leading to study discontinuation, related TEAEs leading to study discontinuation, TEAEs leading to IMP discontinuation, and related TEAEs leading to IMP discontinuation • Laboratory safety parameters 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 antidrug antibodies (ADAs) (before and after administration of IMP) PK: • PK will be assessed on the basis of IFX-1 concentrations. 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. Actual PK sampling times will be determined and the plasma concentration of IFX-1 will be assessed by time point

	PD: • The PD of IFX-1 is primarily measured by plasma concentration of C5a 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 C-reactive protein (CRP) will be assessed by time point and as change from Day 1

Statistical methods	A total of 175 subjects are planned to be 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 so that the multiple contrast test (as part of the multiple comparisons procedure-modelling [MCP-Mod] that will be used to analyze the primary efficacy endpoint) 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. A 1-sided significance level of α = 0.025 will be used. In general, data will be analyzed by cohort and study phase (Main Period and Extension Period) and may be differentiated further (e.g., by visit or by study site). The primary efficacy endpoint of the percentage of subjects with HiSCR at Week 16 will be analyzed using the MCP-Mod procedure. The secondary efficacy endpoint of the percentage of subjects with HiSCR at Week 12 will be analyzed in the same way as the primary endpoint using the MCP-Mod procedure. For all other continuous efficacy endpoints, the absolute values and changes from baseline (absolute and relative) will be analyzed by descriptive statistics (e.g., number of observations, mean, standard deviation, minimum, median, maximum, lower quartile, upper quartile, and upper and lower boundary of the 95% confidence interval [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 efficacy endpoints if deemed necessary. Continuous safety parameters will be analyzed by descriptive statistics for absolute values and changes from baseline (absolute and relative) by time point. Categorical safety parameters will be summarized by absolute and relative frequencies by time point. No formal interim analysis is planned for this study. An independent, unblinded Data Monitoring Committee (DMC) will be established to allow regular monitoring of the study data in order to detect and report early evidence of unanticipated harm to subjects.

Schedules of Assessments

The Schedule of Assessments for Screening and the Main Period is applicable to all subjects. For the Extension Period, separate Schedules of Assessments are provided for subjects according to their responder status at Week 16.

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

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

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

	Extension Period														
	Induction Phase			Maintenance Phase											
	V1NR	V2NR	V3NR	V4NR	V5NR	V6NR	V7NR	V8NR	V9NR	V10NR	V11NR	V12NR	V13NR	V14NR	FUV	USV
	Week 18		Week 19	Week 20	Week 22	Week 24	Week 26	Week 28	Week 30	Week 32	Week 34	Week 36	Week 38	Week 40	Week 44 (b)	Unsch-eduled Visit
	Day 127	Day 130	Day 134	Day 141	Day 155	Day 169	Day 183	Day 197	Day 211	Day 225	Day 239	Day 253	Day 267	Day 281	Day 309	
Accepted time window	± 1 Day	± 1 Day	± 1 Day	± 1 Day	± 2 Days	± 2 Days	± 2 Days	± 2 Days	± 2 Days	± 2 Days	± 2 Days	± 2 Day	± 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	X	X	X	X	X	X	X
HS Clinical Parameters				X	X	X	X	X	X	X	X	X	X	X	X	X
Erythema Assessment				X	X	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					X	
Randomization																
Administration of IMP (d)	X	X	X	X	X	X	X	X	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					X	
Serum and plasma biomarkers (i)										X					X	
Citrate plasma																
IFX-1 (c)	X	X (g)	X	X	X	X	X	X	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					X	
Continuous Documentation																
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Footnote applies to all Schedules of Assessments

AE = adverse event, CRP = C-reactive protein, DLQI = Dermatology Life Quality Index, ECG = electrocardiogram, 5D-5L = EuroQol-5 Dimensions survey, FUV = follow-up visit, h = hour, HADS = Hospital Anxiety and Depression Scale, HBV = hepatitis B virus, HCV = hepatitis C virus, HiSCR = Hidradenitis Suppurativa Clinical Response, HIV = human immunodeficiency virus, HS = hidradenitis suppurativa, IMP = investigational medicinal product, min = minute, OV = optional visit, PK = pharmacokinetic(s), TNF = tumor necrosis factor, USV = unscheduled visit, V = visit, VxR= Visit for HiSCR responders, VxNR= Visit for HiSCR non-responders.

(a) Update some inclusion/exclusion criteria, prior and concomitant therapy, and HS/medical history and surgery information to confirm subject eligibility.

(b) All assessments intended to be performed at Week 44 should also be performed at early discontinuation visits. For subjects who discontinue early, a Post-Treatment Follow-Up visit will take place 3 months after early discontinuation or another HS therapy has been started, whichever occurs first. At the Post-Treatment Follow-Up visit the same parameters as at Week 44 will be assessed.

(c) Blood samples must be obtained before IMP administration.

(d) IMP administered according to dosing schedules in Table 2 and Table 3.

(e) PK substudy in 8 to 10 subjects from each cohort. Blood samples will be obtained for 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.

(f) Height and body weight will be assessed at Screening only.

(g) Blood sample for IFX-1 analysis will be taken before IMP administration and directly after IMP infusion using a separate infusion line, with a time window of + 10 min.

(h) Subjects will have a repeat ECG at Week 44 or at an early discontinuation visit if the subject discontinues before Week 44. If in the opinion of the investigator, clinically relevant AEs have developed during the study that warrant a repeat ECG examination this can be performed at any time during the study.

(i) Blood sampling of serum and plasma biomarkers for future research is not applicable for Denmark.

(j) Test only applicable for France.

(k) Test only applicable for Denmark.

(l) 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.

1 INTRODUCTION

1.1 Background Information on the Indication

Hidradenitis suppurativa (HS) is a chronic devastating skin disorder affecting areas rich in apocrine glands. Nodules appear in the affected areas, progressively become swollen, and rupture with the release of pus. This process occurs repeatedly leading to sinus tract formation and scars [1]. The disease course creates a frustrating situation for patients as well as for physicians. Treatments recommended by guidelines include dietary and behavioral changes, topical and systemic medications (including antibiotics), and timely surgical interventions [2, 3]. Behavioral interventions and topical and systemic medications are most beneficial for preventing new lesions and reducing the inflammatory component of the disease. Surgical interventions are used to eliminate nodules, remove existing sinus tracts and scars, and prevent new sinus tract and scar formation. Despite treatment, relapse is very frequent, leading to severe impairment of the quality of life. The Dermatology Life Quality Index (DLQI) for HS is 8.9, and thereby higher than in any other skin disorder [4].

This devastating disorder has often been neglected and considered a rare condition. From an analysis of commercial health insurance reimbursement data for 2007 from a large group of patients in the United States, Cosmatos et al. determined a prevalence of 0.053% for clinically detected HS, and an estimated 146,000 to 162,000 patients in 2007 [5]. HS seems to indiscriminately affect the global population. A recent large epidemiological survey in France reported 0.97% disease prevalence[6]. However, the point prevalence is reported to range between 1% and 4%[7].

The exact pathophysiology of HS is unknown. Smoking, dietary habits, and genetic predisposition have all been linked with HS [8, 9]. However, a recent survey in 53 patients disclosed a severe derangement of the monocyte function and of subsequent antigen processing in these patients [10]. There the percentage of natural killer cells was increased and that of CD4-lymphocytes decreased compared to healthy controls, probably implying an autoimmune origin of the disorder. Additionally, a defective lipopolysaccharide (LPS)-induced production of the pro-inflammatory cytokines tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-6 by blood monocytes was demonstrated in patients with HS. This down-regulation of systemic cytokine production seems to be counter-regulatory to what happens in the inflamed skin: over-production of pro-inflammatory cytokines mainly TNF-α and IL-1β is ta distinctive feature that, nevertheless, does not seem to follow a specific pattern [11, 12].

The wide range of possible pathogenic mechanisms suggested by different studies denotes that HS may be associated with host mechanisms rather than exogenous factors. Taking into account the paradox that both anti-infectious (e.g., antibiotics) and pro-infectious (e.g., anti-TNF, corticosteroids, and immunosuppressive drugs) therapies may be effective, HS appears as an auto-inflammatory disease based on a defect in the hair follicle innate immunity [13]. The auto-inflammatory nature of HS is further supported by the evidence that pro-inflammatory cytokines such as IL-1β and TNF-α are markedly increased in lesional and perilesional skin[14].

As a consequence, the implication of some autoimmune or auto-inflammatory mechanism in the pathogenesis of HS has been speculated over the last years. The hypothesis is further reinforced by positive results from the administration of TNF antagonists such as adalimumab, which is approved for the treatment of patients with moderate to severe HS in prospective, placebo-controlled studies [15]. In the first study conducted with IFX-1 in subjects with HS (Study IFX-1-P2.3), in which subjects with moderate to severe HS were treated with 9 consecutive infusions of IFX-1 800 mg over 50 days, 83.3% of subjects achieved a Hidradenitis Suppurativa Clinical Response (HiSCR).

1.2 Background Information on IFX-1

IFX-1 is a monoclonal antibody which specifically binds to the soluble human complement split product C5a. 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 (MAC) [16, 17].

Single and repeated intravenous (iv) administration of IFX-1 at doses of up to 50 mg/kg body weight (bw) 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 bw (corresponding to a human equivalent dose of 16.13 mg/kg bw).

IFX-1 is an investigational medicinal product (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 HS.

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 bw) received single iv infusions of IFX-1 or placebo. IFX-1 was safe and well tolerated. The following adverse events (AEs) were reported by the investigator as at least possibly related to IFX-1: nausea, headache, nasopharyngitis, and C-reactive protein (CRP) 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 (PK), pharmacodynamics (PD), and efficacy of IFX-1 were investigated in 3 different dose groups (IFX-1 2 × 2 mg/kg bw, 2 × 4 mg/kg bw, and 3 × 4 mg/kg bw, each with a placebo control). In total, 48 subjects were treated with IFX-1. IFX-1 was safe and well tolerated. The following AEs 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, PK, PD, and safety of single doses of IFX-1 were investigated in 4 different dose groups (IFX-1 1, 2, 4, and 8 mg/kg bw, each with a placebo control). In total, 82 subjects were treated with IFX-1. IFX-1 was safe and well tolerated. The following AEs 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 HS): in this Phase II study in subjects with moderate to severe HS, the safety, PK, PD, 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 AEs reported by the investigator as at least possibly related to IFX-1.

An overview of known and potential risks and benefits of the IMP to human subjects is available in Section 1.4.

Further details on IFX-1 are given in the Investigator's Brochure, the current version of which is available in the investigator site file.

1.3 Rationale for the Phase II Study

HS is diagnosed by its clinical features and its chronicity. It is recognized by the presence of recurrent, painful, deep-seated, rounded nodules usually ending in abscesses and sinus tracts with suppuration and hypertrophic scarring of apocrine gland-bearing skin and is likely to be an auto-inflammatory disease based on a defect in the hair follicle innate immunity [13] (Section 1.1). As complement C5a is involved in the underlying acute inflammatory responses, this study is set up based on the hypothesis that IFX-1 might be able to block C5a induced pro-inflammatory effects such as neutrophil activation and cytokine generation, potentially contributing to the local skin inflammation and tissue damage.

As the dose-response for IFX-1 has not been assessed to date in a chronic disease, the primary rationale of this Phase II study is to investigate a dose-response signal of IFX-1 in subjects with moderate to severe HS according to the HiSCR.

Further important aims of the study are to investigate the PK, PD, and safety of IFX-1 in subjects with HS. The study will also collect data on clinical parameters that could be positively affected by a C5a blocking therapy (e.g., DLQI, Patient's Global Assessment of Skin Pain [Numeric Rating Scale, NRS]).

