A multicentre randomized, double-blind, placebo-controlled Phase 2 study to evaluate the safety, tolerability, efficacy, dose-response, pharmacokinetics and pharmacodynamics of repeat dosing of an anti-LAG3 cell depleting monoclonal antibody (GSK2831781) in patients with active ulcerative colitis

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Primary:- To evaluate the safety and tolerability of repeat doses of GSK2831781 during the Induction Phase.- To characterise the efficacy dose-response of GSK2831781 during the Induction Phase.Secondary:- To evaluate the safety and tolerability of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal inflammatory conditions
Study type	Interventional

Summary

ID

NL-OMON49796

Source
ToetsingOnline

Brief title
204869

Condition

- Gastrointestinal inflammatory conditions

Synonym
inflamatory bowel disease, Ulcerative colitis

Research involving
Human

Sponsors and support

Primary sponsor: GlaxoSmithKline
Source(s) of monetary or material Support: GlaxoSmithKline Research & Development Limited

Intervention

Keyword: ulcerative colitis

Outcome measures

Primary outcome

- Numbers of participants with adverse events and serious adverse events up to

Week 10.

- Numbers of participants with findings of potential clinical importance up to

Week 10 for: Vital signs, Clinical laboratory values (haematology, clinical

chemistry and urinalysis), QTc.

- Change from baseline in Complete Mayo score1 at Week 10.

Secondary outcome

- Numbers of participants with adverse events and serious adverse events in the

Double-Blind Extended Treatment Phase.

- Numbers of participants with findings of potential clinical importance during

the Double-Blind Extended Treatment Phase for: Vital signs, Clinical laboratory

values (haematology, clinical chemistry and urinalysis), QTc.

- Proportion of participants who achieve Adapted Mayo endoscopic score of 0 or

1 at Week 10.

- Proportion of participants who achieve Adapted Mayo clinical remission at

Week 10.

- Proportion of participants who achieve Adapted Mayo clinical response at Week

10.

- Proportion of participants who achieve symptomatic remission3 over time.

- Change from baseline in partial Mayo score over time.

- Change from baseline in Adapted Mayo endoscopic score and Ulcerative Colitis

Endoscopic Index of Severity (UCEIS) at Week 10.

- Change from baseline in histological severity as determined by the Robarts

Histopathology Index, Nancy Histological Index and Geboes Score at Week 10.

- Change from baseline in serum C-reactive protein over time.

- Change from baseline in faecal calprotectin over time.

- GSK2831781 PK parameters: AUC(0-tau), Cmax, tmax.

- Number of participants with anti-drug antibodies at each visit.

- Adverse events, vital signs, clinical laboratory values (haematology,

clinical chemistry, and urinalysis), 12-lead ECG.

- Anti-drug antibodies over time.

Study description

Background summary

T cells are integral to the pathogenesis of ulcerative colitis (UC), and clinical experience with anti-integrin monoclonal antibodies has established the principle of T cell-targeted therapies in the disease. Lymphocyte activation gene-3 (LAG3) is expressed on recently activated T cells, and LAG3+ T cells are present in only low numbers in the circulation and healthy tissues. They are, however, increased in the colon in active UC, where their numbers

correlate with disease activity. GSK2831781 causes targeted depletion of LAG3+ T cells, and has shown preliminary evidence of clinical efficacy in plaque psoriasis (another T cell-mediated disease). It is therefore hypothesized that GSK2831781 will selectively deplete activated mucosal T cells in UC, but with relative sparing of resting T cells.

Study objective

Primary:
- To evaluate the safety and tolerability of repeat doses of GSK2831781 during the Induction Phase.
- To characterise the efficacy dose-response of GSK2831781 during the Induction Phase.

Secondary:
- To evaluate the safety and tolerability of repeat doses of GSK2831781 during the Double-Blind Extended Treatment Phase.
- To investigate the effect of repeat doses of GSK2831781 on clinical efficacy including endoscopic mucosal healing during the Induction Phase.
- To investigate the effect of repeat doses of GSK2831781 on UC histologic disease activity during the Induction Phase.
- To investigate the effect of repeat doses of GSK2831781 on biomarkers of UC disease activity during the Induction Phase.
- To investigate the pharmacokinetics of GSK2831781 following subcutaneous dosing.
- To investigate the immunogenicity of repeat doses of GSK2831781.
- To evaluate the safety and tolerability of repeat doses of GSK2831781 in all trial phases.
- To investigate the immunogenicity of repeat doses of GSK2831781.

