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MASTER PROGRAMM IN

"METHODOLOGY OF BIOMEDICAL RESEARCH, BIOSTATISTICS AND CLINICAL BIOINFORMATICS"

MASTER COURSE THESIS

"A PROTOCOL FOR A RANDOMIZED CONTROLLED TRIAL FOR ASSESSING THE EFFICACY AND SAFETY OF TREATMENTS IN HIDRADENITIS"

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ABSTRACT

CLINICAL PROTOCOL

Title of study: A phase 3, placebo controlled, randomized, double-blind study to evaluate the efficacy and safety of Infliximab (INF)for the treatment of moderate to severe Hidradenitis Suppurativa (HS).

Study phase: 3

Investigational product: Infliximab

Research Hypothesis: We assessed the efficacy and safety of infliximab (IFX) for the treatment of moderate to severe HS

Primary Efficacy Objective: The primary objective of this study is to evaluate the effectiveness of Infliximab (INF) for the treatment of moderate to severe Hidradenitis Suppurativa (HS).

INTRODUCTION

Hidradenitis suppurativa / acne inversa (HS) is a chronic, inflammatory, recurrent, debilitating skin disease of the hair follicle that usually presents after puberty with painful, deep-seated, inflamed lesions in the apocrine gland-bearing areas of the body, most commonly the axillae, inguinal and anogenital regions (Dessau definition, 1st International Conference on Hidradenitis suppurativa/Acne inversa, March 30-April 1, 2006, Dessau, Germany)

Definition: Hidradenitis suppurativa / acne inversa (HS) is a chronic, inflammatory, recurrent, debilitating skin disease of the hair follicle that usually presents after puberty with painful, deep-seated, inflamed lesions in the apocrine gland-bearing areas of the body, most commonly the axillae, inguinal and anogenital regions .

Clinical presentation Recurrent inflammation occurring more than 2x/6 months or 3x/6 months in the inverse regions of the body, presenting with nodules, sinus-tracts and/or scarring .

Primary positive diagnostic criteria

History: Recurrent painful or suppurating lesions more than 2x/6 months. Signs: Involvement of axilla, genitofemoral area, perineum, gluteal area and infra-mammary area of women. Presence of nodules (inflamed or non-inflamed). sinus tracts (inflamed or noninflamed), abscesses, scarring (atrophic, mesh-like, red, hypertrophic or linear).

Secondary positive diagnostic criteria

History: Family history of HS.

Microbiology: A negative swab or the presence of normal skin microbiota may be indicative of HS.

Differential diagnosis

• Staphylococcal infection (lesions are spread in a random fashion and more pustular)

• Cutaneous Crohn's disease (associated intestinal Crohn's disease)

• Simple abscesses (usually single lesions)

• Neoplasms, primary or secondary (systemic and histological signs of tumor)

• Lymphogranuloma venereum

• ***Rare***:

o Cutaneous actinomycosis (presents with sinus tract disease)

o Scrofuloderma type of cutaneous tuberculosis

Classification and severity assessment

Hurley staging

In 1989, a severity classification was first proposed by Hurley (4).

• Stage I: Abscess formation, single or multiple, without sinus tracts and cicatrisation.

• Stage II: Recurrent abscesses with tract formation and cicatrisation, single or multiple, widely separated lesions.

• Stage III: Diffuse or near-diffuse involvement, or multiple interconnected tracts and abscesses across the entire area.

Stage I disease is most common (68% of patients), while stage II occurs in 28% of patients, and 4% of HS patients have stage III . Today, the Hurley classification is still useful for the classification of three severity groups but the classification has limitations. The Hurley classification is not quantitative, consisting of only 3 stages and based on static disease characteristics such as scarring and fistulas. Hence, it is not suitable for monitoring the efficacy of interventions in clinical trials.

Sartorius score

A more detailed and dynamic HS severity score was created by Sartorius et al. and was later modified . The main parameter in the modified Sartorius score is the counting of individual nodules and fistulas. The modified Sartorius score was the first disease specific instrument for dynamically measuring clinical severity. However, it has been argued that its usability is limited in severe cases in which separate lesions become confluent. Even if this score is more dynamic than the Hurley score it still includes lesions, which may not be sensitive to medical treatment (scars; distance between two relevant lesions).

