An exploratory, single-center, double-blinded, healthy volunteer controlled study to characterize psoriasis patients and explore novel biomarkers for the treatment response of psoriasis with a multi-modal patient profiling approach

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The study is divided into two sections:Part A is a healthy volunteer controlled observational study to determine the course of the disease over time to:- Evaluate disease-related biomarkers in psoriasis when compared with healthy volunteers;-...

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

Summary

ID

NL-OMON52891

Source
ToetsingOnline

Brief title
An explorative psoriasis biomarker study

Condition

- Skin and subcutaneous tissue disorders NEC

Synonym
Psoriasis

Research involving

Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: Janssen Biologics B.V.

Intervention

Keyword: Biomarkers, Guselkumab, Psoriasis

Outcome measures

Primary outcome

This study will monitor the change over time in:

• Serum concentration of guselkumab and anti-guselkumab antibodies

• Blood-based biomarkers (whole blood, serum and plasma samples)

o Biomarkers will include, but are not limited to, cellular targets (e.g. T cells, TH17 cells, γδ T cells) from whole blood, comprehensive metabolomic and proteomic analysis from serum and/or plasma covering cytokines (e.g. IL-22, IL21, TNFα), chemokines (e.g. CCL20, CCL17, CXCL8), amines (e.g. amino acids, neurotransmitters) and inflammatory signalling lipids (e.g. prostaglandins, leukotrienes, isoprostanes).

• Blister fluid-based biomarkers

o Biomarkers will include, but are not limited to, cellular targets (e.g. T cells, TH17 cells, γδ T cells) and proteomic analysis covering cytokines (e.g. IL-22, IL21, TNFα), chemokines (e.g. CCL20, CCL17, CXCL8).

• Skin biopsies for:

o mRNA extraction for next-generation RNA sequencing

o Histology by haematoxylin and eosin staining but might also include

additional immunohistochemical stainings focussing on e.g. proliferation, complement activation and presence of cellular immune infiltrate.

• Microbiome (skin, faecal)

• Laser Speckle Contrast Imaging (LSCI)*

• Thermography*

• Clinical assessment (PASI, PGA,BSA)*

• Colorimetry*

• Optical coherence tomography (OCT)*

• Multispectral imaging*

• Total body photography (digital PASI)*

• Patient reported outcomes (pruritus, sleeplessness, QoL, activity by smartwatch, at-home plaque monitoring)*

• Skin surface markers*

• Skin barrier function (TEWL)*

• Lipidomics of stratum corneum by LC-MS*

• Flow-mediated skin fluorescence (FMSF)*

Endpoints marked *** denote non-invasive assessments. Note: if feasible, target areas for invasive measurements will also be investigated non-invasively over time. This will allow exploration of the correlation between molecular/cellular and functional measurements, and evaluation of wound healing.

Secondary outcome

N.A.

Study description

Background summary

Psoriasis is a common skin disorder affecting up to an estimated 3% of the world*s population. The most prevalent form of psoriasis, called psoriasis vulgaris or plaque psoriasis, is characterized by the presence of sharply demarcated erythematous plaques covered with white scales. These lesions can occur all over the body, but are most often seen on the extensor surface of the joints, nether regions and on the scalp. Patients can experience excessive itch, pain and sometimes bleeding of the lesions. Moreover, the visual appearance of psoriatic lesions can severely impact the patients psychological state and quality of life (Boehncke and Schön, 2015).

An abundancy of different factors contributes to the pathogenesis of psoriasis. However, aberrant inflammatory reactions in the skin are thought to be the underlying cause. Excessive infiltration of immune cells in the skin and their interactions with cutaneous resident cells results in the hyper proliferation of keratinocytes and subsequent thickening of the epidermis. Indeed, more and more immunosuppressive biologicals targeting specific components of the immune system, like tumor necrosis factor alpha (TNFα), interleukin (IL-)17 and IL-23, have shown excellent efficacy in treating psoriasis (Dainichi et al., 2018).

Plaque psoriasis may be an ideal model disease to explore potential therapeutic effects of immunosuppressive agents, given the easy accessibility of inflammatory lesions and the good willingness of patients to participate in clinical studies. In this study, the applicability of a systems dermatology approach is investigated in order to better assess the efficacy of psoriasis treatments at an early clinical stage. Up to this point, the clinical manifestation and regression of psoriasis is not yet sufficiently characterized with a multimodal state-of-the-art evaluation tool. The in-house developed *DermaToolbox* enables the determination and subsequent integration of different disease-related biomarkers, including clinical, biophysical, molecular, cellular, and imaging markers as well as patient-reported outcomes (figure 1).