Rationale for Study Population

Patients with HS show elevated serum levels of TNF-α [14, 18]. Additionally, CRP values and white blood cell count (WBC) are increased significantly in patients with moderate or severe HS compared with the mild manifestation of the disease [19]. Because these patients present signs of systemic inflammation, the administration of a compound such as IFX-1, with its multi-faceted anti-inflammatory potential, may be a suitable agent for the management of HS, as shown in Study IFX-1-P2.3. The subjects with moderate to severe HS enrolled in the current study are considered to have a sufficiently severe disease status to evaluate the tolerability, PK, and PD of 4 dosing regimens of IFX-1, compared with placebo.

In line with the conclusions of an HiSCR validation study [20], subjects with a total abscess and inflammatory nodule count (AN) of < 3 at baseline will be excluded to eliminate the possibility that a 1-unit reduction in AN count could lead to an HiSCR response.

To keep the study population as homogenous as possible, subjects will not be enrolled into the study if they have been treated previously with any of the following for prespecified time periods before Screening (Section 4.2): IFX-1, adalimumab or other biologic products, non-stable doses of oral antibiotic treatment permitted for HS (doxycycline or minocycline only), systemic non-biologic therapies for HS with potential therapeutic impact for HS, any other systemic therapy for HS, any iv anti-infective therapy, phototherapy (ultra-violet B [UVB] or psoralen and ultra-violet A [UVA]), analgesics (including opioids) for HS-related pain, prescription-only topical therapies for HS, or oral anti-infectives for infections other than HS.

Rationale for Dosing Regimen

The aim of treatment with IFX-1 is to reach an almost complete blockade of the overall available C5a (existing and newly produced) in human whole blood during the entire treatment period. The rate at which consumed or activated C5 can be regenerated (the so-called C5 turnover rate) is not known. It is plausible to assume that more C5 could be produced in settings of chronic inflammation than in healthy subjects, and thus more C5a could result from the ensuing activation.

From clinical studies conducted so far (IFX-1-P1.1 and -P2.1), it is known that the peak IFX-1 concentration upon administration of 4 mg/kg bw was approximately 100 µg/mL (approximately 650 nM), which could theoretically block approximately 1200 nM of C5a. The expected half-life of IFX-1 is 3 to 4 days, thus, a biweekly dosing interval with a dose range of 400 to 800 mg in subjects with normal body weight is recommended.

In Study IFX-1-P2.3 in subjects with HS, IFX-1 administered at a weekly dose of 800 mg resulted in mean IFX-1 trough concentrations of 50.1 to 79.4 µg/mL. This dosing regimen was well tolerated, with no new safety signals, and clinical improvement of HS was demonstrated in the majority of subjects. The percentage of subjects achieving an HiSCR was higher than in the Phase III studies of adalimumab [11]. An effective dose of IFX-1 is unknown, as is the appropriate interval of administration. Therefore, 4 dosing regimens were selected for the current study to evaluate a dose-response signal for IFX-1 in subjects with HS according to the HiSCR at Week 16. All dosing regimens consist of a 2 weeks induction treatment to achieve blockade of C5a. After this induction treatment, a regular dosing schedule for maintenance treatment will start to maintain a blockade even in subjects on a low dose and in subjects in whom the entire C5 pool is enlarged and "turned over" several times. The toxicology development of IFX-1 is considered adequate to support the planned Phase II clinical study in subjects who will be treated at doses up to 1200 mg IFX-1 over a time period of 40 weeks. There were no relevant findings in the toxicology studies, which would preclude the continued clinical development of IFX-1.

Exposures and safety margins are summarized in Table 1.

Table 1 Exposure and Safety Margins

	NOAEL (26w Tox)	1200 mg Dose (Extrapolated)	Safety Margin
C_{max} [µg/mL]	2,553	ca. 260	ca. 10
AUC_{inf} [µg*h/mL]	464,737	ca. 17,000	ca. 27

AUC_{inf} = area under the curve to infinity; ca. = circa; C_{max} = peak plasma concentration; NOAEL = No Observed Adverse Effect Level

Rationale for Study Design

This is a double-blind, placebo-controlled, multicenter Phase II study to determine the efficacy and safety of IFX-1 in subjects with moderate to severe HS. With the experience gained in an earlier, open-label study of IFX-1 in subjects with HS (Study IFX-1-P2.3), which demonstrated acceptable safety and potentially beneficial efficacy, the double-blind, placebo-controlled design of the current study is deemed appropriate for investigating the efficacy and safety of IFX-1 in subjects with moderate to severe HS. The study design is also deemed appropriate for generating PK and PD data to determine dose ranges for future studies.

The study will be conducted in compliance with this study protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for Good Clinical Practice (GCP), and the applicable regulatory requirement(s) (Section 11).

1.4 Risk-Benefit Assessment

IFX-1 has been successfully investigated in an open-label Phase II study in subjects with moderate to severe HS. Further, considerations on risk-benefit-related aspects are derived from nonclinical data and clinical Phase I data in healthy subjects as well as from clinical data in 2 other Phase II studies conducted in subjects suffering from early, newly developing abdominal or pulmonary derived septic organ dysfunction and in subjects undergoing complex cardiac surgery.

1.4.1 Expected Benefits

The subjects participating in this study who are treated with IFX-1 may benefit from an improvement in HS-related symptoms based on the rationale provided in the sections 1.3 above.

1.4.2 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 bw.

Furthermore, the safety of IFX-1 has been investigated in 3 Phase II studies, conducted in 48 subjects with early septic organ dysfunction treated with up to 3 x 4 mg/kg bw IFX-1 given over 4 days, in 82 subjects undergoing complex cardiac surgery treated with single doses of up to 8 mg/kg bw IFX-1, and in 12 subjects with moderate to severe HS 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.

Thus, it has been demonstrated that IFX-1 was generally well tolerated when administered to subjects with HS.

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

Infections: the mechanism of action for IFX-1 and the 3 known complement pathways (classical, alternative, and lectin pathway) do not suggest any significant impact on C5 activation and MAC formation resulting from the presence of IFX-1 in blood. Data from an in vitro complement activation model and in vivo data from Phase I and II studies provide some evidences that IFX-1 does not interfere with the MAC formation. This is essential because MAC is the final step in the formation of complement activation elements leading to microbial elimination, especially for encapsulated bacteria. 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. See Section 5.6 for the procedures to be followed in case of infections.

Meningitis/meningococcal septicemia: current data do 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. See Section 5.6 for the procedures to be followed in case of meningitis/meningococcal septicemia.

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 II studies. See Section 5.6 for the procedures to be followed in case of anaphylactic reactions and acute systemic allergic hypersensitivity.

1.4.3 Risk Associated with Lack of Efficacy

With the administration of IFX-1 or placebo, no deterioration in health status is expected with respect to HS. Nevertheless, deterioration in HS can occur due to the fluctuating nature of the

disease. In case of a lack of efficacy with IFX-1 treatment, or in case of placebo treatment, subjects will continue to experience their typical HS symptoms.

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 and will not switch to the non-responder schedule.

Subjects who experience WOAI (see Definitions of Terms) at 2 consecutive visits during the Extension Period will be discontinued from the study.

1.4.4 Risk-Benefit Conclusion

HS is a chronic inflammatory skin disease, which affects approximately 1% of the general population in the West, with women affected 2 to 5 times more commonly than men [21], and an average onset age of 23 years. This poorly understood disease is believed to be under-reported by those who suffer from it.

The disease is associated with significant morbidity. Given the pain and consequent physical impairment associated with the tender lesions that are symptomatic of this disease, it has been reported that health-related quality of life (HRQL) is lower in patients with HS than in patients with other dermatological diseases. Furthermore, a recent study estimated that up to 20% of patients with HS report the co-existence of depression, and patients with HS report a high level of stigmatization. Due to the significant physical and emotional burden of this disease, patients often aggressively seek treatment.

The level of disease severity strongly influences the approach to the treatment of HS. Subjects with moderate to severe HS (Hurley Stage II or III disease) will be included in this study. Subjects with Hurley Stage II disease exhibit recurrent inflamed nodules and abscesses, which often lead to sinus tracts and scarring that may not resolve with antibiotic therapy. Subjects with Hurley Stage III disease require preventive and medical therapy, and efficacy in severe HS was shown for adalimumab, infliximab, and acitretin [3].

It is hypothesized that treatment with IFX-1 could block the C5a-mediated inflammatory effect and thus reduce the pain and consequent physical impairment associated with the tender lesions of HS, and may even improve the disease status. During treatment with 9 weekly doses of IFX-1 in a proof-of-concept study in subjects with moderate to severe HS (IFX-1-P2.3), the AN count decreased, the HiSCR increased, and the Hidradenitis Suppurativa- Physician's Global Assessment (HS-PGA) indicated a shift from very severe to moderate disease. This dosing regimen was well tolerated and, as seen in the other Phase I and II studies, IFX-1 had a favorable safety profile.

In case of a lack of efficacy with IFX-1 treatment or in case of placebo treatment, subjects will continue to experience their typical HS symptoms, for which currently only limited treatment options are available.

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

2 OBJECTIVES

2.1 Primary Objective

The primary objective of the study is to evaluate a dose-response signal of IFX-1 in subjects with HS according to the HiSCR at Week 16.

2.2 Secondary Objectives

The secondary objectives of the study are:

- To assess the efficacy of IFX-1 using additional outcome measures
- To assess the safety and tolerability of IFX-1
- To generate data for PK and PD modelling
- To assess patient-reported outcomes
- To evaluate the long-term efficacy and safety of IFX-1

3 STUDY DESIGN

3.1 Overall Design

This is a prospective, randomized, 2-period, placebo-controlled and double-blind (Main Period) and open-label (Maintenance Phase of Extension Period) multicenter study.

After establishing that the inclusion and exclusion criteria have been fulfilled at Screening (Sections 4.1 and 4.2), 175 subjects are planned to be randomized to receive double-blind treatment with IMP in 1 of 5 treatment cohorts in a ratio of 1:1:1:1:1.

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 areas affected by HS. Subjects who consent will have photographs taken at prespecified times (Section 8.2.2.13).

An independent, unblinded Data Monitoring Committee (DMC) will be established to allow regular monitoring of the study data in order to detect and report early evidence of unanticipated harm to subjects (Section 13.3).

Main Period (16 Weeks)

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).

During the Main Period, IMP (IFX-1 or placebo) will be administered in 5 treatment cohorts: placebo, IFX-1 400 mg q4w, IFX-1 800 mg q4w, IFX-1 800 mg q2w, and IFX-1 1200 mg q2w, as summarized in Table 2.

