A Phase 3 Multicenter Study of the Safety and Efficacy of Adalimumab in;Subjects with Moderate to Severe Hidradenitis Suppurativa

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The primary objective of this study is to determine the clinical safety and efficacy of adalimumab compared to placebo in subjects with moderate to severe HS after 12 weeks of treatment. A secondary objective is to evaluate safety and explore…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Skin and subcutaneous tissue disorders
Study type	Interventional

Summary

ID

NL-OMON40003

Source
ToetsingOnline

Brief title
M11-810

Condition

- Skin and subcutaneous tissue disorders

Synonym
acne ectopica, acne inversa

Research involving
Human

Sponsors and support

Primary sponsor: AbbVie BV

Source(s) of monetary or material Support: AbbVie B.V.

Intervention

Keyword: Adalimumab, Hidradenitis Suppurativa, Placebo-controlled, Randomized

Outcome measures

Primary outcome

The primary efficacy variable is the proportion of subjects achieving Hidradenitis Suppurativa Clinical Response (HiSCR) at Week 12.

Secondary outcome

The following secondary efficacy variables will be analyzed according to the rank order as follows:

1. Proportion of subjects achieving AN count of 0, 1, or 2 at Week 12, among subjects with Hurley Stage II at Baseline

2. Proportion of subjects achieving at least 30% reduction and at least 1 unit reduction from Baseline in Patient's Global Assessment of Skin Pain (NRS30) * at worst at Week 12 among subjects with baseline NRS * 1

3. Change in modified Sartorius scale from Baseline to Week 12.

Other efficacy variables to be analyzed at each scheduled visit in Period A, except for the ones included as primary or ranked secondary variables which will be analyzed for visits other than Week 12.

* Proportion of subject achieving HiSCR

* Proportion of subjects achieving AN count of 0, 1, or 2, among subjects with Hurley Stage II at Baseline

* Proportion of subjects achieving NRS30 * at worst, among subjects with

baseline Patient's Global Assessment of Skin Pain (NRS) * 1

* Proportion of subjects achieving NRS30 * on average, among subjects with baseline Patient's Global Assessment of Skin Pain (NRS) * 1

* Change in modified Sartorius scale from Baseline

* Proportion of subjects achieving complete elimination of abscesses at each visit, among subjects who have any abscess at Baseline

* Percentage change from Baseline in number of abscesses, among subjects who have at least one abscess at Baseline

* Change from Baseline in number of abscesses

* Proportion of subjects achieving complete elimination of draining fistulas at each visit, among subjects who have any draining fistulas at Baseline

* Percentage change from Baseline in number of draining fistulas, among subjects who have at least one draining fistula at Baseline

* Change from Baseline in number of draining fistulas

* Percentage change from Baseline in number of inflammatory nodules, among subjects who have at least one inflammatory nodule at Baseline

* Proportion of subjects achieving complete elimination of inflammatory nodules at each visit, among subjects who have any inflammatory nodules at Baseline

* Change from Baseline in number of inflammatory nodules

* Number of interventions during Period A

* Proportion of subjects with DLQI=0

* Proportion of subjects with DLQI=0 or 1

* Change from Baseline in DLQI

* Change from Baseline in WPAI:SHP

* Percentage change from Baseline in Patient's Global Assessment of Skin Pain (NRS) * at worst, among subjects who have baseline NRS * 1

* Percentage change from Baseline in Patient's Global Assessment of Skin Pain (NRS) * on average, among subjects who have baseline NRS * 1

* Change from Baseline in Patient's Global Assessment of Skin Pain (NRS) * at worst

* Change from Baseline in Patient's Global Assessment of Skin Pain (NRS) * on average

* Proportion of subjects achieving AN50 (at least 50% reduction in the AN count relative to Baseline)

* Proportion of subjects achieving AN75 (at least 75% reduction in the AN count relative to Baseline)

* Proportion of subjects achieving AN100 (100% reduction in the AN count relative to Baseline)

* Absolute and percentage change from Baseline in AN count

* Proportion of subjects achieving erythema score of 1 or 0 in all affected anatomic regions among subjects who have erythema score of 2 or more in at least one anatomic region at Baseline

