A Combined Phase 2/3, Double-Blind, Randomized, Placebo-Controlled, Induction and Maintenance Study Evaluating the Safety and Efficacy of GS-5745 in Subjects with Moderately to Severely Active Ulcerative Colitis

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Cohort 1:A data monitoring committee (DMC) will evaluate all available safety data from the study. The first 2 meetings for safety surveillance will occur after 50 and 100 subjects complete or discontinue from the Blinded Induction Phase from Cohort...

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

Summary

ID

NL-OMON43698

Source
ToetsingOnline

Brief title
0035/0113 (GS-US-326-1100)

Condition

- Gastrointestinal inflammatory conditions

Synonym
Ulcerative Colitis

Research involving

Human

Sponsors and support

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

Intervention

Keyword: Ulcerative Colitis

Outcome measures

Primary outcome

Primary Objectives:

* To evaluate the efficacy of GS-5745 to induce EBS clinical remission at Week

8 (Cohort 1)

* To evaluate the efficacy of GS-5745 to maintain EBS clinical remission at

Week 52 (Cohort 2)

* To evaluate the safety and tolerability of GS-5745 (Cohort 1 & 2)

Secondary outcome

Secondary Objectives:

* To evaluate the efficacy of GS-5745 induction treatment on achieving Mayo

Clinical Score (MCS) defined remission and response at Week 8 (Cohort 1)

* To evaluate the efficacy of GS-5745 induction and maintenance treatment on

sustained EBS clinical remission at Week 52, defined as achieving EBS clinical remission at both Week 8 and Week 52 (Cohort 1)

* To evaluate the efficacy of GS-5745 induction and maintenance treatment on sustained MCS clinical remission at Week 52, defined as achieving MCS clinical remission at both Week 8 and Week 52 (Cohort 1)

* To evaluate the efficacy of GS-5745 induction treatment on endoscopic response (endoscopic subscore 0 or 1) and remission (endoscopic subscore of 0) at Week 8 (Cohort 1)

* To evaluate the efficacy of GS-5745 induction treatment on mucosal healing as determined by the Geboes histologic scoring system at Week 8 (Cohort 1)

* To evaluate remission as defined by MCS remission (alternative definition) at Week 8 (Cohort 1)

* To evaluate the efficacy of GS-5745 maintenance treatment on MCS remission at Week 52 (Cohort 2)

* To evaluate the efficacy of GS-5745 maintenance treatment on achieving corticosteroid-free EBS clinical remission at Week 52 (Cohort 2)

* To evaluate the efficacy of GS-5745 maintenance treatment on endoscopic

remission (endoscopic subscore of 0) at Week 52 (Cohort 2)

* To evaluate the efficacy of GS-5745 maintenance treatment on mucosal healing as determined by the Geboes histologic scoring system at Week 52 (Cohort 2)

* To evaluate remission as defined by MCS remission (alternative definition) at Week 52 (Cohort 2)

* To evaluate the efficacy of GS-5745 maintenance treatment on achieving corticosteroid-free EBS clinical remission for at least 24 weeks prior to Week 52 (Cohort 2)

* To assess the PK characteristics of GS-5745 (Cohorts 1 and 2)

* To evaluate the immunogenicity of GS-5745 treatment as measured by the emergence of anti-drug-antibodies (ADA) (Cohorts 1 and 2)

Study description

Background summary

This protocol encompasses an Induction Study (Cohort 1) and a Maintenance Study (Cohort 2).

Cohort 1:
The Induction Study consists of two parts: Part A (the first 150 subjects) and Part B (up to 510 additional subjects), and an Extended Treatment Phase. Screening into Cohort 1 will be halted between Part A and Part B. Results of a futility analysis of safety and endoscopic efficacy data from Part A will be

reviewed by the Data Monitoring Committee (DMC). Continuation to Part B is contingent on the DMC*s recommendation on whether to resume enrollment, modify the study, or discontinue the study.

Cohort 2:
Once the optimal induction treatment is determined from Cohort 1, enrollment into the Maintenance Study (Cohort 2) will be initiated with up to 940 new subjects.
All subjects that complete 52 weeks of treatment including flexible sigmoidoscopy/colonoscopy will have the option to continue receiving open label GS-5745 for an additional 3 years in the Extended Treatment Phase.
Cohort 1 & 2:
The primary endpoint for both studies is termed EBS clinical remission, and is defined as an Endoscopic subscore of 0 or 1, rectal Bleeding subscore of 0, and at least a one point decrease in Stool frequency from baseline to achieve a subscore of 0 or 1.