Study design

This is a Phase 2, multicentre, randomized, double-blind, parallel group, placebo-controlled study to investigate safety, tolerability, efficacy and dose-response of GSK2831781 in participants with moderate to severe active UC as defined by a 4-domain (Complete) Mayo score of 6-12. The study will consist of five arms: GSK2831781 at 450mg, 300mg, 150mg and 45mg and a placebo group, and will investigate the induction (up to Week 10), and maintenance with an Extended Treatment Phase (Weeks 10-30), of clinical response/remission and mucosal healing.
In addition, Non-Responders identified following the Week 10 assessment will be moved to open label treatment consisting of Induction (Weeks 12 to 22) an Extended Treatment Phase (Weeks 22 to 52) and a Follow-Up to week 54.

Intervention

Total duration for participants who respond to GSK2831781 will be approximately 48 weeks (see Schema for details). The study consists of a 5-week screening window, 10-week Induction Phase (IP), 20-week Extended Treatment Phase (ETP), and a 12-week Follow-Up Phase. Non-Responders allocated to Open Label Treatment (GSK2831781 450mg) who subsequently respond to treatment may spend up to 54 weeks in total on study. Intervention groups are shown in the schema, Section 1.2.

Study burden and risks

Risks associated with study procedures/tests are listed below:
* Blood tests. When giving blood, you may feel faint or experience mild pain or bruising from the needle. The total amount of blood to be taken per visit will not exceed 65mL, and over the whole study is no more than 600mL (approximately 1 pint). This does not usually cause ill effects.
* Intravenous cannulation. When having an intravenous cannula (line) inserted for drug administration, you may feel faint or experience mild pain or bruising from the needle. This usually resolves quickly once the line has been placed. The cannula is removed before the end of the visit.
* Subcutaneous drug administration. Each subcutaneous drug administration consists of two injections underneath the skin. This is usually painless, but occasionally can cause mild discomfort or bruising.
* Electrocardiograms (ECGs) and continuous heart monitoring. You may experience some itching or minor irritation/bruising of the skin where the patches are placed to take the heart reading. The skin typically gets back to normal within a short period of time once the electrode patches are taken off.
* Endoscopy and biopsy:
o Discomfort. When undergoing endoscopy, you may feel some discomfort or bloating. This is usually short lasting (typically no more than a few hours), and rarely severe.
o Bleeding. The risk of bleeding is low (about 1-6 per 1000 procedures). Mostly this does not require any treatment, but if severe might require a blood transfusion.
o Perforation (tear). The risk of causing a tear in the bowel lining is very low (around 1 in 5000 chance for sigmoidoscopy, and 1 in 3000 for colonoscopy). If this happens, you may require a scan to confirm the diagnosis. If a tear is small, it may be treated with antibiotics and closely monitored, but if this fails or the tear is large you may require emergency surgery.
o Biopsy. Taking a biopsy is usually painless. Biopsies are approximately 2mm3 (about the size of a pin head), and the risk of serious damage to the bowel is very low. Obtaining up to 9 such biopsies at any one time should not expose you to any additional discomfort or risk.
o Sedation: If sedation is offered, there is a risk of oversedation, which can cause a drop in blood oxygen or blood pressure. If oversedation occurs, you should be monitored closely during and after your procedure for these issues, and should there be any signs of these developing they should be treated immediately. You should not drive or operate heavy machinery while the effects

of sedation are still affecting your body.
o Side effects related to bowel preparation: In general, sigmoidoscopy does not require bowel preparation. However, your doctor will discuss with you whether any preparation is required before your endoscopy. Side effects of restrictions on eating and drinking before the procedure, and/or of medications to clear stool out of the large bowel, can occasionally lead to dehydration or salt imbalances in the blood, which may need treatment with fluid given through an intravenous drip.
Reduction in steroid dosage. If during the study your ulcerative colitis improves sufficiently, you will be asked to gradually reduce the steroid dose (if you are taking them).You will be given specific instructions by the study doctor on how to do this, and you should follow them carefully. There is a possibility this could result in your ulcerative colitis getting worse again.
If this happens, you will be able to increase back up to the original steroid dose you were taking. If your symptoms then improve again, a final attempt to reduce the dose will be started.