Physician global assessment (PGA)

Currently, a PGA is the most frequently used assessment tool to measure clinical improvement in clinical trials of medical treatments. A recently developed six stage PGA was defined as follows:

• Clear: no inflammatory or non-inflammatory nodules

• Minimal: Only the presence of non-inflammatory nodules 5

• Mild: Less than 5 inflammatory nodules or 1 abscess or draining fistula and no inflammatory nodules

• Moderate: Less than 5 inflammatory nodules or one abscess or draining fistula and one or more inflammatory nodules or 2–5 abscesses or draining fistulas and less than ten inflammatory nodules

• Severe: 2–5 abscesses or draining fistulas and ten or more inflammatory nodules

• Very severe: More than 5 abscesses or draining fistulas

Epidemiology

Prevalence and incidence

Several studies aimed to assess frequency of HS using prevalence or incidence estimations in different settings (hospital versus population-based), different time periods (from 1968 to 2008) different diagnosis methods (self-reported, medically assessed, diagnosis of treatments codes through automated requests in medical information systems) leading to an important variability of estimations and uncertainties regarding the actual frequency of HS . One recent study estimated the incidence of HS in an American county (Minnesota) with a population of about 144,000 people. The source was the Rochester Epidemiologic Project, a medical information system gathering records from hospitals, clinics, private practitioners and nursing homes within the county. Between 1968 and 2008, 268 HS cases were identified leading to a mean incidence of 6.0 per 100,000 person-years with a two-fold incidence between the extremities of the period (4 to 10 per 100,000 person-years). This increase may be due to an increase in detection and coding of HS in the medical information system. The strength of this study was to estimate the incidence of HS for the first time. The limit of the study was its retrospective design. Moreover, there may be a selection bias due to recruitment through medical 6 information system leading to a possible under estimation of incidence. There also may be a classification bias due to missed diagnosis of mild early cases.

By postulating a duration of active HS being a maximum of about 20 years for a given subject, the incidence can be extrapolated to prevalence = incidence x duration of the disease. Accordingly, the prevalence would be:

- Max: 10/100,000 years x 20 years = 200/100,000 = 0.20%
- Min: 4/100,000 years x 20 years = 80/100,000 = 0.08%.

This conclusion is supported by expert opinion.

Psychosocial impact

The skin is a very important organ for our proper psychosocial functioning, as it is the largest and most visible part of the body. It plays a crucial role in interpersonal relationships, self-esteem, and perception of self-image and public image. Undoubtedly, HS due to its character has a huge impact on patients' quality of life (QoL). Therefore, many HS sufferers have to deal with depression and embarrassment. In addition, fever and fatigue often arise in extreme cases and may prevent individuals from performing even common everyday-tasks.

Pain

One of the most important problems reported by HS patients is pain, usually linked to the deep seated inflammatory nodules. Patients describe it in many ways, e.g. as hot, burning, pressing, stretching, cutting, sharp, taut, splitting, gnawing, sore,

throbbing or aching. HS patients rated their pain using a Visual Analog Scale (VAS) as 4.5 ± 2.4 points (range, 0-10 points) or by means of a Numeric Rating Scale-11 (NRS) as 3.6 ± 3.2. Moreover, when compared to other dermatological conditions, which served as a control, the difference of pain intensity was of significant importance ($p<0.001$).

Dermatology Life Quality Index

The influence of HS on patients' Quality of Life was quite often evaluated with a population-specific questionnaire - Dermatology Life Quality Index (DLQI). Even though the data is still limited, the observations are consistent and convergent . All of the DLQI subdomains were "hardly" affected, but the greatest impact was reported for 'symptoms and feelings' and 'daily activities'. HS's impact on QoL is estimated as having large or extremely large effect on patient's life for nearly 60% of examined patients . The main predictors of QoL impairment were HS clinical stage assessed accordingly to Hurley classification ($p<0.0001$) number of skin areas involved by HS lesions ($R=0.28$; $p=0.045$) and anogenital localization ($p=0.0051$). Similar findings were revealed in a study by Onderdijk et al. , where patients with more severe disease (with reference to Hurley staging or number of flares during the last month) had markedly higher DLQI scores. ($p<0.05$)

It can be concluded that HS is a highly distressing disease for many patients, probably one of the worst that has been analyzed and evaluated in dermatology to date.

Descriptive studies have shown a positive correlation between disease severity and BMI and tobacco smoking. Although no data exist for improvement of HS lesions after reduction of weight and cessation of tobacco smoking, the general expert opinion is that cigarette smoking and overweight have to be avoided.

Generally, HS affects patients' lives in many ways. The sufferers underline the problems linked to interpersonal contacts, especially in relation to appearance and smell, various emotional reactions, as well as feelings of lack of control. HS has a great emotional influence on patients and promotes the social isolation. Irritation and shame are frequent and relate to smell, pain, scars, and itching. Moreover, not surprisingly, such a chronic and debilitating skin disease has its reflection in socio-economic status tightly related to professional activity. The studies underline the significant work disability rate together with high unemployment rate among HS sufferers, while most of them are in a productive age.