Study objective

The study is divided into two sections:

Part A is a healthy volunteer controlled observational study to determine the course of the disease over time to:
- Evaluate disease-related biomarkers in psoriasis when compared with healthy volunteers;
- Evaluate the variability of the selected biomarkers between subjects, and within subjects over time.

Part B is an interventional and placebo controlled study in psoriasis patients to:
- Evaluate the biomarker for use in disease-monitoring after pharmacological intervention.

Study design

This is an observational and interventional study in up to 40 patients with chronic plaque psoriasis and 10 healthy volunteers (observational only). All volunteers will visit CHDR for a screening and several short visits.

Prior to treatment and following the screening, an initial two-week observational period is scheduled in order to characterize the natural course of the disease compared to a cohort of 10 healthy volunteers. Hereafter, only psoriasis patients will continue with the interventional part. Patients will be randomized in a 3:1 ratio to 16-week guselkumab treatment or placebo.. During this 16-week period, the same assessments will be performed with regular intervals in order to assess the proposed biomarker applicability over a longer time frame. Patients will be recalled for a follow-up visit 8 weeks after the end of the treatment period to assess possible recurrence of psoriasis symptoms.

Study assessments will comprise clinical, patient reported, biophysical, molecular, cellular, and imaging outcomes, of which some require 4 mm skin biopsies or skin blister induction. For psoriasis patients, both lesional and non-lesional skin biopsies will be collected. Suction blisters will be induced on peri-lesional and non-lesional skin.
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Intervention

Guselkumab (Tremfya, Janssen-Cilag) is an anti-interleukin 23 monoclonal antibody indicated for the treatment of moderate-to-severe plaque psoriasis in patients that are candidates for systematic treatment. Guselkumab has been approved for use by the European Medicine Agency in late 2017 after showing high efficacy and safety. Patients will receive either the standard therapeutic dosing regimen of 100 mg guselkumab or placebo administered subcutaneously on day 0, 28 and 84.

Study burden and risks

Guselkumab has been approved by the European Medicine Agency for the treatment of moderate to severe plaque psoriasis in patients applicable for systematic treatment. The European Product Assessment Report states guselkumab shows a remarkable short- and longer-term efficacy accompanied by a favourable tolerability and safety profile in over 1500 patients during phase II and phase III clinical trials. During these trials, the majority of patients treated with

guselkumab obtained a PASI 90 or IGA 0/1 at week 16 (resp. >70.0%, >84.1%), thereby showing superiority in efficacy over adalimumab. On the other hand, guselkumab treated patients are more susceptible to infections compared to placebo (nasopharyngitis; 19.6%, upper respiratory tract infections; 10.2%, oral herpes; 1.6% and tinea pedis; 1.1%). However, their incidence was similar compared to the adalimumab treated control group. Overall, treatment of plaque psoriasis with guselkumab is considered efficacious and safe.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Healthy volunteers
Eligible healthy volunteers must meet all of the following inclusion criteria at screening:

1. Male or non-pregnant female subjects, 18 to 75 years of age (inclusive); during COVID-19 pandemic this is set to 18 to 69 year of age (inclusive)
2. Healthy as defined by the absence of any uncontrolled active or uncontrolled chronic disease following a medical and surgical history, documentation of general symptoms, and a symptom-directed physical examination including vital signs;
3. Willing to give written informed consent and willing and able to comply with the study protocol;

Psoriasis patients
Eligible psoriasis patients must meet all of the following inclusion criteria at screening:
1. Male or non-pregnant female subjects, 18 to 75 years of age (inclusive); during COVID-19 pandemic this is set to 18 to 69 year of age (inclusive)
2. Diagnosed with plaque psoriasis at least 6 months prior to study participation
3. Willing to discontinue any psoriasis therapy other than emollients.
4. Having mild ((BSA PASI >=1 and <= 5) (BSA >=1% andPASI <= 5%) or moderate-to-severe (PASI >= 10) plaque psoriasis
5. Currently not using psoriasis medication and >= 2 plaques suitable for repeated biopsies and target lesion assessments. At least one of these lesions must be located on the extremities, preferably on the elbow or knee, with a minimal target lesion score between 6 and 9. Or, when currently using psoriasis medication and insufficient lesional skin is present, willing to discontinue treatment awaiting rescreening (see also exclusion criteria 3 for psoriatic patients);
6. Willing to give written informed consent and willing and able to comply with the study protocol;

