A multi-centre Phase IIa double-blind, placebo-controlled study to investigate the efficacy and safety of GSK3196165 in subjects with inflammatory hand osteoarthritis

Published: 18-12-2015
Last updated: 20-04-2024

Primary Objective:To assess the efficacy potential of GSK3196165 on pain in inflammatory HOA.Secondary endpoints:To evaluate impact of GSK3196165 on average and worst HOA pain, over time.To assess the impact of GSK3196165 on hand pain (on use),...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Joint disorders
Study type	Interventional

Summary

ID

NL-OMON46207

Source
ToetsingOnline

Brief title
HOA: osteoarthritis

Condition

- Joint disorders

Synonym
cartilage degeneration of the joints in the hand, hand osteoarthritis

Research involving
Human

Sponsors and support

Primary sponsor: GlaxoSmithKline
Source(s) of monetary or material Support: GlaxoSmithKline

Intervention

Keyword: Granulocyte-macrophage colony stimulating factor (GM-CSF), GSK3196165, HOA: hand osteoarthritis, Inflammation

Outcome measures

Primary outcome

Primary study parameter / outcome:

Change from baseline in 24h average hand pain intensity at Week 6, as measured

by daily pain Numerical Rating Scale (NRS) averaged over the 7

days prior to assessment visit.

Secondary outcome

Secundary study pararmeters / outcomes:

Change from baseline in 24h average hand pain intensity at each visit, measured

by daily pain NRS and averaged over the 7 days prior to each

assessment visit.

Change from baseline of worst hand pain intensity over 24h at each visit,

measured by daily NRS and averaged over the 7 days prior to each assessment

visit.

Proportion of subjects in each treatment group achieving a 30% reduction in 24h

average hand pain intensity at each visit, measured by daily NRS

averaged over the 7 days prior to assessment visit.

Proportion of subjects in each treatment group achieving a 50% reduction in 24h average hand pain intensity at each visit, measured by daily NRS averaged over the 7 days prior to assessment visit.

Proportion of subjects in each treatment group achieving a 30% reduction in 24h worst hand pain intensity at each visit, measured by daily NRS averaged over the 7 days prior to assessment visit.

Proportion of subjects in each treatment group achieving a 50% reduction in 24h worst hand pain intensity at each visit, measured by daily NRS averaged over the 7 days prior to assessment visit.

Change from baseline in Australian Canadian Hand Osteoarthritis Index (AUSCAN) 3.1 NRS, total and domains (pain, morning stiffness, function) scores at each visit.

Change in number of swollen and tender hand joints at each visit.

Change from baseline in patient global assessment (PtGA) and physician global assessment (PhGA) of disease activity at Week 6,12 and 22.

Incidence of adverse events and serious adverse events.

Incidence of infections.

Incidence of pulmonary events (cough/dyspnea, PAP and DLCO).

Immunogenicity.

Population pharmacokinetics endpoints such as CL/F, Vss/F, Ka.

Study description

Background summary

Hand osteoarthritis (HOA) is the second most common form of osteoarthritis (OA) which is itself, the most common musculoskeletal disorder. The presentation of HOA is typically with symptoms reflecting underlying inflammation in the proximal joints of the hand affecting the synovium, cartilage and bone.Severe hand pain can significantly impair day to day activities through functional impairment in the form of stiffness, reduced grip strength, reduced hand mobility, and difficulty performing dexterous tasks. Treatment options for both inflammatory and erosive HOA are limited and are focused on alleviating symptoms through pain medication, local steroid injections and surgical intervention but provide limited, if any, benefit.

The etiology of OA is likely to be multifactorial, and recent histological evidence indicates that synovitis is an early feature in OA, even in joints where it could not be detected clinically, with a mixed inflammatory infiltrate consisting mainly of macrophages and with pro-inflammatory mediator production. It has been found that Granulocyte-macrophage colony stimulating factor receptor (GM-CSFR) is expressed in OA synovium. GM-CSF induces the proliferation and activation of macrophage lineage cells leading to strongly increased production of key proinflammatory cytokines. Furthermore, it has been demonstrated pre-clinically that GM-CSF is linked to the development of experimental and spontaneous osteoarthritis and it is associated with pain, function, matrix degrading proteases and structural disease severity. Importantly, GM-CSF neutralization by a therapeutic monoclonal antibody rapidly and completely abolished existing arthritic pain and suppressed the degree of arthritis development in the collagenase induced model of OA.

