A Phase 1 Double-blind, Randomized, Placebo-Controlled, Staggered, Single and Multiple Ascending Dose, Multicenter Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of GS-5745 in Subjects with Moderate to Severe Ulcerative Colitis

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The primary objectives of this study are as follows:* To assess the safety and tolerability of escalating single and multiple doses of GS-5745 in subjects with moderate to severe ulcerativecolitis (UC) as assessed by adverse events (AEs), and…

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

Summary

ID

NL-OMON40621

Source
ToetsingOnline

Brief title
GS-US-326-0101

Condition

- Gastrointestinal inflammatory conditions

Synonym
inflamatory bowel disease, Ulcerative Colitis

Research involving
Human

Sponsors and support

Primary sponsor: Gilead Sciences, Inc.
Source(s) of monetary or material Support: Gilead Sciences;Inc.

Intervention

Keyword: Colitis ulcerosa

Outcome measures

Primary outcome

Safety: Assessment of AEs and concomitant medications will continue throughout the duration of the study. Safety evaluations include documentation of adverse events, physical examination (complete or symptom driven), vital signs, clinical laboratory evaluations (hematology, chemistry, urinalysis), and serum cytokines. ECGs will be performed at Day 1 (pre-dose) and then at defined intervals (see schedule of assessments, Appendix 2 to Appendix 4) throughout the study.

Efficacy: Efficacy will be assessed using the Mayo Score (complete and modified), a validated measure of disease severity in UC, which is composed of 4 sub scores (for stool frequency, rectal bleeding, endoscopic findings and physician*s global assessment), and on which scores range from 0-12. Efficacy in the SAD cohorts will be assessed using the modified Mayo Score, which includes all components except endoscopy (flexible sigmoidoscopy with

biopsies). Efficacy in the MAD cohorts will assessed using the complete and modified Mayo Scores. Exploratory efficacy evaluations will include blood (serum and platelet poor plasma), urine and stool levels of MMP9 and other markers of inflammation.

Intensive blood PK sampling will occur relative to dosing of GS-5745 at the following time points:

* SAD: Day 1 (pre-dose, 1 hour, 2 hours, and 6 hours post-dose), 24 hours, 48 hours, Days 8, 15, 29 and 43.
* MAD: Days 1, 8, 15, 29 (pre-dose, 1 hour, 2 hours, and 6 hours post dose on each dosing day), Days 36, 43, and 71.
* Adaptive MAD: Days 1 and 29 (pre-dose and 6 hours post-dose), Days 8, 15, and 22 (pre-dose, and 2 hours post-dose), Days 32, 36, 39, 43, and 71 post-dose.

GS-5745 concentrations will be determined and PK parameters will be estimated.

Secondary outcome

Secundary endpoints are pharmacokinetic information: Tmax, Clast, Tlast, *z, CL, V, and T1/2.

Other endpoints of interest are change from baseline in complete or modified Mayo Score, serum, stool MMP9, fecal Calprotectin, fecal Lactoferrin, serum CRP, and ESR.

Study description

Background summary

Ulcerative colitis (UC) and Crohn*s disease are the two major inflammatory bowel diseases(IBD). Ulcerative colitis is a chronic disease characterized by an uninterrupted pattern of inflammation of the colonic mucosa, which is limited to the colon and rectum. The disease always involves the rectum and may extend proximally in an uninterrupted pattern. It can involve the entire colon (pan-colitis), the left colon, or isolated recto-sigmoid disease with patients being equally distributed in those three phenotypes. The hallmark symptoms of the disease are bloody diarrhea, rectal urgency, and tenesmus. The clinical course tends to wax and wane with periods of remission, interspersed with periods of active disease. UC is also associated with extra-intestinal manifestations including ocular lesions, skin lesions, arthritis and primary sclerosing cholangitis. Children affected by UC often exhibit failure to thrive with delayed growth and development. The disease is associated with colon cancer. Increased risk of colon cancer depends on the extent, severity, and duration of disease. The exact pathophysiology is not known, but a combination of genetic predisposition and environmental factors appear to contribute to a disordered immune response in these patients
There are several different classes of medications that can be used to treat UC, with treatment being tailored both to the severity of the disease and the location or extent of the disease. Disease that is confined to the distal colon (descending colon, sigmoid and rectum) is best
treated with 5-aminosalicylate (5-ASA) enemas. Corticosteroid enemas and oral 5-ASA preparations have been shown to be effective in managing mild-to-moderate distal colitis as well, but they are inferior to 5-ASA enemas. Oral 5-ASAs are used as first line treatments for
mild-to-moderate UC that extends proximal to the descending colon. Patients with more severe disease, and/or those failing to respond to first line therapies are generally treated with a course of oral corticosteroids. Immunomodulators such as Azathioprine and
6-Mercaptopurine (6-MP) are used to help wean subjects off steroids and to maintain remission. For patients with more severe disease, and those who are refractory to or dependent upon corticosteroids, the chimeric antibody to TNF*, Remicade (Infliximab), is generally used.
Infliximab is administered intravenously at a dose of 5mg/kg at weeks 0, 2 and 8 and then every 8 weeks thereafter to induce and maintain remission without the use of corticosteroids.
The data supporting the use of Infliximab in patients with severe UC suggest that this agent is vastly superior to placebo, particularly, at reducing symptoms within the first 8 weeks of therapy. However, data over the entire 54 week study period suggest that Infliximab is not an
adequate option for long-term maintenance for most of these patients. The