Treatments with Biologics

According to current evidence adalimumab and infliximab are effective in the treatment of moderate to severe HS and improve the quality of patient life, with adalimumab more tolerable.

Adalimumab

Mechanism: Adalimumab is a fully human therapeutic monoclonal antibody. It corresponds to the human immunoglobulin IgG1 and has heavy and light chain variable regions exhibiting specificity for human TNF-α. Adalimumab binds with high affinity and specificity to soluble and membranebound TNF-α. Thus the binding to the TNF-α receptor is prevented (p55 and p75) and blocks the biological effect of TNF-α.

Dosage and duration of treatment:

• a) To condition for a curative surgical procedure: adalimumab 160 mg on day zero and possibly 80 mg one week later.

b) For long-term therapy: adalimumab 40 mg once weekly .

• Adalimumab is administered by subcutaneous injection.

• There is no dose adjustment for patients with obesity (> 100 kg).

Response rate: There are different rates of response to adalimumab reported in case series and in a current, prospective controlled study.

Administration of adalimumab with a cumulative response rate of 58% (improvement ≥50% in 23 patients) has been reported in case reports with 42 patients with moderate to severe HS (10,103- 106) (Table 3). In a prospective, open study with 15 patients with moderate-to-severe HS, medium-term treatment (3 months) with adalimumab resulted in significant reduction of Sartorius score by week 24 with a marked improvement during the first month (107) . VAS score and DLQI showed a significant decrease at week 24. In another prospective, open study with 6 patients with moderate to severe HS, medium-term treatment (3 months) with adalimumab failed to reduce HSSI score in any of the patients at week 2, 4, 8, and 12 (10) . VAS and DLQI scores also failed to show statistically significant improvement.

Follow-up investigations: Relapses after discontinuation of treatment and/or surgery required was reported in 10 of 14 among the case reports patients (71%). Relapses after discontinuation were also reported in the patients group reported. A decrease in response was seen after the switch from adalimumab weekly to every other day dosing in an open follow-up study at weeks 16 to 52.

Complications: Under adalimumab treatment tolerance was satisfactory . In the placebo-controlled studies reaction at the injection site was the most commonly reported adverse drug reaction (adalimumab: 20% of patients, placebo: 14%). No major adverse events could be observed. Under adalimumab therapy increased infections may occur, especially at the upper respiratory tract, bronchitis and urinary tract infections. Reported serious infections are pneumonia, septic arthritis, post-operative infections, erysipelas, diverticulitis, and pyelonephritis. Autoantibodies (ANA, anti-dsDNA antibodies) can be induced; a rare "lupus-like syndrome" was described. Very rarely, malignancies, especially lymphomas occur.

Women should receive contraception up to five months after the last dose of adalimumab. Should pregnancy be diagnosed under adalimumab treatment, it should be discontinued. Damage to the child cannot be expected due to lack of embryo or fetal toxicity (FDA classification B). During lactation Adalimumab is contraindicated due to the potential transition into the milk.

Infliximab

Mechanism: Infliximab is a chimeric (mouse / human) monoclonal antibody against TNF-α. It is an IgG1 immunoglobulin with human sequences in the constant regions and murine sequences in the complementarity-determining regions of the light and heavy chains. It binds specifically to both soluble and transmembrane, receptor-bound TNF-α. Soluble TNF-α is ligated and its proinflammatory activity is neutralized. Moreover, binding to cell membrane-bound TNF-α leads to an elimination of the affected cells, possibly due to complement activation and / or antibodydependent cellular cytotoxicity, but also due to induction of apoptosis. Infliximab has a serum halflife of about 8 to 9.5 days. The elimination period is up to 6 months.

Dosage and duration of treatment:

- To condition for a curative surgical procedure: Infliximab 5 mg / kg body weight may be used.
- For long-term therapy: infliximab 5 mg / kg body weight on day zero, two, six and then regularly every eight weeks.

• With longer intervals between infusions, the probability of the formation of infliximab antibodies increases.

• Infliximab is administered intravenously over a period of two hours. If no infusion reactions occur, it can also be given over one hour. During the infusion and for one hour after it monitoring of patients for infusion reactions is necessary.

Response rate: Administration of infliximab with a cumulative response rate of 58% (improvement ≥50% in 42 patients) has been reported in case reports with 73 patients with moderate to severe HS. In a prospective, randomized, double-blind, placebo-controlled, cross-over study of infliximab treatment (5 mg/kg iv at weeks 0, 2, 6) of 33 patients with HS for 2 months no significant difference in the >50% improvement was detected (primary end point), while a significantly higher 25-50% improvement rate was detected under infliximab (27% vs. 5% under placebo). In a retrospective comparative (1:1) study with 20 patients, a significantly greater reduction was detected for infliximab (5 mg / kg iv at weeks 0, 2 and 6) in mean Sartorius score (56%) in comparison with adalimumab (40 mg sc every other week) (34%).