* Proportion of subjects who experience worsening by at least one Hurley Stage in at least 1 affected anatomic region

* Proportion of subjects who experience improvement by at least one Hurley Stage in at least 1 affected anatomic region

* Change from baseline in TSQM (Treatment Satisfaction Questionnaire - Medication)

* Change from baseline in EQ-5D index

* Change from baseline in EQ-5D VAS

* Proportion of subjects who experience flare, defined as an at least 25% increase in AN counts with a minimum increase of 2 relative to Baseline

* Number of days on flare, calculated from the day when flare is observed to the day prior to the observation that flare is no long present. Of note, there could be multiple periods that flares are observed, in which case, the total days from the multiple periods will be used

* Proportion of subjects who experience at least 25% increase in abscess counts with a minimum increase of 2 relative to Baseline

* Proportion of subjects who experience at least 25% increase in inflammatory nodule counts with a minimum increase of 2 relative to Baseline

* Proportion of subjects who experience at least 25% increase in draining fistula counts with a minimum increase of 2 relative to Baseline

Study description

Background summary

HS is a painful, chronic, skin disease characterized by recurrent inflamed nodules and abscesses, which may rupture to form fistulas and subsequent scarring. The most commonly involved anatomic locations are the inguino-crural and axillary folds, with sub-mammary folds (in women) and the perineal area less commonly involved.
Hidradenitis Suppurativa has a severely negative effect on patients' quality of life. It typically presents with painful, deep-seated nodules, which either resolve spontaneously, persist as non-tender nodules, or progress to form abscesses. Abscesses typically rupture and release purulent drainage. Abscesses and nodules may heal with scarring and the formation of fistulas or sinus tracts. Thus, many patients with HS develop permanent sequelae of past inflammation that are only remediable through surgical excision of the involved

skin areas. The physical and psycho-social morbidity associated with en bloc excision of scarred axillary, inguinal, or groin skin is substantial. Rare complications of
HS include fistula formation into urethra, bladder, rectum, or peritoneum, lymphedema of the limbs or scrotal elephantiasis, and squamous cell carcinomas of the skin originating from HS lesions.
Hidradenitis Suppurativa affects approximately 1% of the general population. Disease onset is typically after puberty. Disease prevalence decreases from 1.5% in those < 25 years of age to 0.5% in those older than 55 years of age. It affects women from 2 to 5 times more commonly than men. Several factors may predispose a person to HS, including genetics, cigarette smoking, and obesity. The histopathologic characteristics of HS include a dense inflammatory cell infiltrate of neutrophils, lymphocytes, and histiocytes. Tumor necrosis factor-alpha (TNF-*), which induces pro-inflammatory cytokines and activates neutrophils and lymphocytes, may have a pathogenic role.

Study objective

The primary objective of this study is to determine the clinical safety and efficacy of adalimumab compared to placebo in subjects with moderate to severe HS after 12 weeks of treatment. A secondary objective is to evaluate safety and explore efficacy for continuous weekly dosing versus dose reduction versus maintenance of response off therapy from Week 12 to Week 36. The pharmacokinetics and immunogenicity of adalimumab following subcutaneous (SC) injection will also be assessed.

Study design

A randomised, double-blind, placebo-controlled multicenter study.

Intervention

The study was designed to enroll 300 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening will not be enrolled.

The study duration will include a 7 to 30-day Screening Period, an initial 12-week double-blind treatment period (Period A), and a subsequent 24-week double-blind treatment period (Period B), plus a Day 70 follow-up phone call 70 days after the last dose of study drug administration.

Period A:
A 12-week double-blind, placebo-controlled treatment period during which subjects are randomized at Day 1, in a 1:1 ratio to receive blinded adalimumab

40 mg every week (ew) or matching placebo for an evaluation of safety and efficacy. The randomization will be stratified by baseline Hurley Stage (II versus III) and baseline concomitant antibiotic use (Yes versus No). A subject's Hurley Stage is determined by
the worst Hurley Stage across all affected anatomic regions.