Contacts

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Scientific
GlaxoSmithKline

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

AGE and WEIGHT:
1. Participant must be 18 years of age or older and >40kg at the time of signing the informed consent.
TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS
Participants who have a:
2. Diagnosis of ulcerative colitis, established at least 3 months prior to screening, as documented by diagnostic sigmoidoscopy or colonoscopy, and biopsy.
3. Complete Mayo Score of 6 to 12, with disease extending *15cm from the anal verge, with a centrally read endoscopic subscore of *2 at screening endoscopy, and a rectal bleeding subscore *1.
4. A history of at least one of the following:
* Inadequate response to, loss of response to, or intolerance to azathioprine or mercaptopurine (including thiopurine methyltransferase (TPMT) genetic mutation precluding use), ciclosporin, tacrolimus or methotrexate.
* Inadequate response to, loss of response to, intolerance to, or demonstrated dependence on oral corticosteroids.
* Inadequate response to, loss of response to, or intolerance to at least one approved advanced therapy for UC, including anti-TNF therapies, anti-integrin therapies, anti-IL-12/23 monoclonal antibodies or JAK inhibitors.
5. Surveillance colonoscopy (performed according to local standards) within 12 months of screening (or during screening, if required) for participants with:
* Pancolitis of >8 years duration; or
* Patients with left-sided colitis of >12 years duration; or
* For patients for whom this criterion does not apply, colorectal cancer surveillance should be undertaken according to local or national guidelines for patients with age *50, or with other known risk factors for colorectal cancer.
SEX:
6. Male and Female participants:
Both male and female participants are eligible to participate.
A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:
* Not a woman of childbearing potential (WOCBP), see Section 10.4.1 of the protocol.
OR
* A WOCBP who agrees to use a highly effective contraceptive method for at least 4 weeks prior to dosing, until the Follow-Up visit. See Section 10.4.2 of the protocol.
INFORMED CONSENT:
7. Capable of giving signed informed consent as described in Section 10.1.3 10.1.3 of the protocol which includes compliance with the requirements and

restrictions listed in the informed consent form (ICF) and in the protocol.

Exclusion criteria

MEDICAL CONDITIONS:
1. Participants with a current diagnosis of indeterminate colitis, inflammatory bowel disease-unclassified, Crohn*s disease, infectious colitis, or ischaemic colitis.
2. Participants with fulminant ulcerative colitis (as defined by 6 bloody stools daily AND 1 or more of: i) body temperature *100.4°F (or 38°C) or ii) heart rate >90 beats per minute), or toxic megacolon.
3. Prior extensive colonic resection, subtotal or total colectomy, or proctocolectomy, or planned surgery for UC.
4. Participants with any uncontrolled medical conditions, other than active UC, that in the opinion of the investigator put the participant at unacceptable risk or interfere with study assessments or integrity of the data. Other medical conditions should be stable at the time of screening and be expected to remain stable for the duration of the study.
5. Unstable lifestyle factors, such as alcohol use to excess or recreational drug use, to the extent that in the opinion of the investigator they would interfere with the ability of a participant to complete the study.
6. An active infection or a history of serious infections as follows:
- Use of antimicrobials (antibacterials, antivirals, antifungals or antiparasitic agents) for an infection within 30 days before first dose (topical treatments may be allowed at the Medical Monitor*s discretion).
- A history of opportunistic infections within 1 year of screening (e.g. Pneumocystis jirovecii, aspergillosis or CMV colitis). This does not include infections that may occur in immunocompetent individuals, such as fungal nail infections or vaginal candidiasis, unless it is of an unusual severity or recurrent nature.
- Recurrent or chronic infection or other active infection that, in the opinion of the Investigator, might cause this study to be detrimental to the patient.
- Symptomatic herpes zoster within 3 months prior to screening.
- History of tuberculosis (active or latent), irrespective of treatment status.
- A positive diagnostic TB test at screening (defined as a positive QuantiFERON test). In cases where the QuantiFERON test is indeterminate, the participant may have the test repeated once and if their second test is negative they will be eligible. In the event a second test is also indeterminate, the investigator has the option to undertake PPD testing. If the PPD reaction is <5 mm, then the participant is eligible. If the reaction is *5 mm, or PPD testing is not undertaken, the participant is not eligible.
- Positive Clostridium difficile toxin test during screening. However, rescreening can be undertaken following successful treatment.
7. Current or history of chronic liver or biliary disease (with the exception of Gilbert*s syndrome, asymptomatic gallstones or uncomplicated fatty liver