Follow-up investigations: Long-term treatment (1 year) of 8 patients with moderate-to-severe HS with infliximab resulted in significant reduction of the number of involved sites and flares. . In a further study with long-term treatment (4 years) of 10 patients with moderate-to-severe HS with infliximab 80% responses were reported. Response (≥50%) occurred after 3 to 7 drug administrations (13 to 45 weeks). Four of 8 patients relapsed despite treatment (after 6 administrations). Moreover, recurrences after discontinuation of treatment and/or surgery required was reported in 15 of 35 among the case reports patients (43%).

Complications: The long-term tolerance (n=8 patients, 1 year) was satisfactory with only 4 minor infections, 1 keratoacanthoma and one case of rapidly resolving hepatitis. In a retrospective 33 comparative study on the safety of infliximab and adalimumab in 5 of 27 patients (18%) who were treated for an average of 12 months with infliximab a polyarthritis was detected, which healed spontaneously 4 months after discontinuation of infliximab . This side effect was not observed under adalimumab treatment. There are extensive data on the safety of treatment with infliximab in inflammatory bowel disease, arthritis and psoriasis vulgaris. Acute infusion reactions with mild chills, headache, flushing, nausea, dyspnea or infiltration at the infusion site are common. The likelihood of an infusion reaction is higher in patients with infliximab-specific antibodies. Anaphylactoid reactions, regardless of whether infliximab-specific antibodies are present, can occur. Retreatment after longer treatment periods may induce arthralgia, myalgia and angioedema. A moderate infusion reaction can be prevented or attenuated by prior administration of antihistaminics or even prevented. By the addition of low-dose methotrexate (5-10 mg / week), the formation of antibodies to infliximab can be reduced. Infections, worsening of heart failure, demyelinating diseases, hepatotoxicity, leukopenia, neutropenia, thrombocytopenia or pancytopenia lupus erythematosus-like syndrome may also occur.

Other TNF-α inhibitors

Treatment of patients with HS with etanercept has also been reported in case reports and a clinical study.

Mechanisms: Etanercept is a fusion recombinant protein, which fuses the TNF receptor and interferes with TNF-α.

Response rate: Administration of etanercept (25 mg sc twice weekly over 3-10 months) with a cumulative response rate of 44% (improvement ≥50% in 15 patients) has been reported in case reports with 34 patients with moderate to severe HS. Relapses after discontinuation of treatment occurred in 10 of 14 patients (71%). In a prospective, randomized, double-blind, placebo-controlled, cross-over study of etanercept treatment (50 mg sc twice weekly) of 20 patients with HS for 3 months no difference compared with placebo could be detected.

Other Biologicals

Treatment of patients with HS with ustekinumab has also been reported in case reports Administration of ustekinumab (three 45 mg sc injections on weeks 0, 4 and 16) with a cumulative response rate of 33% (improvement ≥50% in 1 patient) has been reported in a case series of 3 patients with moderate to severe HS. Relapses after discontinuation of treatment occurred in 2 of 3 patients (66%).

TRIAL DESIGN

Biologic therapies with anti-tumor necrosis factor agents are promising treatments for hidradenitis suppurativa (HS).

Objective: To assess the efficacy and safety of infliximab (IFX) for the treatment of moderate to severe HS

This is a randomized, double-blind treatment phase of 8 week where patients received IFX or placebo was followed by an observational phase.

Primary treatment efficacy will be based on HS Severity Index.

Secondary end points included Dermatology Life Quality Index, visual analog scale, and Physician Global Assessment scores. Inflammatory markers erythrocyte sedimentation rate and C-reactive protein were also assessed.

Committees

Executive Committee

The EC consists of members of the academic leadership of the study and one member from the sponsoring company. The EC will ultimately be responsible for the conduct of the study including addressing any Data Monitoring Committee recommendations and overseeing publication of the results.

Steering Committee

A Steering Committee will be formed consisting of members who are lead investigators from each country/region. The Steering Committee will advise and assist the EC with regard to the scientific and operation aspects of the study.

Independent Data Monitoring Committee

This study will be conducted under the auspices of an independent Data Monitoring Committee (DMC), which will monitor the progress of the study and ensure that the safety subjects enrolled in the study is not compromised. The DMC will have a chairperson and include at least 2 dermatologists, as well as a statistician. This committee will review accumulating data on a regular basis, and may request to review partially unblended accumulating data. The DMC will make recommendations to the Executive Committee and Sponsor regarding the continuing safety of subjects currently enrolled and yet to be enrolled in the trial. At all times during the course of the study, the DMC may request access to the unblended data if needed.