All subjects enrolled in this study who complete Period A are eligible to participate in Period B.

Period B:
A 24-week double-blind, placebo-controlled treatment period. All subjects continuing to Period B, regardless of the treatment in Period A, will be re-randomized at Week 12 to maintain the blind. Subjects randomized to adalimumab in Period A are re-randomized in a 1:1:1 ratio to receive blinded adalimumab 40 mg ew, adalimumab 40 mg every-other-week (eow), or placebo from Week 12 to Week 35. The re-randomization will be stratified by Week 12 HiSCR response (responder versus non-responder) (See Section 1.2 for definition of term) and by baseline Hurley Stage (II versus III). Subjects from the placebo arm in Period A (Arm 2) will continue on blinded placebo from Week 12 to Week 35.

All subjects (Arm 1 and Arm 2) who achieve HiSCR at Week 12 will continue in Period B through Week 36. Subjects who experience a loss of response (LOR), defined as an AN count that is greater than the average of AN counts at Baseline and Week 12, will be discontinued from the study and have the opportunity to enter the open-label extension (OLE) Study M12-555 to receive open-label adalimumab 40 mg ew.

All subjects (Arm 1 and Arm 2) who do not achieve HiSCR at Week 12 will continue in Period B through Week 36. Starting at or after Week 16, subjects who experience a Worsening or Absence of Improvement, defined as an AN count that is greater than or equal to the AN count at Baseline on two consecutive visits (excluding Week 12) occurring at least 14 days apart, they may be discontinued from the study and have the opportunity to enter the OLE Study M12-555 to receive open-label adalimumab 40 mg ew.

At Week 36, all subjects will have the opportunity to enter in the OLE Study M12-555 where they will receive adalimumab 40 mg ew.

Study visits will occur at Baseline, Week 2, Week 4, Week 8, Week 12, Week 14, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, and at the Premature Discontinuation visit if the subject discontinues prior to Week 36.
Additionally, all subjects will be contacted by phone 1 week following the Baseline visit to ensure daily pain assessments are being recorded, and at Weeks 6 and 10 to monitor whether any signs or symptoms of infection are present at or near an HS lesion.

Study burden and risks

The subjects will participate in the study for 36 weeks. During this period, all subjects will visit the hospital 13 times. 70 Days after the last adalimumab injection, the subject will get a follow-up telephone call. During the screening visit, an ECG will be made, and an X-ray of the thorax.
For the X-ray of the thorax, the subject will be exposed to a small amount of radiation. This amount of radiation is not considered a significant risk.
Furthermore, a PPD (Mantoux) or QuantiFERON test will be done. A physical exam will be done during all visits. In total, blood will be withdrawn 13 times, between 6-13 times (in total 310 ml). The drawing of blood can leas to fainting, infection of the artery, pain, bruising, and infections. also bleeding can occur on the site of puncture. The subject has to complete questionnaires. Some of these have to be completed on 8 visits, others 3 or 4 times. All subjects need to take a urine sample to 9 of the visits. Women who can become pregnant need to take a urine sample to all visits.
The subject can have adverse events when using the study medication. Most frequent adverse events are injection site reactions. Subjects can have redness, itching, bruising pain and/or swelling of the injection site. Most reactions are considered mild or moderate, and most reactions disappeared without stopping the treatment with adalimumab. The following adverse events have been reported frequently: upper respiratory tract infection, headache, skin rash, sinusitis, bronchitis, nausea, diarrhea, abdominal pain, joint pain, backpain, urinary tract infections, hypertension and influenza. Women of fertile age have to use a reliable method of contraception as described in the protocol. The use of some medication is not allowed during the study. This is described in the protocol. (Page 34-39, section 5.2.3 Protocol version 25 august 2011)