Exclusion criteria

Healthy volunteers
Eligible healthy volunteers must meet none of the following exclusion criteria at screening:
1. History or symptoms of any uncontrolled, significant disease including (but not limited to), neurological, psychiatric, endocrine, cardiovascular, respiratory, gastrointestinal, hepatic, or renal disorder that may interfere with the study objectives, in the opinion of the Investigator;
2. History of immunological abnormality (e.g., immune suppression, severe allergy or anaphylaxis) that may interfere with study objectives, in the opinion of the Investigator;
3. Known infection requiring antibiotic therapy within the last three months prior to the study;
4. Immunosuppressive or immunomodulatory treatment within 30 days prior to the study;

5. Body mass index (BMI) <= 18.0 or >= 40.0 kg/m2; during COVID-19 pandemic only <= 18.0 or > 33.0 kg/m2
6. Participation in an investigational drug study within 3 months prior to screening or more than 4 times a year;
7. Previous participation in an investigational drug study involving the dosing of an investigational compound targeting an immune pathway within one year prior to screening;
8. Loss or donation of blood over 500 mL within three months prior to screening;
9. The use of any medication or vitamin/mineral/herbal/dietary supplement within less than 5 half-lives prior to study participation, if the Investigator judges that it may interfere with the study objectives. The use of paracetamol (up to 4 g/day) and ibuprofen (up to 1 g/day) is allowed;
10. History of alcohol consumption exceeding 5 standard drinks per day on average within 3 months of screening. Alcohol consumption will be prohibited from at least 12 hours preceding each study visit;
11. Any other condition that could interfere with the conduct of the study or the study objectives, in the opinion of the Investigator.
12. During COVID-19 pandemic: presence of high risk comorbidities: such as cardiovascular, respiratory or immune system disorders

Psoriasis patients
Eligible psoriasis patients must meet none of the following exclusion criteria at screening:
1. Having primarily erythrodermic, pustular or guttate psoriasis;
2. Having medication-induced psoriasis;
3. Having previously failed on anti-IL23 therapy;
4. Having received treatments for psoriasis within the following intervals prior to the start of the study:
a. < 2 weeks for topical treatment, e.g. retinoids, corticosteroids, vitamin D analogs
b. < 4 weeks for phototherapy, e.g. PUVA, PDT
c. < 4 weeks for non-biologic systemic treatment, e.g. retinoids, methotrexate, cyclosporine, fumaric acid esters
d. < 4 weeks for etanercept
e. < 8 weeks for adalimumab
f. < 3 months for anti-IL17, anti-IL12(/23) and anti-IL23 treatments
5. History or symptoms of any significant uncontrolled disease including (but not limited to), neurological, psychiatric, endocrine, cardiovascular, respiratory, gastrointestinal, hepatic, or renal disorder that may interfere with the study objectives, in the opinion of the Investigator, excluding psoriasis and conditions that are related to psoriasis;
6. History of immunological abnormality (e.g., immune suppression, severe allergy or anaphylaxis) that may interfere with study objectives, in the opinion of the Investigator;
7. Known infection requiring antibiotic therapy within the last 3 months prior to the study, including latent tuberculosis;
8. Systemic immunosuppressive or immunomodulatory treatment within 30 days

prior to the study;
9. Body mass index (BMI) <= 18.0 or >= 40.0 kg/m2; during COVID-19 pandemic only <= 18.0 or > 30.0 kg/m2
10. Participation in an investigational drug study within 3 months prior to screening or more than 4 times a year;
11. Loss or donation of blood over 500 mL within three months prior to screening;
12. The use of any medication or vitamin/mineral/herbal/dietary supplement within less than 5 half-lives prior to study participation, if the Investigator judges that it may interfere with the study objectives. The use of paracetamol (up to 4 g/day) and ibuprofen (up to 1 g/day) is allowed;
13. History of alcohol consumption exceeding 5 standard drinks per day on average within 3 months of screening. Alcohol consumption will be prohibited from at least 12 hours preceding each study visit;
14. Any other condition that could interfere with the conduct of the study or the study objectives, in the opinion of the Investigator.
15. During COVID-19 pandemic: presence of high risk comorbidities: such as cardiovascular, respiratory or immune system disorders other than psoriasis and psoriasis arthritis

Study design

Design

Study phase:	4
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):	15-10-2020
Enrollment:	50
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Tremfya
Generic name:	Guselkumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	13-06-2019
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-08-2019
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	27-01-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-02-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-08-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-08-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-12-2020
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-01-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-03-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	02-06-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-06-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-09-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-10-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-01-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-01-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-08-2022
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-09-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	EUCTR2019-002383-27-NL
CCMO	NL70359.028.19