Clinical Endpoint Committee

The Clinical Endpoint Committee (CEC), composed of experts in the relevant fields, will review, in a blinded manner, all reported study outcomes to provide consistency and validity in the assessment of outcomes. Their decisions will be based on blind clinical data. Theirs decisions will be used for the final statistical analyses.

ETHICAL CONSIDERATIONS

This study will be conducted in accordance with Good Clinical Practice (GCP). Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting research studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

INDEPENDENT ETHICS COMMITTEE

The protocol and any amendments, the Investigator's Brochure, the subject informed consent and any information on compensation for study-related injuries or payment to subjects, will receive IRB/IEC approval prior to initiation of the study. During the study the investigator will send to the IRB any reports of adverse events that are serious, unlisted, and associated with the investigational drug and any new information that may adversely affect the safety of the subjects or the conduct of the study. The personnel involved in this study will be qualified by education, training and experience to perform their respective task.

INFORMED CONSENT

It is the investigators' responsibility to ensure that subjects, are legally acceptable representatives, are clearly and fully informed about the aims, methods, anticipated benefits, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

The written ICF should be prepared in the local language of the potential study population. The informed consent should be approved by the responsible IB in advance of use.

Subjects unable to give their written consent may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with the subject's understanding. If the subject or a subject's legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion.

In order to successfully maintain the safety objectives of this endpoint driven trial, it is essential that each subject's follow-up and vital status be maintained through the end of the study. All reasonable efforts must be made to locate subjects to determine and report their current and ongoing status. The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of both science and society.

SUBJECT CONFIDENTIALITY

The investigators and the Sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations.

The investigator must ensure that the subject's anonymity is maintained. On the eCRFs or other documents submitted to the Sponsor of the CRO, subjects should be identified by a unique subject identifier as designated by the Sponsor. Sponsor

personnel whose responsibilities require access to personal data should agree to keep the identity of study subjects confidential.

SELECTION OF SUBJECTS- STUDY POPULATION

The study population will consist of adult subjects with moderate to severe Hidradenitis Suppurativa (HS).

INCLUSION CRITERIA

For entry into the study, the following criteria MUST be met:

1) Age > 18 years
2) A clinical diagnosis of moderate to severe HS defined as Hurley II or Hurley III for at least 6 months, where:

Hurley II: Recurrent abscesses, single or multiple widely separated lesion, with sinus track formation. (Frequent inflammation restricts movement and may require minor surgery such as incision and drainage)

Hurley III: Diffuse or broad involvement across a regional area with multiple interconnected sinus tracts and abscesses. (Inflammation of sites to the size of golf balls, or sometimes baseballs; scarring develops, including subcutaneous tracts of infection.
Obviously, patients at this stage may be unable to function.

Male or female patients older than 18 years included in the trial had moderate to severe HS as defined by a HS Severity Index (HSSI) score greater than 8. HSSI is a composite score ranging from 0 to 19. The score was

- obtained by assessing the number of sites involved,
- percent of body surface involved (the palm of the hand was used to represent 1% of body surface area),
- number of erythematous and painful lesions,
- Number of dressing changes during working and leisure hours (which reflects interference in daily activities),
- pain as quantified by the visual analog scale (VAS).

HSSI was used to ascertain the activity and severity of HS in patients.

- In addition to the HSSI score greater than 8, patients had at least one of the following: (1) HS duration for longer than 1 year with multiple emergency department or doctor visits related to HS
- Intralesional steroid injections of more than 5/year, however, none within 2 weeks of entry
- failed systemic retinoid treatment, but not within 3 months of entry
- Failed at least one prior course of antibiotic therapy, which must not have been administered within 2 weeks of entry to the study (excluding the recommended antibiotic regimen given immediately before randomization for active local or systemic infection)
- History of reconstructive surgery, but not within 3 months of entry.

Other inclusion criteria will be generally good health as assessed by blood laboratory tests, and w similar to those criteria for patients treated with IFX for other diseases.

All subjects must provide **signed written informed consent.**

EXCLUSION CRITERIA

Potential subjects who meet any of the following criteria will be excluded from participating in the study:

Pre treatment assessment:

• Exclusion of acute infection.
• Exclusion of tuberculosis in accordance with current recommendations of the Paul Ehrlich Institute in Germany.
• HIV infection or viral hepatitis should be excluded with appropriate patient history, clinical and/or laboratory evidence.
• Pregnancy in women of childbearing age should be excluded and secure contraception.
• Patients should be advised that the course of infections could be more severe or atypical during treatment and that they have to early visit a physician in uncertain cases.