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

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])

- 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	

Exclusion Criteria	Rationale	Criteria Checked at	
		Screening	Day 1
4. Prior treatment with adalimumab or another biologic product during the 24 weeks before Screening	Safety concern	X	
5. Prior treatment with IFX-1	Safety concern	X	
6. 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	Effectiveness	X	
7. 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)	Effectiveness	X	
8. Prior treatment with any of the following medications during the 28 days before Screening: a. Any other systemic therapy for HS b. Any iv anti-infective therapy c. Phototherapy (UVB or psoralen and UVA)	Effectiveness	X	
9. Prior treatment with any of the following medications during the 14 days prior to IMP administration: a. Analgesics (including opioids) for HS-related pain b. Prescription-only topical therapies for HS c. Oral anti-infectives for infections other than HS	Effectiveness	X	
10. History of moderate to severe heart failure (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	Safety concern	X	

Exclusion Criteria	Rationale	Criteria Checked at	
		Screening	Day 1
11. One of the following abnormal laboratory findings: a. WBC < 2500/mm^3 b. Neutrophil count < 1000/mm^3 c. Serum creatinine > 3 × UNL d. Total bilirubin > 3 × UNL e. Alanine aminotransferase > 5 × UNL f. Aspartate aminotransferase > 5 × UNL g. Positive Screening test for HIV-1 or 2, or hepatitis B or C virus <u>For Canada only:</u> One of the following abnormal laboratory findings: a. WBC < 2500/mm^3 b. Neutrophil count < 1000/mm^3 c. Serum creatinine > 3 × UNL d. Total bilirubin > 1.5 × UNL e. Alanine aminotransferase > 2.5 × UNL f. Aspartate aminotransferase > 2.5 × UNL g. Positive Screening test for HIV-1 or 2, or hepatitis B or C virus	Safety concern	X	
12. 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	Safety concern	X	
13. 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 ECG	Safety concern		X

14. 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 IMP. <u>For France only:</u> the methods of contraception are applicable during the study and for at least 3 months after last administration of IMP.	Safety concern	X	X
15. History of drug or alcohol abuse during the 24 weeks before Screening	Safety concern	X	
16. Pregnancy, as verified by a positive pregnancy test, or nursing woman	Safety concern	X	X
17. Evidence or suspicion that the subject might not comply with the requirements of the study protocol	Safety concern	X	
18. Any other factor which, in the investigator's opinion, is likely to compromise the subject's ability to participate in the study	Safety concern	X	
19. The subject is an employee or direct relative of an employee at the study site or sponsor	Administrative	X	
20. The subject is imprisoned or lawfully kept in an institution	Administrative	X	
21. The subject has participated in a clinical study during the 3 months before Screening, or plans to participate in a clinical study	Administrative	X	
22. <u>For Denmark only:</u> Hypersensitivity to any excipients of IFX-1	Safety concern	X	

ECG = electrocardiogram, HIV = human immunodeficiency virus, HS = hidradenitis suppurativa, IMP = investigational medicinal product, iv = intravenous, NYHA = New York Heart Association, UNL = upper normal limit, UVA = ultra-violet A, UVB = ultra-violet B, WBC = white blood cell count.

4.3 Lifestyle Considerations

No restrictions pertaining to lifestyle and/or diet will apply during the study.

4.4 Screen Failures

Screen failures are defined as participants who consent to participate in the study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet

the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any non-treatment-emergent serious adverse event (SAE).

Subjects who do not meet the criteria for participation in this study (screen failure) may be rescreened once.

4.5 Rationale for Gender Distribution

No randomization stratified by gender is planned. All potential subjects will be asked for informed consent for participation in the study regardless of their gender. Because more women than men are affected by HS, a 2:1 distribution of women and men is expected to be enrolled in the study.

5 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

All IMP supplied by the sponsor for use in this study will have been manufactured, tested, and released according to the standards of Good Manufacturing Practice.

5.1 Investigational Medicinal Product

5.1.1 IFX-1

IFX-1 is a monoclonal anti-human C5a immunoglobulin as active pharmaceutical ingredient, which is formulated in a phosphate buffered saline and Polysorbate 80.

IFX-1 will be supplied in 10 mL glass vials at a concentration of 10 mg/mL (i.e., 100 mg per vial) for iv administration and will have the following composition:

Ingredient	Strength
IFX-1	10 mg/mL
Sodium chloride	150 mM
Sodium phosphate	10 mM
Polysorbate 80	0.05%

5.1.2 Placebo

Placebo will be supplied in 10 mL glass vials for iv administration and will have the following composition:

Ingredient	Strength
Sodium chloride	150 mM
Sodium phosphate	10 mM
Polysorbate 80	0.05%

The placebo vials and content have the same appearance as the IFX-1 vials and additives.

5.2 Packaging and Labeling

The IMP will be packaged in cardboard boxes and labeled in accordance with all legal requirements.

The cardboard boxes will be labeled with a unique number (“medcode”). The glass vials containing the IMP will be labeled with the same medcode as the cardboard box in which they are packed.

The labels are part of the Clinical Trial Application documentation.

5.3 Supply, Storage, and Accountability

5.3.1 Supply

The IMP will be supplied to study sites on behalf of the sponsor by Almac. The IMP should be shipped at a temperature of 2°C to 8°C, and should not be frozen. For each subject, the IMP will be sent from Almac to the study site after the subject has been enrolled into the study at Screening. Because it may take up to 10 days for the IMP to reach the study site, at least 10 days should be allowed between Screening and first administration of 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 the sponsor or the delegate at the earliest opportunity and the IMP should not be used.

The authorized personnel will be responsible for adequate handling 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.

5.3.2 Storage

The IMP must be stored between 2 and 8°C and should not be frozen.

To record the temperature, 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 Clinical Research Organization (CRO). At a minimum, the daily (working day) minimum and maximum temperatures must be documented.

All IMP supplies must be stored separately from normal hospital inventories, in a locked facility with access limited to authorized personnel.

5.3.3 Accountability

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, all records regarding the IMP will be provided to the sponsor, who will decide on the return or destruction of any unused IMP.

In case any unused IMP should be destroyed at the site, this destruction must be documented on the form provided by the sponsor for this purpose. If unused IMP cannot be destroyed at the site, it needs to be returned to the depot.

5.4 Reconstitution and Administration of the Investigational Medicinal Product

5.4.1 Reconstitution

The IMP will be prepared in a blinded manner at the study site or site pharmacy, respectively. Depending on the dose to be administered (Table 2 and Table 3), the amount of IMP for a single infusion is 400, 800, or 1200 mg IFX-1, or placebo. IMP or placebo will be diluted in sterile sodium chloride. To keep the blinding of site personnel and subjects, the total volume in the infusion bag for each infusion should be 250 mL. Details of IMP preparation and application will be outlined in the respective IMP manual.

5.4.2 Administration and Compliance

Main Period: after Screening, subjects will be randomized to 1 of 5 treatment cohorts in a ratio of 1:1:1:1:1 (Section 5.5) and then receive IMP in the 16-week Main Period as shown in Table 2.

Table 2 Dosing Schedule by Cohort in Main Period (Double-Blind)

	Induction Phase				**Maintenance Phase**						
Visit	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**
Week	**0**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**
Day	**1**	**4**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**
Cohort 1 (Placebo)	P	P	P	P	P	P	P	P	P	P	P
Cohort 2 (400 mg q4w)	**400**	**400**	P	P	**400**	P	**400**	P	**400**	P	**400**
	Cumulative IFX-1 dose: 2000 mg										
Cohort 3 (800 mg q4w)	**800**	**800**	**800**	P	**800**	P	**800**	P	**800**	P	**800**
	Cumulative IFX-1 dose: 4800 mg										
Cohort 4 (800 mg q2w)	**800**	**800**	**800**	**800**	**800**	**800**	**800**	**800**	**800**	**800**	**800**
	Cumulative IFX-1 dose: 8000 mg										
Cohort 5 (1200 mg q2w)	**800**	**800**	**800**	**1200**	**1200**	**1200**	**1200**	**1200**	**1200**	**1200**	**1200**
	Cumulative IFX-1 dose: 10,800 mg										

HiSCR = Hidradenitis Suppurativa Clinical Response; IMP = investigational medicinal product; P = infusion of placebo; q2w = every two weeks; q4w = every four weeks; V = scheduled visit for all subjects.
400, 800, or 1200 = infusion of 400, 800, or 1200 mg IFX-1.
NOTE: cumulative doses refer to the amount of IFX-1 (doses marked in bold) received at the time the primary efficacy endpoint is assessed at Week 16 (percentage of subjects with a response, as measured by HiSCR [Section 8.2.2.2]), before administration of IMP at Week 16.

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.

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

	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.

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

assignment is warranted. Subject safety must always be the first consideration in making such a determination.

If the investigator decides that unblinding is warranted, he or she should make every effort to contact the sponsor before unblinding a subject's treatment assignment unless this could delay emergency treatment. If a subject's treatment assignment is unblinded, the sponsor will be notified via the IRT and the subject should discontinue treatment. The date and reason why the blind was broken must be recorded in the source documentation and in the eCRF, as applicable.

5.6 Procedures in Case of Specific Side Effects

To date, IFX-1 has been tested in healthy subjects and subjects with early septic organ dysfunction, complex cardiac surgery, and HS. An overview of side effects (i.e., ADRs that occurred in these studies) is provided in the Investigator's Brochure.

If a side effect occurs or is suspected after administration of IMP, subjects must be closely monitored and carefully observed, and as applicable the side effect must be reported as an AE (Section 9). Any treatment deemed as medically appropriate should be initiated.

In case of the following specific types of side effects, the procedures reported below must be applied.

Infections: because IFX-1 blocks C5a, there is a theoretical risk of an increased rate of infections. Therefore, the investigator (and other health care professionals who take care of the subjects) should be alert to signs and symptoms of infections in general. In case a subject develops a clinical picture that is difficult to distinguish from that associated with invasive infection, routine blood cultures and early start of antibiotic treatment is recommended. In subjects with bacterial infection, depending on the severity of the infections, it is important that concomitant antibiotic therapy be administered during treatment with IFX-1 to ensure appropriate control of the source of the infection. The investigator should pay close attention to the choice of an appropriate broad spectrum antibiotic treatment according to applicable guidelines. The IMP can be temporarily or permanently interrupted at the investigator's discretion. Any invasive infection has to be reported as an adverse event of special interest (AESI) (Section 9.3).

Meningitis/Meningococcal Sepsis: in case of signs of meningitis at any time during the study period, the subject must be carefully observed and the guideline for "ambulatory acquired bacterial meningoencephalitis"[22] should be followed. This includes lumbar puncture, blood culture testing, immediate start of treatment with dexamethasone and iv antibiotics (combination therapy with ampicillin and 3rd generation cephalosporin), and search for infectious focus (e.g., computed tomography or magnetic resonance tomography). The IMP should be interrupted immediately in case of signs and symptoms of meningitis and withdrawn if meningitis is confirmed.

Infusion-Related Reactions/Anaphylactic Reactions and Acute Systemic Allergic Hypersensitivity: In case of any severe, acute systemic hypersensitivity reaction during, or shortly after, infusion of IFX-1, the infusion should be stopped immediately and the subject discontinued from further dosing. In such cases, subjects should be closely monitored for any changes in blood pressure, heart rate, metabolic conditions, or organ function, and appropriate measures should be taken to stabilize all vital signs. Fluid resuscitation may be needed, as well as vasopressor therapy or other measures to treat changes in blood pressure, vital signs, or metabolic conditions in general. In cases of emergency with immediate life-threatening potential such as cardiac arrest or similar life-threatening changes, appropriate cardio-pulmonary resuscitation should be started immediately according to applicable guidelines, or as established at the study sites through existing standard operating procedures or other algorithms for cardio-pulmonary resuscitation according to current recommended resuscitation guidelines.

For any potential infusion-related event, the physician should check for a potentially developing or existing anaphylactic reaction. In case an anaphylactic reaction is anticipated, 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 algorithms.

If the investigator abstains from further dosing, the subject should be discontinued from the study and handled as drop-out.

In case of an emergency or other situation in which it is medically imperative for the investigator to identify the IMP that a subject has received or is receiving during the Main Period and during the Induction Phase of the Extension Period, the procedure for emergency identification of IMP described in Section 5.5 must be followed.

5.7 Overdose

The consequences of an overdose with IFX-1 are not known.

If overdosing occurs or is suspected, subjects must be closely monitored and carefully observed for any symptoms. In case of any symptoms, treatment as deemed medically appropriate by the investigator should be initiated. Overdoses must be recorded as treatment-emergent adverse events (TEAEs).