disease).
8. Hereditary or acquired immunodeficiency disorder, including immunoglobulin deficiency (unless the participant has a documented history of selective IgA deficiency).
9. A major organ transplant (e.g. heart, lung, kidney, liver, pancreas) or haematopoietic stem cell/marrow transplant.
10. Any planned major surgical procedure during the study.
11. A history of malignant neoplasm within the last 5 years, except for adequately treated non-metastatic basal or squamous cell cancers of the skin (within 1 year) or carcinoma in situ of the uterine cervix (within 3 years) that has been fully treated and shows no evidence of recurrence.

PRIOR/CONCOMITANT THERAPY:
12. A change in dose of oral sulfasalazine or aminosalicylate within 2 weeks prior to baseline endoscopy.
13. Greater than 20 mg/day oral prednisolone (or equivalent, see SRM), or a change in dose of corticosteroid within 2 weeks prior to baseline endoscopy, or anticipated inability to maintain a stable dose of corticosteroids (*20 mg oral prednisolone or equivalent, see SRM) until Week 12.
14. Topical (rectal) corticosteroids or topical (rectal) aminosalicylate within 2 weeks prior to baseline endoscopy.
15. Initiation or a change in dose of mercaptopurine or azathioprine (including initiation or discontinuation of allopurinol) or methotrexate within 8 weeks prior to baseline endoscopy.
16. Treatment with ciclosporin, tacrolimus or thalidomide within 4 weeks prior to baseline endoscopy.
17. Treatment with an anti-TNF biologic within 8 weeks prior to baseline endoscopy, anti-integrin or anti-IL-12/23 biologics within 12 weeks prior to baseline endoscopy, or a JAK inhibitor within 4 weeks prior to baseline endoscopy.
18. A history of inadequate response, loss of response, or intolerance to more than three classes of approved advanced therapies for UC (including anti-TNF therapies, anti-integrin therapies, anti-IL-12/23 monoclonal antibodies, or JAK inhibitors; but excluding exposure within a clinical trial setting), of which participants must not have had inadequate response (primary non-response) to more than two classes.
19. Received faecal microbiota transplantation within 4 weeks prior to baseline endoscopy.
20. Received live vaccination within 4 weeks of Day 1 or plan to receive during the study until Follow-Up.

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE:
21. The participant has participated in a clinical trial and has received an investigational product within the following time period prior to the screening endoscopy day in the current study:
a. Biologics: 3 months, 5 half-lives, or twice the duration of the biological effect of the investigational product (whichever is longer);

b. New Chemical Entities (NCEs): 30 days, 5 half-lives or twice the duration of the biological effect (whichever is longer).

DIAGNOSTIC ASSESSMENTS:
22. Absolute neutrophil count <1.5x109/L or a haemoglobin <80 g/L or lymphocyte count <0.8x109/L.
23. Estimated glomerular filtration rate (GFR) by Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) calculation <60 ml/min/1.73m2 at screening.
24. ALT >2x ULN and bilirubin >1.5x ULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) at screening.
25. Other clinically significant abnormalities of laboratory assessments, as judged by the investigator and/or GSK Medical Monitor, that could affect the safety of the participant, or the interpretation of the data from the study.
26. Presence of hepatitis B surface antigen (HBsAg) or Hepatitis B core antibody (HBcAb), or positive hepatitis C antibody result at screening (NB. participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled only if a confirmatory negative Hepatitis C RNA test is obtained).
27. Positive serology for HIV at screening.
28. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 3 months.
29. QTc >450 msec or QTc >480 msec for participants with bundle branch block at screening and Day 1. The QTc is the QT interval corrected for heart rate according to either Bazett*s formula (QTcB), Fridericia*s formula (QTcF), or another method, machine or over read

OTHER EXCLUSION CRITERIA:
30. Participants with hypersensitivity to GSK2831781 or any excipients in the clinical formulation of GSK2831781 (See GSK2831781 Investigator Brochure).

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):	11-09-2020
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	GSK2831781
Generic name:	GSK2831781

Ethics review

Approved WMO Date:	22-07-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-12-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-02-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-12-2020
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	EUCTR2018-003278-28-NL
CCMO	NL69213.018.19

Study results

Date completed: 12-04-2021

Actual enrolment: 3

Summary results
Trial is onging in other countries