Contacts

Public
AbbVie BV

Wegalaan 9
Hoofddorp 2132 JD
NL
Scientific
AbbVie BV

Wegalaan 9
Hoofddorp 2132 JD
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Adult subjects must have a diagnosis of HS for at least 1 year (365 days) prior to Baseline;;* HS lesions must be present in at least two distinct anatomic areas, one of which must be at least Hurley Stage II or Hurley Stage III;;* Subject must have stable HS for at least 2 months (60 days) prior to Screening and also at the Baseline visit as determined by the investigator through subject interview and review of medical history; ;* Subject must have had an inadequate response to at least a 3-month (90 days) trial of an oral antibiotic for treatment of HS (or demonstrated intolerance to, or have a contraindication to, oral antibiotics for treatment of their HS);;* Subject must have an AN count of greater than or equal to 3 at the Baseline visit;;* Subject has a negative TB screening assessment (including a PPD test and/or Quantiferon-TB Gold test, or equivalent) and negative chest x-ray (CXR) (posterior-anterior [PA] and lateral view) at Screening;;* Subject must agree to daily use (and throughout the entirety of the study) of one of the following over-the-counter topical antiseptics on their HS lesions: chlorhexidine gluconate, triclosan, benzoyl peroxide, or dilute bleach in bathwater;;* Subject is judged to be in good general health, as determined by the Principal Investigator based upon the results of a medical history, physical examination, laboratory profile, CXR and a 12 lead ECG performed during the Screening period and confirmed at Baseline.

Exclusion criteria

* Prior treatment with adalimumab or other anti-TNF therapy (e.g., infliximab or etanercept), or participation in an adalimumab trial;;* Subjects on permitted oral antibiotic treatment (doxcycline or minocycline only) for HS who have not been on a stable dose for at least 28 days prior to the Baseline visit; ;* Subject received oral concomitant analgesics (including opioids) for HS-related pain within 14 days prior to the Baseline visit; ;* If entering the study on concomitant oral analgesics for non-HS-related pain:;* Subject on opioid analgesics within 14 days prior to Baseline visit;;* Subject not on a stable dose of non-opioid oral analgesics for at least 14 days prior to the Baseline visit (PRN is not considered a stable dose).;* Subject

requires, or is expected to require, opioid analgesics for any reason (excluding tramadol);;* Subject received prescription topical therapies for the treatment of HS within 14 days prior to the Baseline visit;;* Subject received systemic non-biologic therapies for HS with potential therapeutic impact for HS less than 28 days prior to Baseline visit (other than permitted oral antibiotics);;* Subject has a draining fistula count of greater than 20 at the Baseline visit;;* Infection(s) requiring treatment with intravenous (IV) anti-infectives (antibiotics, antivirals, antifungals) within 30 days prior to Baseline or oral anti-infectives (antibiotics, antivirals, antifungals) within 14 days prior to Baseline, except as required as part of an anti-TB regimen;;* Any other active skin disease or condition (e.g., bacterial, fungal or viral infection) that may interfere with assessment of HS;;* History of demyelinating disease (including myeleitis) or neurologic symptoms suggestive of demyelinating disease;;* History of invasive infection (e.g., listeriosis, histoplasmosis), human immunodeficiency virus (HIV);;* Subject has an active systemic viral infection or any active viral infection that based on the investigator's clinical assessment make the subject an unsuitable candidate for the study;;* Hepatitis B: HBsAg positive (+) or detected sensitivity on the HBV-DNA PCR qualitative test for HBc Ab/HBsAb positive subjects;;* Chronic recurring infections or active TB;;* History of moderate to severe congestive heart failure (NYHA class III or IV), recent cerebrovascular accident and any other condition which, in the opinion of the investigator, would put the subject at risk by participation in the protocol;;* Evidence of dysplasia or history of malignancy (including lymphoma and leukemia) other than a successfully treated non-metastatic cutaneous squamous cell carcinoma, basal cell carcinoma or localized carcinoma in situ of the cervix;;* Pregnant or lactating females.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-10-2012

Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Humira
Generic name:	Adalimumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Placebo
Generic name:	Placebo

Ethics review

Approved WMO Date:	10-04-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-06-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-07-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-07-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-09-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	03-12-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-12-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-07-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-10-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-12-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-08-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-10-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2011-003406-24-NL
ClinicalTrials.gov	NCT01468233
CCMO	NL38118.018.12