5.8 Prior and Concomitant Therapy

Any medication, vaccine (including, but not limited to, over-the-counter or prescription medicines such as aspirin, antacids, vitamins, mineral supplements, and/or herbal supplements), or procedure (e.g., phototherapy or laser-surgical therapy) that the subject received during 3 months before Screening, at Screening, or receives during the study, must be recorded in the source documentation and in the eCRF, with details on the reason for use, date(s) of administration (with start and end dates), and dosing information, including dose, route, and frequency of administration.

5.8.1 Prior Therapy

Any prior treatment with phototherapy, laser-surgical therapy, or antibiotics (see Section 5.8.2.2) during at least the 3 months before Screening will be documented in the eCRF. Subjects must have been on a stable dose of doxycycline or minocycline during the 28 days before Screening (“as needed” dosing is not considered stable).

Any prior treatment with oral corticosteroids, immunosuppressive drugs, biologics, biosimilars, investigational treatment, any other systemic therapy for HS, any iv anti-infective therapy, analgesics (including opioids) for HS-related pain (see Section 5.8.2.3), prescription-only topical therapies for HS, and oral anti-infectives for infections other than HS during the 28 days before Screening will be documented.

Any biologic treatment for HS used previously, including details on reason for discontinuation will be documented.

All information on the use of prior medication will be recorded in the source documentation and in the eCRF.

Prior therapy should also include a detailed history of prior therapies used to treat HS.

All medications will be documented in the eCRF by verbatim name, dosing regimen, route of administration, start and end date of administration, and indication.

5.8.2 Concomitant Therapy

All concomitant therapy (including topical treatments for HS) taken during the study will be documented.

5.8.2.1 Wound Care

Concomitant use of wound care dressings on HS wounds is permitted but is limited to alginates, hydrocolloids, and hydrogels.

5.8.2.2 Antibiotic Therapy

Concomitant use of permitted oral antibiotic therapy for treatment of HS is permitted provided the dosing regimen (dose and frequency) has been stable during the 28 days before Screening (refer to exclusion criterion #6, Section 4.2). The dosing regimen must remain stable throughout study participation. Antibiotics taken on an “as needed” basis are not considered a stable dose.

Permitted oral concomitant antibiotics include:

- Doxycycline (at an oral dose of up to 100 mg twice daily)
- Minocycline (at an oral dose of up to 100 mg twice daily)

An adequate test of oral antibiotic therapy is considered to be at least 90 days in duration. If, after ≥ 90 days of oral antibiotic therapy, any of the following has occurred, the subject will be considered to have had an inadequate response, or loss of response, to oral antibiotics:

- Progression of Hurley Stage (i.e., the Hurley Stage of at least 1 affected anatomic region has progressed from II to III or, after having improved to I during the study [inclusion criterion #4, Section 4.1], progressed from I to II or from I to III)
- Subject requires at least 1 intervention (e.g., incision and drainage or intralesional injection of corticosteroid)
- Subject experiences pain interfering with activities of daily living, with unsatisfactory relief from over-the-counter analgesics (e.g., ibuprofen or acetaminophen)
- Subject experiences pain requiring opioids, including tramadol
- Subject experiences drainage interfering with activities of daily life (e.g., requires multiple dressing changes and/or change of clothes daily)
- Subject experiences an increase in the number of anatomic regions affected by HS
- Subject experiences at least 1 new abscess or 1 new draining fistula

A subject is defined as intolerant to oral antibiotic therapy when the therapy has been discontinued by a physician as a result of a significant adverse reaction to the therapy in question.

An adverse reaction is considered significant if it is at least moderately severe (i.e., the reaction causes discomfort and interrupts the subject's usual activities or functions). Examples of significant adverse reactions include, but are not limited to, the following:

- Nausea resulting in decreased oral intake
- Macular or papular eruption or erythema with pruritus or other associated symptoms
- Dizziness, disequilibrium, lightheadedness, or vertigo interfering with function
- Allergic reaction manifesting as rash, flushing, urticaria, dyspnea, or fever ≥ 38°C

- Diarrhea with a stool frequency of at least 4 stools per day
- The inadequate response, loss of response, or intolerance to antibiotics is decided upon at the discretion of the investigator.

5.8.2.3 Analgesic Therapy

Subjects who received prior analgesic therapy will be required to washout all analgesics during the 14 days before starting treatment with IMP on Day 1. This includes analgesics for HS-related pain and other pain (non-HS-related).

If a subject's pain (HS-related or non-HS-related) worsens after Day 1, they may initiate analgesic therapy at any time during the study as follows:

For HS-related pain, permitted analgesics are limited to:

- Ibuprofen (at an oral dose of up to 800 mg every 6 h), not to exceed 3.2 g/24 h, or lower, according to the maximum dose allowed per local requirements
- Acetaminophen as per local labeling
- Tramadol (at an oral dose of up to 100 mg every 4 h), not to exceed 400 mg/24 h, in case of HS-related pain that remains uncontrolled with ibuprofen or acetaminophen given according to the dosing regimens above after Day 1

Dose adjustments of ibuprofen, acetaminophen, or tramadol and use of these analgesics as needed for HS-related pain up to the maximum permitted dose and frequency are permitted during the study.

Subjects will be required to report taking any analgesics. All use of analgesics and any dose adjustments will be recorded in the source documentation and in the eCRF.

For non-HS-related pain:

- Oral opioid analgesics are prohibited
- All other analgesics (including tramadol) are allowed at the recommended or prescribed dose

5.8.2.4 Lesion Intervention

In case an acutely painful lesion occurs that requires immediate intervention, physicians may perform either of the following permitted interventions:

- Injection with intralesional triamcinolone acetonide suspension (at a concentration of up to 5 mg/mL, up to 1 mL), and incision and drainage
- If incision and drainage are performed, an over-the-counter antiseptic wash should be used. New systemic and topical therapies following incision and drainage (including antibiotics) are not permitted. Concomitant use of wound care dressings is allowed, but limited to alginates, hydrocolloids, and hydrogels

Subjects should continue using any ongoing oral and topical treatment (with the constraints described in Section 5.8.3) during the study.

The use of concomitant therapy associated with the lesion intervention(s) must be captured in the source documentation and in the eCRF.

Main Period: a total of 2 permitted interventions are allowed during the Main Period. An intervention can be applied to a maximum of 2 different lesions at the same visit to the study site, or to the same lesion at 2 different visits. The same lesion cannot be treated twice at the

same visit. If a subject requires more than 2 interventions within the first 16 weeks of the study, then they must be discontinued from the study.

Extension Period: a maximum of 2 interventions are permitted every 4 weeks during the Extension Period. An intervention can be applied to a maximum of 2 different lesions at the same visit to the study site, or to the same lesion at 2 different visits. Within each 4-week period, the same type of intervention cannot be applied twice on the same lesion. If a subject requires more than 2 interventions within a 4-week period, or has 2 of the same interventions for the same lesion within a 4-week period, then they must be discontinued from the study.

All the assessments and procedures scheduled for a given visit to the study site must occur before any interventions are applied. Any lesion that undergoes an intervention will be documented. The site will be required to count any lesion that undergoes an intervention as permanently present from the date of intervention, and must account for it in the source documentation and in the eCRF.

5.8.3 Prohibited Therapy

The following therapies are prohibited for all subjects during the study:

- Phototherapy (UVB or psoralen and UVA)
- All biologic therapy with a potential therapeutic impact on the disease being studied including, but not limited to, the following:
    - Abatacept (Orencia®)
    - Anakinra (Kineret®)
    - Belimumab (Benlysta®)
    - Certolizumab pegol (Cimzia®)
    - Efalizumab (Raptiva®)
    - Etanercept (Enbrel®)
    - Golimumab (Simponi®)
    - Infliximab (Remicade®)
    - Natalizumab (Tysabri®)
    - Rituximab (Rituxan®)
    - Tocilizumab (Actemra®)
    - Ustekinumab (Stelara®)
- Any investigational agent
- Any other systemic medication for HS, including, but not limited to, antibiotics (except as specified in Section 5.8.2.2), methotrexate, cyclosporine, retinoids, and fumaric acid esters
- Oral or injectable corticosteroids
- Oral analgesics for HS not listed in Section 5.8.2.3
- Oral opioid analgesics for non-HS-related pain (for HS-related pain, see Section 5.8.2.3)
- New prescription topical therapies for HS
- Over-the-counter topical antiseptic washes, creams, soaps, ointments, gels, and liquids containing antibacterial agents to treat HS, not listed in Section 5.8.2
- Surgical or laser intervention for an HS lesion

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

6 DISCONTINUATION OF STUDY INTERVENTION

6.1 Discontinuation of Study

The study may be discontinued by the sponsor at any site in case 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 clinical monitor 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 will promptly inform the competent regulatory authorities of the discontinuation and its reason(s), and the investigator or sponsor will promptly inform the Institutional Ethics Committee.

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

6.2 Discontinuation of Individual Subject Participation

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 at the end of the study (i.e., at Week 44) at the time when the subject's participation in the study is discontinued. Subjects who have been discontinued from the study will have a Post-Treatment FUV 3 months after discontinuation or when another HS therapy has been started.

6.2.1 Withdrawal of Informed Consent

Subjects may discontinue their participation in the study by withdrawing their consent at any time without giving reasons. Nevertheless, they should be asked about the reason for discontinuation after being informed that they do not need to do so. Information as to when they withdrew consent must be documented.

Subjects are to be informed that when consent is withdrawn, the stored and captured data as well as blood samples taken until the time of termination may be used further to:

- Assess effects of the IMP being tested

- Guarantee that the subject's personal interests are not adversely affected
- Comply with the requirement to provide complete documentation when seeking marketing authorization

6.2.2 Discontinuation of Treatment With Investigational Medicinal Product

Subjects must be discontinued from treatment with the IMP under any of the following circumstances:

- 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 necessitates the subject being removed
- Application of lesion interventions exceeding the permitted number (see section 5.8.2.4)
- Biopsy confirmation of any malignancy
- Pregnancy
- Subjects who receive 800mg q4w and have a loss of response (see Definition of Terms) during the Extension Period 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 receive 800mg q2w and experience WOAI (see Definition of Terms) at 2 consecutive visits in the Maintenance Period of the Extension Period will be discontinued from the study

Subjects who have been discontinued will have a Post-Treatment FUV 3 months after discontinuation or when another HS therapy has been started.

6.2.3 Omitted Investigational Medicinal Product Infusions

Subjects who omit more than 2 scheduled infusions during either the Main Period or during the Extension Period will be discontinued from the study.

6.2.4 Lost to Follow-Up

Lost to follow-up is defined as an unsuccessful attempt at contacting a subject after that subject has withdrawn consent and/or discontinued from treatment with the IMP.

At least 3 phone calls at 3 different times on consecutive days, and a further phone call a week later, should be performed, and if all are unsuccessful at contacting the subject then that subject is to be declared as lost to follow-up.

The date of being lost to follow-up is defined as the last date with any assessment of the subject.

7 STUDY ASSESSMENTS AND PROCEDURES

7.1 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 between 28 days and 10 days before first administration of IMP. The findings from the Screening procedures will be documented in the Subject Screening/Enrollment Log.

For each subject, the IMP will be sent from Almac to the study site after the subject has been enrolled into the study at Screening. 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.