ultimate goal with UC patients is to induce and maintain steroid-free remission over the long term, yet Infliximab mostly fails to achieve these objectives. Only 20% of patients achieve a remission by week 8 and remain in remission through 54 weeks, with the majority of patients relapsing by week 30. Similarly, only 26% of patients were able to achieve a long-term remission completely free of corticosteroids. When the less stringent endpoint of response is evaluated instead of remission (indicating an incomplete reduction in symptoms), approximately 60% of patients fail to maintain this degree of relief over 30 or 54 weeks.

Currently, there are no good treatment options for the 80% of patients who fail to achieve long-term remission on Infliximab therapy. Cyclosporine has been shown to be effective at delaying the need for surgery in patients hospitalized for fulminant UC, but its efficacy as a
maintenance therapy has not been established. Surgery, consisting of a two-step total colectomy with ileal pouch anal anastomosis (IPAA) is curative. A total colectomy is, however, an undesirable outcome for many patients, committing them to lifelong frequent bowel movements, a high risk of sexual dysfunction, and a 50% risk of developing pouchitis (an inflamed J pouch that results in diarrhea with or without rectal bleeding, tenesmus, urgency, pain, incontinence and fevers). Furthermore, the risk of female infertility is highly increased following IPAA surgery. GS-5745 is a fully humanized high-affinity monoclonal antibody selective for MMP9.
MMP9 promotes pathology through its destructive remodeling of basement membrane and other structural proteins, and by increasing both vascular permeability and the activation of growth factors and cytokines * factors that wholly contribute to the pathophysiology of
ulcerative colitis. Therefore, GS-5745 may be an alternative treatment option in moderate to severe UC, working through a non-immunosuppressive mechanism, which may result in an improved safety profile compared to immunosuppressive agents, and the possibility of achieving efficacy in patients who fail on currently approved therapy.

Study objective

The primary objectives of this study are as follows:
* To assess the safety and tolerability of escalating single and multiple doses of GS-5745 in subjects with moderate to severe ulcerative
colitis (UC) as assessed by adverse events (AEs), and laboratory abnormalities
* To assess the pharmacokinetics (PK) of GS-5745 in subjects with moderate to severe ulcerative colitis (UC)
The exploratory objectives of this study are as follows:
* To determine the efficacy of GS-5745 in subjects with moderate to severe ulcerative colitis (UC)
* To identify potential biomarkers predictive of benefit of GS-5745 in blood urine and stool
* To explore the effect of GS-5745 in reducing inflammation by measuring pre

and post treatment fecal calprotectin, fecal lactoferrin,
serum C-reactive protein (CRP) and Erythroid Sedimentation Rate (ESR)

Study design

This is a Phase 1, double-blind, randomized, placebo-controlled, staggered, single and multiple ascending dose, and multicenter study. Approximately 74 subjects with moderate to severe, active ulcerative colitis (UC) will be evaluated in SAD (single ascending dose) and MAD (multiple ascending dose) cohorts. The SAD and MAD cohorts will be conducted in a staggered parallel cohort design as described below.
In the SAD cohorts, 24 subjects will be entered sequentially into one of 4 dose groups, starting from the lowest dose group. Within each group, 6 subjects will be randomized in a 5:1 ratio to receive a single intravenous (IV) dose of GS-5745 or placebo. In each SAD cohort, the first 2 subjects will be dosed in a staggered fashion 24 hours apart. Provided that there are no significant safety signals up to 24 hours post-dose for the first 2 subjects, the remaining 4 subjects will be dosed. In the MAD cohorts, 40 subjects will be sequentially randomized into one of 4 dose groups starting from the lowest dose group. Within each group, 10 subjects will be randomized in an 8:2 ratio to receive multiple (three) intravenous (IV) doses of GS-5745 or placebo every two weeks (Days 1, 15, 29). Dosing will not commence in the first MAD cohort until safety data from the second dose level SAD cohort has been reviewed through Day 15. Successive MAD cohorts will only be dosed after safety data from the previous, lower dose MAD cohort through Day 43 and the next higher dose SAD cohort through Day 15, are reviewed. An additional Adaptive MAD cohort will explore a subcutaneous dosing of 150 mg prefilled syringe (1.2 mL) once a week for 5 weeks. This cohort will include 10 subjects enrolled to receive 5 open-label doses of GS-5745 on Days 1, 8, 15, 22, and 29. The site of the subcutaneous injection can either be on the front of the thighs or the stomach area (abdomen). If the abdomen area is chosen, study personnel should avoid the area 2 inches around the belly button (navel). Efficacy, assessed by the Mayo Score (complete and modified), will be evaluated. Subjects in the MAD and Adaptive MAD cohorts only will have flexible sigmoidoscopies with biopsies, performed within 10 days of Baseline (Day 1) and on Day 36.
After Day 36 visit is completed from each MAD cohort and Adaptive MAD cohort, safety and efficacy analyses, including PK and biomarkers, will be performed in an unblinded manner to determine dose escalation and/or to enable development program planning. The Gilead Clinical Operations team directly interacting with the study center will, however, remain blinded to the subject treatment assignment. In the event of a safety concern, the Gilead Medical Monitor and other required Gilead study team members may be unblinded even earlier. The study center staff and subjects will remain blinded at all times.
No more than 2 subjects may be replaced in each cohort.