Taken together, pre-clinical and clinical data suggest that blocking GM-CSF should interfere with several pathophysiological pathways and significantly reduce inflammation by inhibiting activation of inflammatory cells within the OA joint and by blocking the chemotaxis recruitment of such non-resident inflammatory cells, thus leading to a benefit on inflammatory pain and inhibiting bone and cartilage destruction. GSK3196165 is a high-affinity recombinant human monoclonal antibody (mAb) that binds specifically to human GM-CSF and neutralises its biological function by blocking the interaction of GM-CSF with its cell surface receptor.

This study is designed to investigate whether GSK3196165 may offer a treatment benefit for subjects with inflammatory hand osteoarthritis.

Study objective

Primary Objective:
To assess the efficacy potential of GSK3196165 on pain in inflammatory HOA.

Secondary endpoints:

To evaluate impact of GSK3196165 on average and worst HOA pain, over time.
To assess the impact of GSK3196165 on hand pain (on use), stiffness and function, over time.
To assess the impact of GSK3196165 on HOA inflammation
To assess potential impact of GSK3196165 on disease activity in HOA,
To assess safety of GSK3196165 in HOA patients, over the study duration.
To assess population pharmacokinetics of GSK3196165 in HOA.

Study design

This study will be double-blinded (subjects, investigators and sponsor blinded), however at least one unblinded drug administrator will be required at each site to administer the study treatment.

For screening, baseline and efficacy assessments, the average pain intensity over 7 days prior to assessment date will be used. This is calculated from collected daily pain NRS data over 7 days.

Imaging MRI will be carried out at screening, Week 12 and Week 22. (Note: MRI at screening will serve as the baseline measurement).

At baseline subjects will be evaluated by pain NRS (average 7 days prior to visit), AUSCAN 3.1 NRS, PtGA, PhGA, number of tender and swollen joints in their hands and blood will be collected for safety, biomarker monitoring, and pharmacokinetics.

Throughout the study treatment period, subjects will be assessed for hand pain using a daily pain NRS questionnaire (daily from screening to Week 12). In addition, at the specified time points (see Section 7.1, time and events table), function and disease state will be assessed using the AUSCAN 3.1 NRS, PtGA and PhGA. The number of tender and swollen joints in affected hands will also be assessed and blood samples will be collected for safety, biomarkers monitoring, and pharmacokinetics.

At the Week 22 follow up visit, blood will again be collected for safety monitoring as well an assessment of pain NRS (average 7 days prior to visit), PtGA, PhGA and MRI imaging of the affected hand.

For MRI endpoints the assessments are based on one hand only. In cases where both hands are affected by HOA and both meet the inclusion criteria, then the dominant hand will be documented at screening and this hand will be used for the MRI assessments throughout the study.

Intervention

The Study consists of 2 arms: treatment with GSK3196165 or placebo will be given as a single subcutaneous injection (shielded to subjects) to the abdomen or thigh, by an unblinded administrator weekly for 5 injections, from Week 0 to Week 4 (Days 1, 8, 15, 22, 29), then every other week for 3 further injections, from Week 6 until Week 10 (Days 43, 57 and 71). In total, each subject will receive up to 8 doses of study treatment.

Safety should be monitored for 1 hour after the injection, for the first 3 injections, then for 30 minutes thereafter. Such monitoring will include general safety monitoring including monitoring for systemic hypersensitivity infusion reactions and local injection site reactions.

Study burden and risks

During the conduct of the study, the subjects will visit the hospital 12 times and will undergo the following assessments:
12-lead ECG (at screening, baseline and week 12)
Vital signs and physical examination (screening, baseline, week 2, 4, 8 and 12)
Blood draws (at screening, baseline, week 1, 2, 4, 6, 8, 10, 12 and 22): potential risks associated with local reactions (e.g., swelling, induration, pain).
Pulmonology assessments (at screening, baseline, week 1, 2, 4, 6, 8, 10, 12 and 22):
Spirometry (at screening, baseline and week 12 and 22)
Swollen and tender joints assessment (at screening, baseline, week 1, 2, 4, 6, 8, 10, 12 and 22):
MRI (week Screening, week 12 and week 22): potential risks associated with

exposure to a high field MRI magnet and Gadolinium (Gd) containing MRI contrast agents)
Questionnaires: questionnaires (Pain NRS, AUSCAN 3.1 NRS, Patient Global Assessment of Disease Activity [PtGA]) will be completed at relevant study visits or at home as described in the Time and Events Table (Section 7.1 of the protocol).