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 1 or both 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

After subjects have provided written informed consent, potentially eligible subjects 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
- Review all inclusion and exclusion criteria (see Sections 4.1 and 4.2)
- Serum pregnancy test, required for all women of childbearing potential
- Blood sample for analysis of safety laboratory parameters
- Blood sample to test for human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV)
- Medical and surgical history during the 6 months before Screening
- Review and record prior therapy for chronic diseases taken during the 3 months before Screening
- Review and record prior and concomitant therapy as specified in the exclusion criteria (Section 4.2)
- Demographics and baseline characteristics
- HS medical and surgical history
- Physical examination
- 12-lead Electrocardiogram (ECG)
- Vital signs
- HS clinical parameters
- Erythema assessment

- 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])*

- 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:

- Administration of IMP according to the dosing schedule shown in Table 2 *(Weeks 0 [Days 1 and 4], 1, 2, 4, 6, 8, 10, 12, 14, 16)*

After administration of IMP:

- Citrate plasma sample for analysis of IFX-1, to be taken after end of IMP administration (+ 10 min) using a separate infusion line *(Weeks 0 [Day 4], 2)*
- *For subjects participating in the PK substudy*: citrate plasma samples for analysis of IFX-1 will be taken 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 *(Weeks 2, 16)*

7.3 Extension Period (28 Weeks)

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 still have a loss of response at the optional visit will be discontinued from the study and will not switch to the non-responder schedule.

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.

Subjects who have been discontinued will have a Post-Treatment FUV 3 months after discontinuation or when another HS therapy has been started.

Due to the distinction between subjects according to their HiSCR responder status at Week 16, separate Schedules of Assessments are available for HiSCR responders (Schedule of Assessments - Extension Period (HiSCR Responders at Week 16)]) and HiSCR non-responders (Schedule of Assessments - Extension Period (HiSCR Non-Responders at Week 16)]).

HiSCR Responders at Week 16

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

- Urine pregnancy test, required for all women of childbearing potential (Weeks 20, 24, 28, 32, 36, 40), only applicable for France
- Blood sample for analysis of safety laboratory parameters *(Weeks 20 [Denmark and France], 24 [France only], 28 [France only], 32, 36 [France only], 40 [France only])*
- Physical examination *(Week 32)*
- ECG *(Week 32)*
- Vital signs *(Weeks 20, 24, 28, 32, 36, 40, and at optional visits)*
- HS clinical parameters *(Weeks 20, 24, 28, 32, 36, 40, and at optional visits)*
- Erythema assessment *(Weeks 20, 24, 28, 32, 36, 40, and at optional visits)*
- Continue documentation of patient-reported outcomes:

- Patient's Global Assessment of Skin Pain (NRS) *(daily in e-diary throughout Extension Period)*
- Analgesic therapy *(daily in e-diary throughout Extension Period)*
- Patient's Assessment of Drainage *(daily in e-diary throughout Extension Period)*
- DLQI *(Week 32)*
- HADS *(Week 32)*
- SF-36v2 *(Week 32)*
- EQ-5D-5L *(Week 32)*

- Citrate plasma sample for analysis of:
  - IFX-1 *(Weeks 20, 24, 28, 32, 36, 40)*
- Plasma sample for analysis of:
  - C3a *(Week 32)*
  - C5a (*Weeks 24, 32*)
- Serum and plasma biomarker sample *(Week 32), not applicable for Denmark*
- Serum sample for analysis of:
  - CH50 *(Week 32)*
  - CRP *(Weeks 20 [France only], 24 [France only], 28 [France only], 32, 36 [France only], 40 [France only])*
  - ADAs *(Weeks 24, 32)*
- Photographic documentation of affected areas (*Weeks 24, 32*)
- Documentation of AEs *(Weeks 20, 24, 28, 32, 36, 40, and at optional visits)*
- Documentation of concomitant therapy *(Weeks 20, 24, 28, 32, 36, 40, and at optional visits)*

After the assessments and procedures listed above have been completed:

- Administration of IMP according to the dosing schedule shown in Table 3 *(Weeks 20, 24, 28, 32, 36, 40 for q4w dosing)*

HiSCR Non-Responders at Week 16

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

- Urine pregnancy test, required for all women of childbearing potential (Weeks 20, 24, 28, 32, 36, 40), only applicable for France
- Blood sample for analysis of safety laboratory parameters *(Weeks 20 [Denmark and France], 24 [France only], 28 [France only], 32, 36 [France only], 40 [France only])*
- Physical examination *(Week 32)*
- ECG *(Week 32)*
- Vital signs *(Weeks 18 [Days 127 and 130], 19, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40)*
- HS clinical parameters *(Weeks 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40)*
- Erythema assessment *(Weeks 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40)*

- Continue documentation of patient-reported outcomes:
    - Patient's Global Assessment of Skin Pain (NRS) *(daily in e-diary throughout Extension Period)*
    - Analgesic therapy *(daily in e-diary throughout Extension Period)*
    - Patient's Assessment of Drainage *(daily in e-diary throughout Extension Period)*
    - DLQI *(Week 32)*
    - HADS *(Week 32)*
    - SF-36v2 *(Week 32)*
    - EQ-5D-5L *(Week 32)*
- Citrate plasma sample for analysis of:
    - IFX-1 *(Weeks 18 [Days 127 and 130], 19, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40)*
- Plasma sample for analysis of:
    - C3a *(Week 32)*
    - C5a (*Weeks 18 [Day 127], 24, 32*)
- Serum and plasma biomarker sample *(Week 32), not applicable for Denmark*
- Serum sample for analysis of:
    - CH50 *(Week 32)*
    - CRP *(Weeks 20 [France only], 24 [France only], 28 [France only], 32, 36 [France only], 40 [France only])*
    - ADAs *(Weeks 18 [Day 127], 24, 32)*
- Photographic documentation of affected areas (*Weeks 18 [Day 127], 24, 32*)
- Documentation of AEs *(Weeks 18 [Days 127 and 130], 19, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40)*
- Documentation of concomitant therapy *(Weeks 18 [Days 127 and 130], 19, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40)*

After the assessments and procedures listed above have been completed:

- Administration of IMP according to the dosing schedule shown in Table 3 *(Weeks 18 [Days 127 and 130], 19, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40)*

After administration of IMP:

- Citrate plasma sample for analysis of IFX-1, to be taken after end of IMP administration (+ 10 min) using a separate infusion line *(Week 18 [Day 130])*

Follow-Up Visit at Week 44 (Safety Follow-Up)/3-Month Post-Treatment Follow-Up Visit

The following assessments and procedures will be performed at the FUV to the study site at Week 44, as indicated:

- Blood sample for analysis of safety laboratory parameters
- Serum pregnancy test, required for all women of childbearing potential
- Physical examination

- ECG
- Vital signs
- HS clinical parameters
- Erythema assessment
- Conclude 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*)
    - DLQI
    - HADS
    - SF-36v2
    - EQ-5D-5L
- Citrate plasma sample for analysis of:
    - IFX-1
- Plasma sample for analysis of:
    - C3a
    - C5a
- Serum and plasma biomarker sample, *not applicable for Denmark*
- Serum sample for analysis of:
    - CH50
    - CRP
    - ADAs
- Photographic documentation of affected areas
- Conclude documentation of AEs
- Conclude documentation of concomitant therapy

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. The subjects will be asked about any AEs and any concomitant therapy used since the previous visit to the study site.

7.4 Unscheduled Visits

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

The following assessments and procedures will be performed at USVs to the study site, as indicated:

- Vital signs
- HS clinical parameters

- 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

- 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.

- Number and type of lesions (i.e., abscesses, inflammatory nodules, non-inflammatory nodules, non-draining fistulas, draining fistulas, hypertrophic scars, other lesions [folliculitis, pustules])
- Longest distance between 2 relevant lesions (mm)
- Are lesions clearly separated by normal skin? (yes/no)

8.2.2.2 Hidradenitis Suppurativa Clinical Response (HiSCR)

The HiSCR is defined by the status of 3 types of lesions [20]:

- Abscesses
- Inflammatory nodules
- Draining fistulas

The definition for response to treatment based on HiSCR relative to Day 1 is:

- At least 50% reduction in AN count
- No increase in number of abscesses
- No increase in number of draining fistulas

A subject is considered to be a HiSCR responder only if all 3 criteria above are fulfilled. If any 1 of the 3 criteria is missing, the HiSCR response will be recorded as missing. Additionally, the HiSCR25 response will be calculated. The definition of a HiSCR25 responder relative to Day 1 is:

- An at least 25% reduction in AN count
- No increase in number of abscesses
- No increase in number of draining fistulas

A subject is considered to be a HiSCR25 responder only if all 3 criteria above are fulfilled.

The HiSCR will be assessed at each of the prespecified times when the HS clinical parameters are scheduled to be assessed during the study after Day 1, as outlined in the Schedules of Assessments. The score will be calculated using data recorded for HS clinical parameters in the eCRF (Section 8.2.2.1).

8.2.2.3 Hidradenitis Suppurativa-Physician's Global Assessment (HS-PGA)

The HS-PGA is a physician-rated HS disease severity scale with a score ranging from 0 (least severe) to 5 (most severe) based on counts of abscesses, draining fistulas, inflammatory nodules, and non-inflammatory nodules measured as HS clinical parameters (Appendix 17.2). The HS-PGA will be calculated based on the HS clinical parameters at each of the prespecified times when the HS clinical parameters are scheduled to be assessed during the study, as outlined in the Schedules of Assessments. Lesions are counted by considering all anatomical regions.

A further efficacy endpoint is the achievement of clear or minimal severity among subjects with at least 2 grades of improvement (reduction) from Day 1 to each time point.

8.2.2.4 Modified Sartorius Score (mSS)

The mSS is a summation of HS lesions based on a number of factors including anatomical region, number and type of lesions, and distance between relevant lesions measured as HS

clinical parameters [23]. The mSS has a minimum value of 0 and no upper limit and is calculated using data recorded for HS clinical parameters in the eCRF (Section 8.2.2.1) according to the algorithm in Appendix 17.3.

The mSS and the corresponding change from Day 1 will be assessed at each of the prespecified times when the HS clinical parameters are scheduled to be assessed during the study, as outlined in Schedules of Assessments.

8.2.2.5 Lesions

Lesion counts are defined as the number of all abscesses, inflammatory nodules, non-inflammatory nodules, non-draining fistulas, draining fistulas, hypertrophic scars, and other lesions. Lesion counts will be recorded at each of the prespecified times when the HS clinical parameters are scheduled to be assessed during the study (as outlined in the Schedules of Assessments).

8.2.2.6 Erythema Assessment

For each anatomic region affected by HS, the investigator will assess the overall degree of erythema using a 4-point ordinal scale ranging between 0 and 3 (0 = no redness, 1 = faint but discernible pink coloration, 2 = moderate red coloration, 3 = very red or bright red coloration) (Appendix 17.4) through Week 44 (as outlined in the Schedules of Assessments) or early discontinuation visit and the 3-month Post-Treatment Follow-Up visit if the subject discontinues before Week 44.

The erythema assessment will be used to assess the worst and average degree of erythema for each affected anatomic region and overall.

8.2.2.7 Patient's Assessment of Drainage

The Patient's Assessment of Drainage (Appendix 17.5) will be assessed daily by subjects in an e-diary from Screening through the FUV at Week 44

The Patient's Assessment of Drainage will be used to assess the amount of drainage due to HS. Ratings affected by HS will range from 0 (no drainage) to 10 (drainage as bad as you can imagine).

8.2.2.8 Analgesic Therapy

Subjects will be required to report taking any analgesics. All use of analgesics and any dose adjustments will be recorded in the source documentation and in the eCRF. For further details refer to section 5.8.2.3.

8.2.2.9 Patient's Global Assessment of Skin Pain (NRS)

The Patient's Global Assessment of Skin Pain (NRS) (Appendix 17.6) will be assessed by subjects every day in an e-diary from Screening through the FUV at Week 44.