Study objective

Cohort 1:
A data monitoring committee (DMC) will evaluate all available safety data from the study. The first 2 meetings for safety surveillance will occur after 50 and 100 subjects complete or discontinue from the Blinded Induction Phase from Cohort 1 Part A. The third meeting will occur after all 150 subjects from Cohort 1 Part A complete or discontinue from the Blinded Induction Phase of the study.
Cohort 1 & 2:
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, and clinical laboratory evaluations (hematology, chemistry, urinalysis). ECGs will be performed at Screening, Weeks 8 and 52 or ET.
After cohort 1A, the DMC will evaluate all available data (safety and endoscopic efficacy) to make a recommendation based on the pre-defined futility criteria. If the study resumes, meetings thereafter will be held up to three times a year for the remainder of the study based on enrollment rate.
Efficacy: Efficacy will be assessed using the MCS composed of 4 sub-scores (stool frequency, rectal bleeding, endoscopic findings and physician*s global assessment), the total of the sub-scores range from 0-12. Assessments during non-endoscopic visits will use the partial MCS, which includes all components except flexible sigmoidoscopy/colonoscopy.
Pharmacokinetics: Plasma PK sampling for GS-5745 will be collected at pre-dose at Weeks 1, 5, 8, 9, 16, 28, and 40 and then Week 52.
An optional PK substudy will be performed in a subset of subjects (approximately 30 subjects from Cohort 1 and approximately 30 subjects from Cohort 2). In the PK substudy, additional plasma PK samples will be collected following the first dose on Week 0 + 3 (± 1) days and Week 0 + 5 (± 1) days.

There must be at least 1 day separating the 2 collection time points.
Immunogenicity: Serum sampling for anti-drug antibodies (ADA) will be collected at pre-dose Weeks 0, 1, 5, 8, 16, 28, 40, 52, and Week 55 (for subjects not entering the Extended Treatment Phase only). For subjects in the Extended Treatment Phase, additional ADA samples should be collected every 24 weeks starting at Week 76.

Study design

Background Cohort 1 & Cohort 2:
There are two components to the study being conducted under this protocol: An Induction Study (Cohort 1) and a Maintenance Study (Cohort 2), both of which have the Extended Treatment Phase. Subjects in Cohort 1 are not eligible to participate in Cohort 2. All subjects that complete 52 weeks of treatment (in either study) will have the option to enter the Extended Treatment Phase.

Cohort 1:
Induction Study (Cohort 1, up to 660 subjects):
* Screening (Days -30 to -1)
* Blinded Induction Phase (Week 0 * Week 7) consisting of Part A and Part B
* Week 8 assessments including flexible sigmoidoscopy/colonoscopy, followed by an additional dose of blinded study drug
* Central review of Week 8 flexible sigmoidoscopy/colonoscopy
* Subjects achieving EBS clinical remission and/or MCS response based on the Week 8 assessments will continue on the same dosing regimen into the Blinded Maintenance Phase (Week 9 * Week 51)
* Post treatment assessment visit (Week 52)
* Extended Treatment Phase (Week 52 * Week 207)
* Follow-up visit at Week 55 for subjects not entering Extended Treatment Phase (or 30 within days after last dose of study drug for early termination)

The induction component of this study is divided into two sequential parts (Part A and Part B).

Cohort 1, Part A:
Part A includes the first 150 subjects randomized (approximately 50 per group). After the 150th subject has been randomized, all screening will be halted. An interim futility analysis will be performed and results will be reviewed by the DMC using safety and endoscopic data from the first 150 subjects that have been randomized into the Blinded Induction Phase of Cohort 1. The DMC will make a recommendation to resume screening, modify the study, or discontinue the study based on pre-specified criteria (Appendix 1).

Cohort 1, Part B:
If criteria for continuation of the study are met as outlined in Appendix 1, screening and enrollment will restart with either one or both GS-5745 treatment

groups, and the placebo group.

Cohort 2:
Once all subjects complete the Blinded Induction Phase, an analysis will be performed to determine the optimal regimen of GS-5745 for the Cohort 2 Optimal Open-Label Induction Phase and enrollment into Cohort 2 will be initiated.
MaintenanceStudy(Cohort2,approximately940subjects):
* Screening (Days -30 to -1)
* Optimal Open-Label Induction Phase, as determined from Cohort 1 (Week 0 * Week 7)
* Week 8 assessments including flexible sigmoidoscopy/colonoscopy, followed by an additional open-label dose of GS-5745
* Central review of Week 8 flexible sigmoidoscopy/colonoscopy
* Subjects achieving EBS clinical remission and/or MCS response based on the Week 8 assessments will be randomized to the Blinded Maintenance Phase (Week 9 * Week 51)
* Post treatment assessment visit (Week 52)
* Extended Treatment Phase (Week 52 * Week 207)
* Follow-up visit at Week 55 for subjects not entering Extended Treatment Phase (or 30 within days after last dose of study drug for early termination)