Treatment of GSK3196165 might be associated with an increased risk to the following uncommon side effects:
Increased risk of infection.
Increased risk to the extremely rare condition of PAP (Pulmonary alveolar proteinosis).
There is a potential risk of hypersensitivity reactions, including anaphylaxis.
Subcutaneous injections may be associated with local reactions (e.g., swelling,induration, pain).
Increased risk of neutropenia
Increased risk on malignancies

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

1. Age * 18 years at the time of signing the informed consent.
2. Meets ACR classification of OA and is intolerant to, or has not responded to analgesics (level 1 and 2) or to NSAIDs for at least 10 days in the past 3 months.
3. Must have active disease with at least two swollen and tender PIP and/or DIP joints in the affected hand*.
and tender PIP and/or DIP joints in the affected hand*; with the same two joints affected at both screening and randomization.
4. Signs of inflammation such as synovitis in the MRI scan of the affected hand*.
5. Must have a patient*s self assessment of 24h average hand pain intensity of at least *5* on an 11-point NRS (0-10), calculated as an average using data from the 7 days prior to assessment date.
6. Body weight <= or > 45 kg.
7. Male or female subjects are eligible to participate so long as they meet and agree to abide by the contraceptive criteria.
8. Written informed consent prior to any of the screening procedures including discontinuation of prohibited medications.
9. Diffusing capacity of the lung for carbon monoxide (DLCO) * 70 % predicted and forced expiratory volume in 1 second (FEV1) * 80 % predicted.
10. No evidence of active or latent infection with Mycobacterium tuberculosis (TB), as defined by all of the following:
a. No history of active or latent TB infection irrespective of treatment status.
b. A negative diagnostic TB test within 28 days of baseline (Day 1) defined as: a negative QuantiFERON Gold test or T-spot test (may be performed locally) (NB: 2 successive indeterminate QuantiFERON tests will be considered as a positive result).

Exclusion criteria

1. Pregnant or lactating females.
2. Significant unstable or uncontrolled acute or chronic disease (e.g., cardiovascular including uncompensated congestive cardiac failure NYHA III or IV, myocardial infarction within 12 months, unstable angina pectoris, uncontrolled hypertension, hypercholesterolemia) pulmonary, hematologic, gastrointestinal (including Crohn*s Disease or ulcerative colitis), hepatic, renal, neurological, psychiatric, malignancy, endocrinological, immunologic or infectious diseases, which, in the opinion of the investigator, could confound the results of the study or put the subject at undue risk.