The NRS will be used to assess the worst and average skin pain due to HS. Ratings for these 2 items range from 0 (no skin pain) to 10 (skin pain as bad as you can imagine).

Subjects should be instructed to respond to the items based on a recall period of the "last 24 h". They should also document any analgesic therapy in the e-diary.

8.2.2.10 Dermatology Life Quality Index (DLQI)

The DLQI 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 DLQI will be assessed by subjects on Day 1 (Week 0) 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.

A score is documented for each of the 10 DLQI items, ranging from 0 to 3 for each item. The total score is the sum of the responses to all 10 DLQI items, ranging from 0 to 30. A higher score corresponds to worse HRQL [20]. Guidelines with regard to the scoring of each question and the handling of incorrectly completed questionnaires are taken from the DLQI manual (http://sites.cardiff.ac.uk/dermatology/quality-of-life/dermatology-quality-of-life-index-dlqi/dlqi-instructions-for-use-and-scoring/). Details of the subject questionnaire and the evaluation of the total DLQI score are available in Appendix 17.7.

The DLQI score yields an efficacy endpoint.

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.

8.2.2.11 Hospital Anxiety and Depression Scale (HADS)

Subjects will complete the HADS questionnaire (Appendix 17.8) on Day 1 (Week 0) 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. The HADS is a subject-rated scale designed to screen for anxiety and depressive states. It consists of 2 sub-scales: the D-scale measures depression and the A-scale measures anxiety. Each sub-scale contains 7 items and each item is rated from 0 (absent) to 3 (maximum severity). The score of each sub-scale ranges from 0 to 21.

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.

8.2.2.12 36-Item Short Form Survey (SF-36v2)

Subjects will complete the SF-36v2 questionnaire (Appendix 17.9) on Day 1 (Week 0) 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. The SF-36v2 is a subject-reported generic measurement of health status that has proven useful in studies of both general and specific populations, comparing the relative burden of diseases and the health benefits produced by different treatments [24].

The SF-36v2 consists of 36 questions from the following 8 domains: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health.

Each domain is directly transformed into a scale from 0 to100 on the assumption that each question carries equal weight. A lower score indicates a poorer health status; a higher score indicates a better health status (i.e., a score of 0 is equal to maximum disability and a score of 100 is equal to no disability). The 8 domains are summarized to form 2 distinct higher-ordered clusters (physical health and mental health).

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.

8.2.2.13 EuroQol-5L Dimensions Survey (EQ-5D-5L)

Subjects will complete the EQ-5D-5L questionnaire (Appendix 17.10) on Day 1 (Week 0), 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. The EQ-5D-5L is a standardized subject-reported measure of health status in terms of quality-of-life parameters, such as the subject's mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. There are 5 categorical response choices for each of the 5 measures. In addition, subjects are asked to indicate "the state of your health today" on a visual analog scale of 0 to 100 (0 = worst imaginable health state, 100 = best imaginable health state) [25].

The EQ-5D-5L relates to the respondent's situation at the time the assessment is completed, therefore the subject does not need to recall their health status over the preceding days or weeks.

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.

8.2.2.14 Photographic Documentation of Affected Areas

Subjects at prospectively selected sites may be asked to have photographs taken of the affected areas during the study. Subjects who consent will have photographs taken 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. No formal analysis is foreseen.

8.3 Safety Variables

8.3.1 Overview of Variables

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

- AEs
- Physical examination
- Vital signs
- ECG
- Laboratory safety parameters
- Pregnancy test
- Status of HIV, HBV, and HCV status at Screening
- ADA status

8.3.2 Methods of Assessment

8.3.2.1 Adverse Events

The incidence, severity, and causality of AEs will be assessed at every visit from signature of the informed consent form at Screening to the subject's last evaluation according to the procedures described in Section 9.

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.

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.

Analyses for the presence of anti-hepatitis C antibodies in serum will be conducted by a central laboratory using a standard chemiluminescence assay.

8.3.2.8 Antidrug Antibodies

ADAs will be assessed on Day 1 (before first administration of IMP) and during the study at prespecified times through Week 44 (as outlined in the Schedules of Assessments). A portion of the samples will be collected for possible future analysis; this is not applicable for patients in Denmark.

In addition, serum samples for future research taken at Week 2 (Day 15) will be used for ADA measurement.

ADAs will be measured in serum samples at a specialized laboratory using a validated homogeneous electrochemiluminescence-based bridging enzyme-linked immunosorbent assay for initial detection as well as an additional confirmatory assay in case of positive findings detected in the initial test. Samples that are confirmed as ADA-positive will be quasi-quantified by titration.

8.4 Pharmacokinetics and Pharmacodynamics

8.4.1 Overview of Variables

PK will be assessed on the basis of IFX-1 concentrations.

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

- Complement factors C3a and C5a
- CH50
- CRP

8.4.2 Methods of Assessment

8.4.2.1 Pharmacokinetic Variables

Concentrations of IFX-1 in citrate plasma will be analyzed on Day 4 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.

In the PK substudy, the PK of IFX-1 will be assessed in approximately 10 subjects from each Cohort at Weeks 2 and 16 of the Main Period. At these times, blood samples will be obtained for the analysis of IFX-1 in citrate plasma before IMP infusion (0 h) and at 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.

IFX-1 will be analyzed by a specialized laboratory with an ELISA test system.

8.4.2.2 Pharmacodynamic Variables

The PD variables will be assessed on Day 1 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.

Complement factor C3a will be analyzed in plasma samples by a specialized laboratory with an ELISA test system.

Complement factor C5a will be analyzed in plasma samples by the specialized laboratory at InflaRx with an ELISA test system.

Total complement hemolytic activity CH50 will be analyzed in serum samples by the central laboratory with a liposome immunoassay.

CRP will be analyzed in serum samples by the central laboratory with a standard assay.

8.4.2.3 Serum and Plasma Biomarker Variables

Samples to assess serum and plasma biomarkers will be taken on Day 1 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.

The collection of serum and plasma biomarker samples are not applicable for Denmark.

Samples may be analyzed for plasma and serum proteins, peptides, and non-protein soluble factors such as lipids that could help predict disease behavior or help determine more severe disease phenotypes. The samples may be analyzed as part of a multi-study assessment of factors involved in the response to IFX-1. The samples may also be used for the development of diagnostic tests related to IFX-1. The results of any such analyses may be reported separately.

Serum samples taken at Week 2 (Day 15) will be used for ADA measurement (Section 8.3.2.8).

9 ADVERSE EVENTS

9.1 Adverse Events

9.1.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a subject administered an IMP; an AE does not necessarily have to have a causal relationship with this treatment.

AEs encompass any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease that arises or worsens after the inclusion of the subject into the study.

AEs may include:

- The significant worsening of the disease or symptoms of the disease under investigation following administration of an IMP
- Illnesses that coincide with an onset after administration of an IMP
- Exacerbation (i.e., increase in frequency or severity) of a pre-existing condition. Chronic illnesses present prior to study entry, other than the indication being investigated, should be recorded in the medical history page of the eCRF and only be reported as AEs if there is an increase in the frequency or severity of the condition during the study
- For laboratory safety parameters, any absolute values outside of the reference range or changes after initial administration of the IMP that are considered by the investigator as CS must be recorded in the eCRF as AEs if not previously documented as ongoing medical conditions or as ongoing AEs. Examples of laboratory abnormalities that should be considered as AEs include those that result in discontinuation of treatment with the

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:

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)

9.2 Serious Adverse Events

9.2.1 Definition of Serious Adverse Events

An AE is defined as serious (i.e., as an SAE) according to the ICH E2A guideline if any of the following criteria are fulfilled:

- Results in death
- Is life-threatening

  NOTE: the term “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 had it been more severe
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above

Medical and scientific judgement should be exercised in deciding whether expedited 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 intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

The following hospitalizations are not considered to be serious AEs because there is no “adverse event” (i.e., there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalization for respite care
- Hospitalization planned prior to informed consent (where the condition requiring the hospitalization has not changed after administration of IMP)

9.2.2 Documentation and Reporting Obligations of Serious Adverse Events

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

Any SAE 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 study completion.

SAEs have to be documented on “SAE forms” and the investigator must report them immediately to the CRO, or no later than 24 h after becoming aware of the SAE. If more information about the SAE becomes available later, this must also be reported immediately or no later than 24 h after becoming aware of the SAE.

In case of a subject’s death, the investigator will provide the applicable Ethics Committee(s) and the applicable responsible authorities with any further information requested.

In all reports, personal data are to be anonymized by using the subject identification number. It must be possible to relate the initial and all follow-up reports to each other by means of the subject identification number, or name and address, or the like.

The investigator must report all SAEs to the following address:

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

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

- 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.

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.

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

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

deviation, minimum, median, maximum, lower quartile, upper quartile, geometric mean) by time point.

All PD parameters will be analyzed based on the FAS with all values and assessments available. Some analyses may be repeated for the PPS.

10.6 Demographics and Baseline Characteristics

Baseline characteristics and demographic information (including medical/HS history and surgeries) will be summarized by cohort and overall. A baseline measurement will be defined as the latest measurement obtained prior to the first administration of IMP, if applicable.

10.7 Prior and Concomitant Therapies

Prior and concomitant therapies will be summarized by absolute and relative frequencies by cohort and overall. Therapies will be defined as concomitant if the start or end date is later than the date of first IMP administration, or if no end date is available (ongoing therapy).

10.8 Subject Disposition

The disposition of subjects who were enrolled (i.e., signed the informed consent form) in the study as well as reasons for discontinuation from study and from treatment will be summarized for each cohort.

10.9 Treatment Exposure

The administration of IMP will be summarized by cohort and will include the number and percentage of subjects completing each treatment visit. The actually received cumulative dose in mg relative to the planned cumulative dose will be calculated per subject and will be summarized for each cohort.

10.10 Handling of Missing Data

Data imputation rules are defined for missing values for the primary efficacy endpoint of percentage of subjects with a response, as measured by HiSCR at Week 16. Subjects with missing baseline assessments (baseline assessments might be obtained at Screening or at Day 1 before first infusion of IMP) necessary for the calculation of the HiSCR at Week 16 will not be randomized (i.e., there shall be no missing baseline values for HiSCR). Missing values for assessments at Week 16 necessary for the calculation of HiSCR at Week 16 will be replaced by multiple imputation, as described in section 10.5.1.

All other missing data will not be replaced.

Sensitivity analyses will be conducted based on the PPS. Further sensitivity analyses (e.g., evaluating patients with missing HiSCR at Week 16 as non-responders) will be defined in the statistical analysis plan if deemed necessary.

10.11 Interim Analysis

No formal interim analysis is planned for this study. The database will be locked for the analysis of the Main Period when all data up to and including Week 16 have been collected and cleaned, and the BDRM has taken place. All endpoints in the Main Period will be analyzed after unblinding, which will take place after all subjects have completed the assessments at Week 20 due to operational reasons. A database snapshot will be performed during the Extension

Period. A second database lock will be performed after all data of the Extension Period have been collected and cleaned, and the corresponding analyses of endpoints will be performed.

An independent, unblinded Data Monitoring Committee (DMC) will receive data for safety reviews at prespecified time points in order to detect and report early evidence of unanticipated harm to subjects (see Section 13.3). To maintain the blind, the data for the safety reviews will be delivered by an unblinded CRO biostatistics team located at a different geographical site to the blinded CRO biostatistics personnel involved in the study.