Intervention

SAD: A single dose-escalation with 4 pre-specified cohorts will be employed. Within each cohort, subjects will be randomized to receive either active GS-5745 (n=5) or matching placebo (n=1) intravenously. In each SAD cohort, the first 2 subjects will be dosed in a staggered fashion 24 hours apart. Provided that there are no significant safety signals up to 24 hours post-dose for the first 2 subjects, the remaining 4 subjects will be dosed. Successive cohorts will not be dosed until all safety data through Day 15 are reviewed from the prior cohort. The planned doses are as follows:
Single Ascending Doses (SAD):
Cohort 1: 0.3 mg/kg GS-5745 or placebo, intravenous (IV)
Cohort 2: 1.0 mg/kg GS-5745 or placebo, intravenous (IV)
Cohort 3: 2.5 mg/kg GS-5745 or placebo, intravenous (IV)
Cohort 4: 5.0 mg/kg GS-5745 or placebo, intravenous (IV)

MAD: A multiple dose-escalation with 4 cohorts will be employed. Within each cohort, subjects will be randomized to receive either active GS-5745 (n=8) or matching placebo (n=2) intravenously on Days 1, 15 and 29. Dosing will not commence in the first MAD cohort until safety data from the second dose level SAD cohort is reviewed through Day 15. Successive MAD cohorts will not be dosed until all safety data from the previous, lower dose MAD cohort through Day 43 and the next higher dose SAD cohort through Day 15 are reviewed. The planned doses are as follows:

Multiple Ascending Doses (MAD):
Cohort 1: Not to exceed 0.3 mg/kg GS-5745 or placebo, intravenous (IV)
Cohort 2: Not to exceed 1.0 mg/kg GS-5745 or placebo, intravenous (IV)
Cohort 3: Not to exceed 2.5 mg/kg GS-5745 or placebo, intravenous (IV)
Cohort 4: Not to exceed 5.0 mg/kg GS-5745 or placebo, intravenous (IV)
Planned doses in the SAD and MAD cohorts may be revised based on emerging safety data.

Adaptive MAD Cohort
A single cohort with subjects enrolled to receive 150 mg of active GS-5745 subcutaneously on Days 1, 8, 15, 22 and 29.
Clinic Confinement and Follow-up
In the SAD cohorts, the subjects will be dosed on Day 1 with outpatient visits on Days 2, 3 and 8, and follow-up visits on Days 15, 29 and 43. In the MAD cohorts, infusions will occur on Days 1, 15 and 29 with an outpatient visit on Day 8 and follow-up visits on Days 36, 43 and 71. Subjects in the Adaptive MAD cohort will be administered drug subcutaneously on Days 1, 8, 15, 22 and 29. Follow-up visits in the Adaptive MAD cohort will occur on Days 36, 43 and 71, and additional PK visits on Days 32 and 39. All subjects in the SAD and MAD cohorts will be confined to clinic for 6 hours after each infusion for serial PK draws. All subjects in the Adaptive MAD cohort will be confined to clinic for 6 hours after each subcutaneous injection on Days 1 and 29, and will be

confined to clinic for 2 hours after each subcutaneous injection on Days 8, 15, and 22 for serial PK draws.

Dose Escalation and Stopping Rules
Dosing of a SAD cohort at a higher dose level will occur after review of all safety data through Day 15 in the lower SAD cohort. Dosing will not commence in the first MAD cohort until safety data from the second dose level SAD cohort has been reviewed through day 15. Subsequent
MAD cohorts will only be dosed after safety data from the previous, lower dose MAD cohort through Day 43 and the next higher dose SAD
cohort through day 15, are reviewed. At the end of each cohort, blinded safety data will be reviewed by the Gilead Sciences Medical Monitor and
the lead investigator.