Contraindications:

Absolute contraindications

• Heart failure NYHA class III-IV

• Known hypersensitivity to mouse proteins

• Pre-existing tuberculosis or other severe infections

• Pregnancy and lactation Important relative contraindications

• Malignancies (except: basal cell carcinoma) and lymphoproliferative disorders as well as a history of malignancy

• Vaccination with live vaccines 32

• Autoimmune diseases

• Demyelinating processes

Discontinuation of treatment- Withdrawal of Subjects

Individual subjects may prematurely discontinue study drug. Reasons for study drug discontinuation are:

- Safety concerns (e.g. adverse event, infections, worsening of heart failure, demyelinating diseases, hepatotoxicity, leukopenia, neutropenia, thrombocytopenia or pancytopenia lupus erythematosus-like syndrome).
- Noncompliance of study drug
- The need for an excluded concomitant medication

A subject will be withdrawn from the study for any of the following reasons:

- Withdrawal of informed consent form
- Death
- Lost to follow up

In case a subject is lost-to-follow up, every possible effort must be made by the study site personnel to contact the subject to obtain complete data and determine the reason of withdrawal. This reason should be documented on the CRF and in the source document.

Subjects, who discontinue treatment before the end of the study, and those who are withdrawn from the study, should have a follow-up visit approximately 30 days after

the study drug discontinuation visit and they will be contacted every 3 months until the study ends to assess efficacy endpoint events.

RANDOMIZATION AND BLINDING

Central randomization will be implemented in conducting this study. At the time of enrollment, each subject will be assigned a unique sequential subject number by the IVRS (interactive voice response system) and a treatment code, which will dictate the treatment assignment for the subject. The IVRS will be available 24 hours per day, seven days a week. The subject number will consist of a unique 5 digit number which is assigned sequentially within the study (starting with 00001) by the IVRS. This number will be used for identification throughout the study and will not be used for any other subject. Subjects will be randomly assigned in a 1:1 ratio (infliximab : placebo) to 1 and 2 treatment groups and the randomization will be stratified by country. So the IVRS will then also assign a medication kit (and subsequent medication kits) that matches the treatment code to which the subject has been randomized.

The Investigator will not be provided with randomization codes. The codes will be maintained within the IVRS, which has the functionality to allow the Investigator to break the blind for an individual subject.

This study has a double-blind design. Neither the subjects nor any of the Investigators or Sponsor staff involved in the treatment or clinical evaluation of the subjects will be aware of the treatments received. There will be an independent DMC to monitor the data in an unblended manner on a periodic basis. An independent statistician, not otherwise involved in the study, will prepare and provide the required reports to the DMC.

The blind should be broken only if specific emergency treatment would be dictated by knowing the treatment status of the subject. If for any reason, the Investigator needs to become unblended to the treatment subject, he/she will make every attempt to first call the sponsor and discuss the need for unblinding and obtain agreement. If the Investigator is unable to contact the sponsor, the Investigator may in an emergency determine the identity of the treatment by telephoning IVRS. The sponsor must be informed as soon as possible by the investigator. Efforts should be made to limit access to knowledge of the treatment assignment to only those individuals who need to know the information and the subject should continue the study.

STUDY ASSESSMENTS AND PROCEDURES

Procedures by Visit

The study is divided into 3 periods: a screening period, a double-blind treatment period and a post-treatment observation period. All randomized subjects will be followed until the study ends, even if they did not take study drug or prematurely discontinued study drug.

Screening period

As part of study qualification which takes place before randomization, potential subjects will have the study risks and benefits explained to them, the associated ICF, reviewed with them, and all questions answered for them. Before the performance of any protocol-specific procedure, written informed consent should have been obtained by the investigator.

Screening procedures will be performed within 15 days before randomization.

The investigator will:

- obtain relevant medical history
- obtain vital signs
- perform physical examination
- perform chest radiograph
- obtain purified protein derivative skin test
- obtain clinical assessment of disease activity and severity
- obtain clinical chemistry and hematology, and serology for HIV, hepatitis B and C, and pregnancy were conducted 1 week before baseline.

Treatment period

Day 1-randomization

Eligible subjects will be randomized to study medication as described and study drug will be administered. The subjects should infusing study drug the same day. Placebo treated patients will receive identical-looking injections with no active ingredients.