11 ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

11.1 Good Clinical Practice Statement

All persons participating in the conduct of the study (sponsor, investigators, etc.) commit themselves to observe the Declaration of Helsinki (version Fortaleza 2013) as well as all pertinent national laws and the ICH guidelines for GCP issued in June 1996 and CPMP/ICH/135/95 from September 1997.

11.2 Submission to the Ethics Committee and Responsible Regulatory Authority

The protocol and other associated documents will be submitted to the applicable Ethics Committee for approval. The study documents will be submitted to the applicable regulatory authority.

The study can only start after obtaining a positive evaluation by the applicable Ethics Committee and approval from the applicable regulatory authority. The written approval of the applicable Ethics Committee 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.

11.3 Subject Information and Informed Consent

The investigator must explain to each study subject 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. They must be informed that participation in the study is voluntary, that they may withdraw their consent to participate at any time, and that withdrawal of consent will not affect the subsequent medical treatment of the study subject or the relationship to the treating physician.

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 informed consent of the subject must also refer specifically to the assessment and processing of data on the subject's health. The subject is to be informed explicitly on the purpose and extent of the assessment and the use of their personal data, especially the health-related data.

Subjects may also be asked to provide informed consent to have photographs taken of their disease response during the study.

An additional informed consent form respecting the principles described above will be used for subjects participating in the PK substudy.

11.4 Protocol Amendments

Changes made to the protocol that was appraised positively by the Ethics Committee and approved by the responsible federal authority must be positively reappraised and approved by the Ethics Committee and the responsible federal authority if the changes:

- Are such that they may affect the subjects' safety
- Are fundamental to the therapeutic procedures
- Result in further data collection that necessitates changes to the subject information and/or informed consent form
- Affect the interpretation of the scientific documents upon which the study is based or the significance of the results of the study
- Significantly affect the leadership or conduct of the study
- Concern the quality or the innocuousness of the investigational drug

Protocol amendments need the authorization of the sponsor, the coordinating investigator, and the responsible biostatistician, if applicable. All protocol amendments will be:

- Submitted to the Ethics Committee and, where applicable, to the responsible federal authority
- Provided in written form to the responsible parties
- Filed in the trial master file

12 DOCUMENTATION

12.1 Electronic Case Report Forms

All data beside ePRO required by this clinical study protocol will be collected in an eCRF and entered into a database validated by the CRO for eCRFs.

The sponsor or its designee will supply the study site with eCRFs. The sponsor or its designee will make arrangements to train appropriate study site personnel in the use of the eCRF.

These eCRFs are used to transmit information collected on the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English.

Data entered in the eCRF will be stored in a centralized database on a remote server. Data will be entered by study site personnel who can access the system through a personal user identification and password assigned by the system administrator.

Data will be entered directly into the eCRF via a single data entry process. In the eCRF, subjects will be identified by their subject numbers. The eCRF is to be dated and signed by the investigator or a qualified person who has been delegated by the investigator to do so on his/her behalf, as documented on a signature delegation log filed in the investigator site file.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data and questionable values. Queries may be issued by sponsor personnel (or designees) and will be answered by the site.

Corrections to the eCRF database are recorded in an audit trail that captures a complete record of all information. The new information, identification of the person making the correction, the date the correction was made, and the reason for change are captured in a new record.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the principal investigator must retain full responsibility for the accuracy and authenticity of all data entered into the eCRFs.

The eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the clinical monitor. The sponsor and/or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

Further information on handling of the eCRF data (e.g., data entry, clarification, and validation) will be defined in the data management plan.

12.2 Archiving

Because the study is being conducted to obtain marketing authorization, the requirements of ICH Guideline E6 section 5.5.11 and 5.5.12 shall be taken into account.

The investigator is responsible for archiving the investigator site file, the subject's records, and the source data according to applicable regulatory requirements. These documents have to be archived for at least 10 years, but should be retained for longer if required by regulatory stipulations or by agreement with the sponsor.

If the investigator can no longer maintain the archive of study records (e.g., due to retirement or relocation), the sponsor must be informed in writing about any change in responsibility for record retention, including the name of the new responsible party, contact information, and location of the study records. Records must not be destroyed without prior written consent from the sponsor.

13 SUPERVISION OF THE CLINICAL STUDY

13.1 Access to Source Data

According to ICH guidelines for GCP and the applicable laws, the investigator must permit all authorized third parties access to the study site and the medical records of the study subjects (source data). These include the clinical monitors, auditors, and other authorized employees of the sponsor as well as members of the local or federal authorities. All these persons are bound to strict confidentiality.

13.2 Monitoring

Monitoring of the study sites will be performed by a CRO designated by the sponsor and will be based on the CRO's monitoring standard operating procedures (SOPs) 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 CRO 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 SOPs.

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the subjects treated under this protocol. The investigator agrees to maintain accurate source documentation and eCRFs as part of the case histories.

Study records are comprised of source documents, eCRFs, and all other administrative documents (e.g., correspondence, clinical study materials, supply shipping manifests, or monitoring logs). An investigator site file will be provided with instructions for the maintenance of study records.

13.3 Independent Data Monitoring Committee

An independent, unblinded DMC will be established to allow regular monitoring of the study data in order to detect and report early evidence of unanticipated harm to subjects. The Independent DMC will meet after a defined number of subjects have completed the Main Period. The number of subjects is defined in the Independent DMC Charta. Further ad hoc reviews may be arranged and conducted if deemed necessary.

The reviews will focus on safety data from the double-blind treatment phases, including but not limited to TEAEs, drug exposure, laboratory test results, and vital sign measurements. Further details of the data and outputs to be provided to the DMC will be described in the DMC SAP. A DMC charter will provide further details on the DMC membership, the responsibilities of the DMC, the purpose and timing of the reviews, and the procedures for ensuring confidentiality and proper communication. The charter will also outline the required content of the written report to be provided by the DMC after each safety review, including their recommendations for the future conduct of the study.

To maintain the blind, the data for the safety reviews will be delivered by an unblinded CRO biostatistics team located at a different geographical site to the blinded CRO biostatistics personnel involved in the study. Apart from the actual decisions, these data will not be shared with anyone outside of the attendees of the safety review meeting until after the double-blind treatment phase database lock. A detailed blinding and communication plan will be agreed upon by InflaRx and the responsible CRO to clarify the distribution of the unblinded information and the level of blinding (eg, summary data, individual data).

13.4 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.

13.5 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.

14 DATA PROTECTION AND CONFIDENTIALITY

Within this study, personal data from the study subjects and data regarding the treatment and the course of subject's welfare will be collected.

The data will be stored and processed in anonymized form (i.e., without reference to the subject's name) with the aid of a unique subject identification number.

Data will be managed by a sponsor designated CRO (data entry, data cleaning, and data exports). The safety concept ensures among other things that data access is limited to authorized persons, that measures are taken to prevent loss of data, and that the applicable laws pertaining to data protection are observed. The data are protected from third party access and only members of the study team are permitted access. These members are bound to strict confidentiality.

Personal data will be stored in an anonymous manner after reaching finishing completion status of all concomitant scientific projects for at least 15 years, if no other or new regulatory requirements come into effect warranting different time periods for archiving.

14.1 Declaration Regarding Data Protection

During data entry, processing, and analysis by a sponsor designated CRO, all requirements of the data protection act will be taken into account. Access to data is strictly limited to authorized persons. Data are protected against unauthorized access.

14.2 Declaration Regarding the Anonymized Transfer of Personal Data

The sponsor certifies herewith that the transfer of anonymized personal data will take place according to the applicable local laws. Moreover, the sponsor certifies that study subjects who do not permit the transfer of data will not be admitted to the study.

15 ADMINISTRATIVE AGREEMENTS

15.1 Adherence to the Protocol/Protocol Violations

The clinical study described here will be conducted and analyzed in accordance with local laws and ICH guidelines for GCP.

After a subject has been enrolled, it is the investigator's responsibility to avoid protocol violations in order to obtain unbiased data for the analysis of the study.

All protocol violations will be documented and discussed with the responsible biostatistician before closing the database and carrying out the statistical analyses.

15.2 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.

15.3 Notification of the Local Authorities

The sponsor, their contractors, and all investigators and their deputies are responsible for notifying the local regulatory authority of their participation in the study prior to enrollment of the first subject in the study. Responsibility for notification to the local authorities has been delegated to a sponsor designated CRO.

This extends also to amendments, discontinuation of study arms or of the entire study, and the regular conclusion of the study.

15.4 Publication Policy and Registration

15.4.1 Publication Policy

The rights and obligations of investigators and the sponsor concerning any formal presentation or publication of data collected as a direct or indirect result of this study will be addressed specifically in the Clinical Study Agreement for the study.

The first publication must be based upon all data obtained from all analyses, as stipulated in the study protocol.

The sponsor must receive a copy of any intended communications in advance of the proposed submission date. This is to allow the sponsor time to review the communication for accuracy (thus avoiding potential discrepancies with submissions to regulatory authorities), to verify that confidential and/or proprietary information is not inadvertently divulged, to provide any relevant supplementary information, and to allow establishment of co-authorship (as appropriate). The authorship of communications arising from pooled data will include investigators from study sites that contributed data as well as relevant personnel from the sponsor. Ownership of all data will remain with the sponsor.

Furthermore, the publication policy will follow the recommendations of Good Scientific Practice of the Deutsche Forschungsgemeinschaft (www.dfg.de) and will meet the criteria of the International Committee of Medical Journal Editors (http://www.icmje.org).

15.4.2 Registration

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).

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17 APPENDIX

17.1 Hurley Stages

Evaluation of disease severity after Hurley [13].

Grade I	Abscess formation, single or multiple, without sinus tracts or cicatrization
Grade II	Recurrent abscesses, with sinus tract formation and cicatrization; single or multiple, widely separated lesions One or more widely separated recurrent abscesses with tract formation and cicatrization
Grade III	Diffuse or near-diffuse involvement, or multiple interconnected tracts and abscesses across entire area Multiple interconnected tracts and abscesses across the entire area, with diffuse or near-diffuse involvement

17.2 Hidradenitis Suppurativa-Physician's Global Assessment

The HS-PGA disease severity scale includes the following definitions [20]:

Severity	Score	Definition
Clear	0	0 abscesses, 0 draining fistulas, 0 inflammatory nodules, and 0 non-inflammatory nodules
Minimal	1	0 abscesses, 0 draining fistulas, 0 inflammatory nodules, and presence of non-inflammatory nodules
Mild	2	0 abscesses, 0 draining fistulas, and 1 to 4 inflammatory nodules **or** 1 abscess or draining fistula (sum of abscesses and draining fistulas is 1) and 0 inflammatory nodules
Moderate	3	0 abscesses, 0 draining fistulas, and ≥ 5 inflammatory nodules **or** 1 abscess or draining fistula and ≥ 1 inflammatory nodule **or** 2 to 5 abscesses or draining fistulas (sum of abscesses and draining fistulas is 2 to 5) and < 10 inflammatory nodules
Severe	4	2 to 5 abscesses or draining fistulas and ≥ 10 inflammatory nodules
Very severe	5	> 5 abscesses or draining fistulas (sum of abscesses and draining fistulas > 5)

17.3 Modified Sartorius Score

Algorithm for calculating the mSS [23].

Calculate several regional scores for each valid local anatomical region. The total mSS is obtained by adding together the single regional mSS.