3. History of any clinically significant inflammatory disease other than inflammatory HOA, especially, but not limited to, rheumatoid arthritis or spondylarthropathies.
4. Diagnosis of rheumatoid arthritis, fibromyalgia, gout, calcium pyrophosphate deposition disease CPPD, pseudogout, hemochromatosis or other inflammatory rheumatological or autoimmune disorders.
5. Clinical suspicion of, or previous investigation for CPPD or pseudogout, or history of chondrocalcinosis.
6. Any injury, medical or surgical procedure to the affected joint(s) that may interfere with evaluation of the target HOA joint(s).
7. History of any clinically-significant respiratory disease that required treatment and/or follow up under the direction of a physician or any respiratory disease which in the opinion of the Investigator would compromise the ability of the subject to complete the study (e.g. interstitial lung disease, such as pulmonary fibrosis, chronic obstructive pulmonary disease [COPD], moderate-severe asthma, bronchiectasis, pneumonitis, pulmonary alveolar proteinosis (PAP), significant exposure to pneumotoxins (e.g. inhaled silica).
8. Clinically-significant or unstable (in the opinion of the Investigator) persistent cough or dyspnea that is unexplained.
9. QTc > 450 msec or QTc > 480 msec in subjects with Bundle Branch Block based on averaged values of triplicate electrocardiograms obtained over a brief (e.g. 5-10 minute) recording period.
* The QTc is the QT interval corrected for heart rate according to Bazett*s formula (QTcB), Fridericia*s formula (QTcF), and/or another method, machine-read or manually over-read.
10. ALT >2xULN and bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
11. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
12. A history of malignant neoplasm within the last 10 years or breast cancer within the last 20 years, except for non-melanoma skin cancers that have been excised and cured or carcinoma in situ of the uterine cervix.
13. Kidney disease: Current or history of renal disease, or estimated creatinine clearance <60 mL/min/1.73m2 or serum creatinine >1.5xULN within 28 days of Day 1.
14. Hereditary or acquired immunodeficiency disorder, including immunoglobulin deficiency.
15. History of infected joint prosthesis at any time, with the prosthesis still in situ. History of leg ulcers, catheters, chronic sinusitis or recurrent chest or urinary tract infections.
16. Active infections, or history of recurrent infections (excluding recurrent fungal infections of the nail bed), or have required management of acute or chronic infections, as follows:
a. Currently on any suppressive therapy for a chronic infection (such as tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria).
OR
b. Hospitalization for treatment of infection within 26 weeks of Day 1.
OR
c. Use of parenteral (IV or IM) antimicrobials (antibacterials, antivirals, antifungals,

or antiparasitic agents) within 26 weeks of Day 1 or oral antimicrobials within 14 days of Day 1.
17. A vaccination (live or attenuated) within 30 days of Day 1 or BCG vaccination within 365 days of Day 1, or a live vaccination planned during the course of the study.
18. Any surgical procedure, including bone or joint surgery/synovectomy within 12 weeks prior to Day 1 or any planned surgery within the duration of the study or follow-up period.
19. Contraindication to MRI scanning (as assessed by local MRI safety questionnaire) which includes but not limited to:
a. Intracranial aneurysm clips (except Sugita) or other metallic objects,
b. History of intra-orbital metal fragments that have not been removed by an medical professional.,
c. Pacemakers or other implanted cardiac rhythm management devices and non-MR compatible heart valves,
d.Inner ear implants, except MR-conditional implants scanned within manufacturer guidelines,
e. History of claustrophobia which may impact participation
20. Use any of prohibited medications, as listed in Section 6.10.2, throughout the study until after completion of the week 22 follow-up visit. Prohibited medications must be discontinued for the stated time in Section 6.10.2 prior to Day 1.
21. Have current drug or alcohol abuse or dependence, or a history of drug or alcohol abuse or dependence within a year prior to Day 1.
22. History of sensitivity to any of the study treatments, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or GSK Medical Monitor, contraindicates their participation.
23. Contraindication to gadolinium contrast agent as assessed by the site.
24. Must have negative titer rheumatoid factor (RF) and anti-CCP antibody.
25. Any Grade 3 or 4 hematology or clinical chemistry laboratory abnormality [CTCAE, 2009 v4.0] within 28 days of Day 1.
26. Hemoglobin *9 g/dL; white blood cell count *3.0 x109/L; platelet count *100 X 109/L; absolute neutrophil count *1.5 x 109/L; lymphocyte count *0.8 x 109/L within 28 days of Day 1.
27. Presence of hepatitis B surface antigen (HBsAg) and/or presence of hepatitis B core antibody (HBcAb) at screening.
28. Positive hepatitis C antibody test result at screening. Subjects with positive Hepatitis C antibody due to prior resolved disease can be enrolled only if a confirmatory negative Hepatitis C RNA PCR test is obtained.
29. Positive serology for human immunodeficiency virus (HIV) 1 or 2 (within 28 days of Day 1).
30. A positive pre-study drug/alcohol screen.
31. The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).
32. Exposure to more than 4 investigational medicinal products within 12 months prior to

the first dosing day.

Study design

Design

Study phase:	2
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):	31-05-2016
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NVT
Generic name:	monoclonal antibody, IgG1 lambda

Ethics review

Approved WMO

Date:	18-12-2015
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	05-04-2016
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-07-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-08-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-12-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-01-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-03-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-04-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2015-003089-96-NL
CCMO	NL55882.100.15