Stopping Rules:
If a SAE or Grade 4 laboratory abnormality occurs in 2 or more subjects in a cohort determined to be related to study drug, the study will be stopped, with no further dosing for ongoing subjects in the cohort, and no escalation to the next cohort.

Study burden and risks

No information about the safety profile of GS-5745 in humans is available at this time. However, the medical procedures in this study are known to have the following risks or discomforts associated.
Blood Draws:
Drawing blood from a vein may cause local pain, bruising, occasional lightheadedness, fainting, and very rarely, infection at the site of the blood draw.
ECG:
After you have an ECG, you may have mild irritation, slight redness, and itching at the places on your skin where the recording patches are placed. You may have to have your chest shaved for this procedure.
Sigmoidoscopy with Biopsy:
Preparation for this test may require use of an enema or laxative, or both, which may cause abdominal discomfort and increased loose stools during the preparation period. You may experience cramping from the air used to inflate your colon during the procedure, which will pass. Puncture of the colon is a rare side effect from this test. If you experience fever, chills, severe abdominal pain, or heavy rectal bleeding of more than a teaspoon at a time, call your doctor immediately.

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. Have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study procedures
2. Males or non-pregnant, non-lactating females, ages 18 to 65 years, inclusive
3. Females of childbearing potential (see definition in Section 7.9) must have a negative pregnancy test at Screening and Baseline.
4. All sexually active female subjects, of childbearing potential, must agree to use a highly effective method of contraception during heterosexual intercourse from Screening to study completion, and up to 90 days post last dose of the study drug.
5. Male subjects who are sexually active are required to use barrier contraception (condom with spermicide) during heterosexual intercourse from Screening to study completion, and up to 90 days post last dose of the study drug.
6. Documented diagnosis of UC with a minimum disease extent of

15 cm from the anal verge
7. Mayo Score:
* SAD cohort: Minimum modified Mayo Score of 3 (score > 3), with a rectal bleeding and stool frequency sub-score of at least 1
* MAD cohort: Minimum Mayo Score of 6 (score > 6), with a Mayo endoscopic sub-score of at least 2
8. Laboratory parameters:
* Hepatic panel (AST, ALT, total bilirubin, direct bilirubin, alkaline phosphatase, LDH) * 2 times the ULN
* Serum creatinine * 1.5 times the ULN
* Hemoglobin * 10 g/dL (both males and females)
* Absolute neutrophil count (ANC) * 1.5 x 109/L (1,500 mm3)
* Platelets * 100 x 109/L

Exclusion criteria

1. Pregnant or lactating subjects
2. Known hypersensitivity to the study investigational medicinal products, the metabolites or formulation excipients.
3. Exhibit severe UC as defined by the following criteria:
* *6 bloody stools daily AND one or more of the following:
* Oral temperature > 100.3°F (or 38°C)
* Pulse > 90 beats/minute
* Hemoglobin < 10 g/dL (both males and females)
4. Current use of oral corticosteroids at a dose equivalent to > 20 mg/day of prednisone
5. Any dose adjustment in oral corticosteroids or oral immunosuppressants (6-MP, Azathioprine) , or oral 5-ASA compounds within 30 days of Baseline
6. Use of rectal formulations of 5-ASA compounds or corticosteroids within 2 weeks prior to randomization
7. Crohn*s disease or indeterminate colitis
8. History of colectomy, partial colectomy, or dysplasia on biopsy
9. Stool sample positive for Clostridium difficile (C. difficile) toxin, E. coli, Salmonella, Shigella, Campylobacter or Yersinia
10. Treatment with Infliximab, Adalimumab, Natalizumab, Golimumab, Vedolizumab or Certolizumab within 8 weeks of randomization
11. Clinically significant active infection
12. Chronic medical or psychiatric problem that may interfere with subject*s ability to comply with study procedures
13. Alcohol or drug abuse in the opinion of the Investigator
14. History of malignancy within the last 5 years except for patients who have been treated for non-melanoma skin cancer or cervical carcinoma in situ
15. Any other investigational therapy or investigational biologics use

within 8 weeks of randomization
16. Any chronic medical condition (including, but not limited to, cardiac or pulmonary disease) that, in the opinion of the Investigator, would make the subject unsuitable for the study or would prevent compliance with the study protocol

Study design

Design

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):	03-06-2014
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	GS-5745
Generic name:	GS-5745

Ethics review

Approved WMO

Date:	31-05-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO Date:	12-09-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-11-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-11-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-04-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-04-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-05-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-05-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-12-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-12-2014
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	EUCTR2013-000305-23-NL
ClinicalTrials.gov	NCT01831427
CCMO	NL44671.018.13