After randomization, the Investigator will:

- Administer study drug
- Assess for adverse events (AE)
- Assess changes in concomitant medication use
- Assess for outcomes

Monthly visits

Subjects will return for visits at week 0,2,6 and then every 4 weeks during the double-blind period. (Additional interim visits may be scheduled, at the Investigators discretion, if necessary)

During these visits:

- Adverse events should be recorded
- Efficacy endpoints events should be assessed
- Study drug should be infused, as needed
- Unused study drug injections should be counted
- Targeted concomitant medications should be recorded
- Vital signs should be recorded

In addition, clinical assessment of disease activity, hematology, and clinical laboratory tests would be conducted at weeks 8, 16, 22, 30, and 52 Disease activity was assessed using HSSI, static Physician Global Assessment (PGA) tool, the Dermatology Life Quality Index (DLQI), VAS, and the change in the number of daily dressing changes at 1-week intervals as reported by the patient. The HSSI assesses a composite score of symptoms and signs ranging from 0 to 19, as mild (0-7), moderate (8-12), or severe ([13). The static PGA 6-point scale assesses extent of skin involvement, and reports symptoms as cleared (100% improvement), excellent (75%-99% improvement), good (50%-74% improvement), fair (25%-49% improvement), slight (1%-24% improvement), and worse.

In addition, customarily instruments such as DLQI and VAS will be used to assess disease activity. A daily diary card was maintained by patients and returned at each scheduled visit. The diary page included dates of data entry, the number of dressing changes during working and nonworking hours, and a VAS assessment of pain.

Study drug discontinuation visit

Individual subjects may prematurely discontinue study drug. Reasons for study drug discontinuation are safety concerns, noncompliance, and the need of an excluded medication or withdrawal of informed consent.

Assessment of treatment efficacy will based on HSSI, DLQI, VAS, PGA, erythrocyte sedimentation rate (ESR), and Creactive protein (CRP) values and

assessment of safety will be based on reported and observed adverse events (AE) and laboratory test results, which included hematology, blood chemistry, and vital signs.

Study end visit

After the last infusion, patients returned on a monthly basis to assess time to relapse, defined as an increase of 40% or more of HSSI score achieved at 8 weeks after starting IFX infusion (eg, if a patient's baseline score of 10 decreased to 5 after 8 weeks of treatment with IFX, the patient was assessed as having relapsed at an HSSI score of 7 [40% of 5 = 2, 5 1 2 = 7]). Severity of AE will be classified as mild (well tolerated), moderate (discomfort that interferes with daily activity), and severe (incapacitation or impairment of function).

EFFICACY ASSESSMENTS

Primary efficacy assessment

The primary efficacy end point of this study will be the proportion of patients with a clinical response at week 8 (end of period 1), defined according to the Hidradenitis Suppurativa Clinical Response (HiSCR) measure as at least a 50% reduction from baseline in the total abscess and inflammatory-nodule count, with no increase in the abscess or draining-fistula count. These changes have been identified as clinically meaningful by patients.

Secondary efficacy assessment

Three secondary end points will be rank-ordered at week 8. First will be a total abscess and inflammatory-nodule count of 0, 1, or 2 among patients with Hurley stage II disease (defined as recurrent abscesses, single or multiple, with sinus tract formation and scarring) at baseline. Second will be at least a 30% reduction and at least a 1-unit reduction from baseline in the pain score (on a numerical rating scale of the patient's global assessment of skin pain, with 0 indicating no pain and 10 indicating the worst pain imaginable), on the basis of 24-hour recall of the worst pain, among patients with a baseline score of 3 or higher. Third will be the change from baseline in the modified Sartorius score (a score of 4 indicates the least severe disease, and higher scores [no upper limit] indicate increasingly severe disease).

Additional, non-ranked secondary outcome measures will be also assessed at each visit in each period.

Adverse events that may emerge during treatment will be monitored throughout the studies until 70 days after discontinuation of the study drug. Clinical laboratory measurements, assessment of vital signs, and physical examinations will be also performed. Bacteriologic culturing is not a routine diagnostic test for Hidradenitis
Suppurativa and will not be performed in this trial.

SAFETY ASSESSMENTS

Cellulitis assessment

If patients present at screening with signs and symptoms of cellulitis, appropriate therapy will to be initiated as specified in the study protocol.

- For mild cellulitis without fever and constitutional symptoms, the site would be cultured and oral antibiotic treatment initiated at a dose and for a period determined by the investigator.
- For severe cellulitis, patients would be hospitalized and treatment determined by the investigator, including intravenous antimicrobial therapy. This same treatment protocol would be initiated if patients present with cellulitis during the study except that trial drug would be withdrawn for cases with severe cellulitis.

STATISTICAL CONSIDERATIONS

The primary efficacy end point will be the proportion of patients with a clinical response at week 8 (end of period 1), defined according to the Hidradenitis Suppurativa Clinical Response (HiSCR) measure as at least a 50% reduction from baseline in the total abscess and inflammatory-nodule count, with no increase in the abscess or draining-fistula count; these changes will be identified as clinically meaningful by patients.