The following algorithm is used for calculating the regional score based on lesion counts in 12 anatomic regions:

- Left axilla
- Right axilla
- Left sub/inframammary area
- Right sub/inframammary area
- Intermammary area
- Left buttock
- Right buttock
- Left inguino-crural fold
- Right inguino-crural fold
- Perianal
- Perineal area
- Other (to be specified)

For each anatomic region, calculate the regional score as follows:

1. Count 3 points for each regional mSS to account for the identified local region involved
2. For each regional mSS, add points per number and score of lesions (abscesses, nodules, fistulas, scars) within the respective identified local anatomical region:
    - + 2 * Number of inflammatory nodules
    - + 2 * Number of non-inflammatory nodules
    - + 4 * Number of abscesses
    - + 4 * Number of draining fistulas
    - + 4 * Number of non-draining fistulas
    - + 1 * Number of hypertrophic scars
3. For each regional score, add the following points for the longest distance between 2 relevant lesions (i.e., nodules and fistulas) in each identified local anatomical region, or size of lesion:
    - 0 points, if no active lesions
    - 2 points, if the longest distance between 2 relevant lesions or size (if only 1 lesion is present, the diameter of the corresponding lesion is measured) is < 50 mm
    - 4 points, if the longest distance between 2 relevant lesions or size is ≥ 50 mm and < 100 mm
    - 6 points, if the longest distance between 2 relevant lesions or size is > 100 mm

4. Are lesions clearly separated by normal skin?
    - Yes: 0 points
    - No: 6 points

    If this question was left unanswered and is thus missing for 1 identified local anatomical region, the score will be recorded as missing for the corresponding subject and time point.

The total mSS is the sum of the 12 regional scores.

17.4 Erythema Assessment

At every visit, for each anatomic region affected by HS, the investigator will assess the overall degree of erythema using a 4-point ordinal scale ranging between 0 and 3.

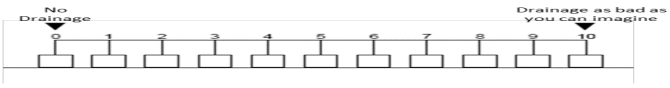
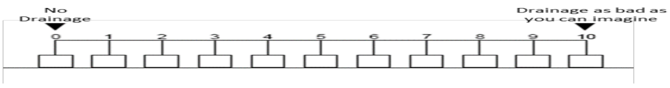
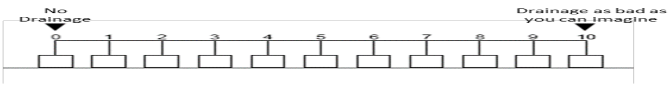
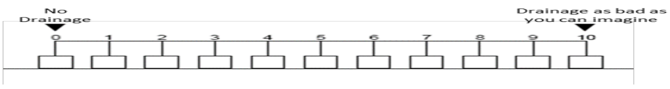
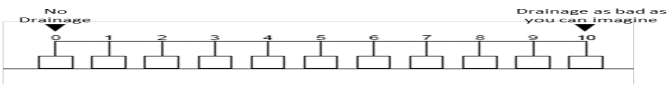
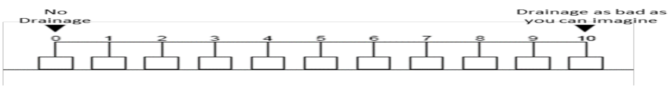
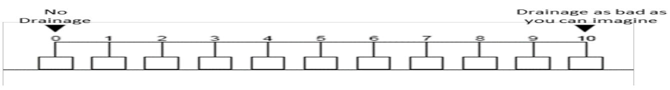
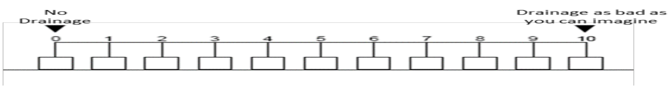
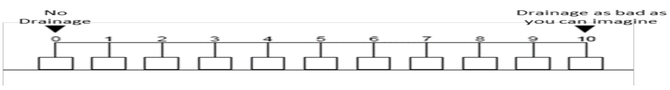
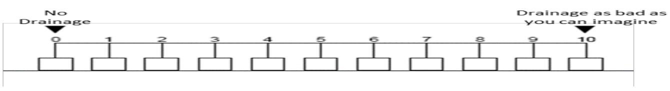
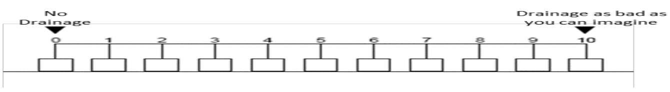
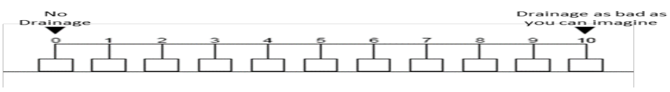
Region (Assessed at Every Visit)	Degree of Erythema
Left axilla	
Right axilla	
Left sub/inframammary area	
Right sub/inframammary area	
Intermammary area	
Left buttock	
Right buttock	
Left inguino-crural fold	
Right inguino-crural fold	
Perianal	
Perineal area	
Other (to be specified)	

0 = no redness; 1 = faint but discernible pink coloration; 2 = moderate red coloration; 3 = very red or bright red coloration

17.5 Patient’s Assessment of Drainage

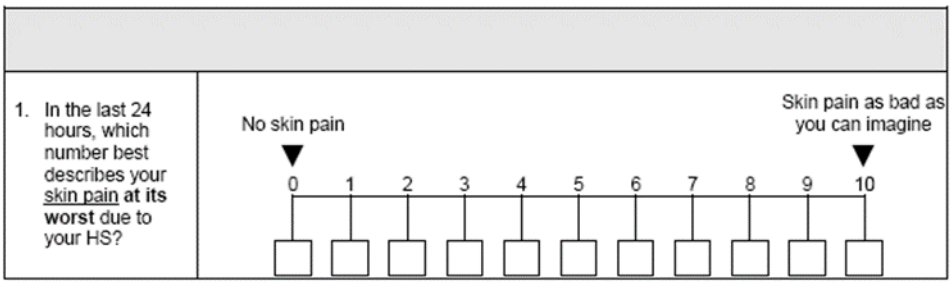
Please answer the questions before you go to bed. Mark an “X” in the box that describes the severity of drainage affected by HS:

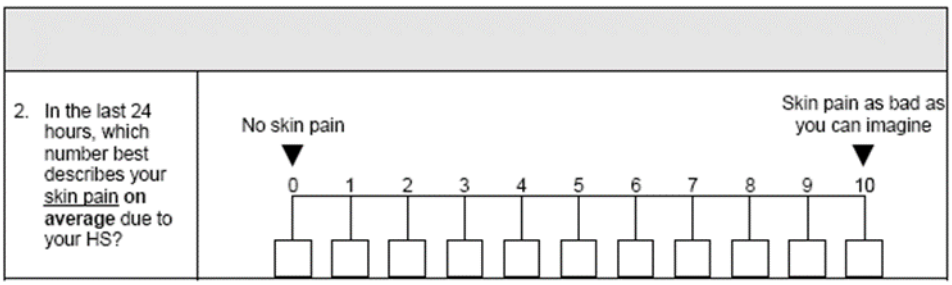
In the last 24 hours, which number best describes the worst severity of drainage due to HS?

Severity of Drainage due to HS













17.6 Patient's Global Assessment of Skin Pain

Please answer the questions below **before you go to bed**. Please mark an "X" in the box (☒) which best describes the severity of your skin pain in the **last 24 hours**.





17.7 The Dermatology Life Quality Index

The aim of this questionnaire is to measure how much the subjects' skin problem has affected their life OVER THE LAST WEEK.				
1.	Over the last week, how **itchy**, **sore**, **painful,** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed** or **self-conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **yard?**	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	yes no	☐ ☐	Not relevant ☐
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐

The total DLQI Score is classified as follows [20]:

0-1	No effect on subject's life
2-5	Small effect on subject's life
6-10	Moderate effect on subject's life
11-20	Very large effect on subject's life
21-30	Extreme effect on subject's life

17.8 The Hospital Anxiety and Depression Scale

Hospital Anxiety and Depression Scale (HADS)

GL assessment
the measure of potential

Name: _____ Date: _____

FOLD HERE

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **underline the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

A	D		A	D
		I feel tense or 'wound up'		
3		Most of the time		3
2		A lot of the time		2
1		From time to time, occasionally		1
0		Not at all		0
		I still enjoy the things I used to enjoy		
	0	Definitely as much		
	1	Not quite so much		
	2	Only a little		
	3	Hardly at all		
		I get a sort of frightened feeling as if something awful is about to happen		
3		Very definitely and quite badly		
2		Yes, but not too badly		
1		A little, but it doesn't worry me		
0		Not at all		
		I can laugh and see the funny side of things		
	0	As much as I always could		
	1	Not quite so much now		
	2	Definitely not so much now		
	3	Not at all		
		Worrying thoughts go through my mind		
3		A great deal of the time		
2		A lot of the time		
1		Not too often		
0		Very little		
		I feel cheerful		
	3	Never		
	2	Not often		
	1	Sometimes		
	0	Most of the time		
		I can sit at ease and feel relaxed		
0		Definitely		
1		Usually		
2		Not often		
3		Not at all		
		I feel as if I am slowed down		
		Nearly all the time		3
		Very often		2
		Sometimes		1
		Not at all		0
		I get a sort of frightened feeling like 'butterflies' in the stomach		
		Not at all	0	
		Occasionally	1	
		Quite often	2	
		Very often	3	
		I have lost interest in my appearance		
		Definitely		3
		I don't take as much care as I should		2
		I may not take quite as much care		1
		I take just as much care as ever		0
		I feel restless as if I have to be on the move		
		Very much indeed	3	
		Quite a lot	2	
		Not very much	1	
		Not at all	0	
		I look forward with enjoyment to things		
		As much as I ever did		0
		Rather less than I used to		1
		Definitely less than I used to		2
		Hardly at all		3
		I get sudden feelings of panic		
		Very often indeed	3	
		Quite often	2	
		Not very often	1	
		Not at all	0	
		I can enjoy a good book or radio or television programme		
		Often		0
		Sometimes		1
		Not often		2
		Very seldom		3

Now check that you have answered all the questions

	A	D
TOTAL		

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17.9 The 36-Item Short Form Survey

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c. Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d. Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e. Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f. Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g. Walking more than a mile	☐ 1	☐ 2	☐ 3
h. Walking several hundred yards	☐ 1	☐ 2	☐ 3
i. Walking one hundred yards	☐ 1	☐ 2	☐ 3
j. Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

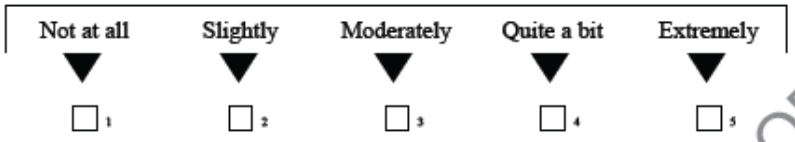
4. **During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

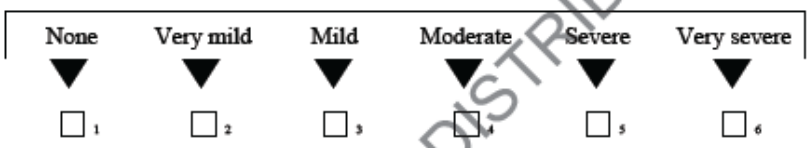
5. **During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

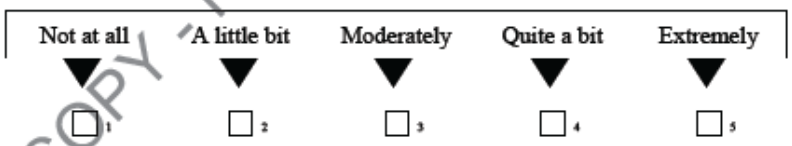
6. **During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**



7. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?**



8. **During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**



9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g. Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h. Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i. Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

17.10 The EuroQol-5 Dimensions Survey

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