Three secondary end points will be rank-ordered at week 12. First would be a total abscess and inflammatory-nodule count of 0, 1, or 2 among patients with Hurley stage II disease (defined as recurrent abscesses, single or multiple, with sinus tract formation and scarring) at baseline. Second will be at least a 30% reduction and at

least a 1-unit reduction from baseline in the pain score (on a numerical rating scale of the patient's global assessment of skin pain, with 0 indicating no pain and 10 indicating the worst pain imaginable), on the basis of 24-hour recall of the worst pain, among patients with a baseline score of 3 or higher. Third will be the change from baseline in the modified Sartorius score a score of 4 indicates the least severe disease, and higher scores [no upper limit] indicate increasingly severe disease). Additional, non-ranked secondary outcome measures will be assessed at each visit in each period; outcomes in period 1 for all non-ranked secondary end points are provided in the Supplementary Appendix. All period 1 assessments were also performed in period 2. Adverse events that emerged during treatment will be monitored throughout the studies until 70 days after discontinuation of the study drug. Clinical laboratory measurements, assessment of vital signs, and physical examinations will also be performed.

ADVERSE EVENTS

Definitions

An adverse event (AE) is defined as nay new untoward medical occurance or worsening of a pre-existing medical condition in a subject or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

Serious Adverse Events

A seriouw AE (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (defined as an event in which the subject was at risk of death at the same time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires impatient hospitalization or causes prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (note: reports of congenital anomalies/birth defects must also be reported on the Pregnancy Supplemental Form)

- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g. medical, surgical) to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

Severity of Adverse Event

- Mild (Grande1)- Awareness of event but easily tolerated
- Moderate(Grande 2)-Discomfort enough to cause some interference with usual activity
- Severe(Grande 3)- Inability to carry out usual activity
- Very severe(Grande 4)- Life-threatening or disabling AE

Collection and reporting

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs)

If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. The following information should be captured for all AEs: onset, duration, intensity, seriousness, relationship to investigational product, and action taken. The investigator shall supply the sponsor and Ethics Committee with any additional requested information, notably for reported deaths of subjects.

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/ identified during the course of the study.

Following the subject's written consent to participate in the study, all SAEs must be collected, including those thought to be associated with clinical study procedures. All SAEs must be collected which occur within 30 days of discontinuation of dosing with double-blind study drug. All SAEs must be followed until resolution. In addition, the Investigator should notify BMS of any SAE which may occur after this time period which they believe to be certainly probably or possibly related to investigational product.

Serious adverse events, whether related or unrelated to investigational product, must be recorded on the SAE page of the CRF and reported expeditiously to BMS (or designee) to comply with regulatory requirements. An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

If the Investigator believes that an SAE is not related to the investigational product, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE page of the CRF. Moreover, if an ongoing SAE changes in its intensity or relationship to the investigational product, a follow-up SAE report should be sent immediately to the sponsor. As follow-up information becomes available it should be sent immediately using the same procedure used for transmitting the initial SAE report. Supporting documentation such as hospital discharge summaries and autopsy reports should be forwarded to BMS in the same manner. All SAEs should be followed to resolution or stabilization.

Overdose

Overdose is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

ADMINISTRATIVE SECTION

Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The Investigator should not implement any deviation or change to the protocol without prior view and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects. Any significant deviation must be documented in the CRF.

Records Retention

The Investigator must retain investigational product disposition records, copies of CRFs (or electronic files), and source documents for the maximum period required by

applicable regulations and guidelines, or institution procedures or for the period specified by the sponsor, whichever is longer. The Investigator must contact BMS prior to destroying any records associated with the study. BMS will notify the Investigator when the study records are no longer needed. If the Investigator withdraws from the study (e.g. relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g. another Investigator, IRB). Notice of such transfer will be given in writing to BMS.

Case Report Forms

An Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality entries and/or corrections on CRFs.

The completed CRF, including any paper SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by a qualified physician who is an investigator or subinvestigator. For electronic CRFs, review and approval/ signature is completed electronically through the BMS electronic data capture tool. The Investigator must retain a copy of the CRFs including records for the changes and corrections.

LIST OF ABBREVIATIONS

AE: adverse event

CRP: C-reactive protein

DLQI: Dermatology Life Quality Index

ESR: erythrocyte sedimentation rate

HS: hidradenitis suppurativa

HSSI: Hidradenitis Suppurativa Severity Index

PGA: Physician Global Assessment

TNF: tumor necrosis factor

VAS: visual analog scale

AE: Adverse Event

CEC: Clinical Endpoint Committee

CRF: Case Report Form

DMC: Data Monitoring Committee

GCP: Good Clinical Practice

ICH: International Conference of Harmonization

IVRS: Interactive Voice Response System

SAE: Serious Adverse Event

IFX: Infliximab

QoF : Quality of Life

NRS: Numeric Rating Scale

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