Open-LabelMaintenancePhase:
* All subjects who do not achieve EBS clinical remission or MCS response after the Week 8 assessments have been completed will be offered GS-5745 open-label study drug
* Subjects who meet protocol specified disease worsening discontinuation criteria (Section 6.9 Criteria for Discontinuation of Study Treatment) any time after the Week 8 assessments have been completed will be offered GS-5745 open-label study drug

Extended Treatment Phase:
* All Subjects who complete all week 52 assessments including flexible sigmoidoscopy/colonoscopy will be offered open-label 150 mg GS-5745 administered by subcutaneous injections via a single-use prefilled syringe weekly for an additional 156 weeks
* Subjects will not complete a follow-up visit at Week 55
* Follow-up visit within 30 days after last dose of study drug

Intervention

150 mg GS-5745 at a concentration of 150 mg/mL to be administered subcutaneously in a 1mL pre-filled syringe.

GS-5745 matching placebo to be administered as a 1 mL injection subcutaneously in a 1 mL pre-filled syringe.

Study burden and risks

See section E9.

Contacts

Public
Gilead Sciences

Lakeside Drive 333
Foster City CA 94404
US
Scientific
Gilead Sciences

Lakeside Drive 333
Foster City CA 94404
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

InclusionCriteria:
Subjects will be eligible if they meet all of the following inclusion criteria:
1) Must 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 females (non-pregnant, non-lactating), ages 18 to 75 years, inclusive based on the date of the screening visit

3) Documented diagnosis of UC of at least 6 months AND with a minimum disease extent of 15 cm from the anal verge
4) A surveillance colonoscopy is required at screening in subjects with a history of ulcerative colitis for 8 or more years, if one was not performed in the prior 24 months
5) Moderately to severely active UC as determined by a centrally read endoscopy score * 2, a rectal bleeding score * 1, a stool frequency score * 1 and PGA of 2 or 3 as determined by the Mayo clinical scoring system with endoscopy occurring within 14 days to first dose of study drug
6) Demonstrated at any time over the prior 5 years, an inadequate clinical response or loss of response to, or intolerance of atleastone of the following agents:
* Corticosteroids
* Immunomodulators
* TNF* Antagonists
* Vedolizumab
7) May be receiving the following drugs:
* Oral 5-ASA compounds provided the dose has been stable for at least 2 weeks prior to screening, and/or
* Oral corticosteroid therapy (prednisone at a stable dose of
* 30 mg/day or equivalent) provided the dose has been stable for 2 weeks prior to screening, and/or
* Azathioprine or 6-MP or methotrexate provided the dose has been stable for 8 weeks prior to screening
8) Females of childbearing potential (see definition in Appendix 7) must have a negative pregnancy test at screening and baseline.
9) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 7.

Exclusion criteria

ExclusionCriteria:;Subjects will be ineligible if they meet any of the following exclusion criteria:;1) Known hypersensitivity to the study investigational medicinal products
2) Exhibit severe UC as defined by the following criteria:
* * 6 bloody stools daily ANDoneormore of the following:
* Oral temperature > 100.3 °F (or 38 °C)
* Pulse > 90 beats/minute
3) Laboratory parameters:
* Liver panel (AST, ALT, total bilirubin, alkaline phosphatase)
> 3 times the ULN
* Serum creatinine > 2 times the ULN
* Hemoglobin < 8 g/dL (both males and females)
* Absolute neutrophil count (ANC) < 1.5 × 109/L (1,500 mm3)
* Platelets < 100 × 109/L
4) Use of rectal formulations of 5-ASA compounds or corticosteroids 2 weeks prior to screening

5) Crohn*s disease or indeterminate colitis
6) History of colectomy, partial colectomy, or dysplasia on biopsy
7) History of colonic or small bowel stoma
8) Stool sample positive for clostridium difficile (C. difficile) toxin, Escherichia coli, Salmonella, Shigella, Campylobacter or Yersinia
9) Stool sample positive for ova and parasites test (O&P) unless approved by the medical monitor
10) Treatment with infliximab, adalimumab, natalizumab, golimumab, vedolizumab, certolizumab, or TNF* biosimilar agent 4 weeks prior to screening (and last dose must be at least 8 weeks prior to randomization)
11) Treatment with non-biologic therapies (eg, cyclosporine, thalidomide) other than those permitted in Section 5.4 at least 4 weeks prior to screening
12) Other clinically significant active infection
13) Chronic medical or psychiatric problem that may interfere with subject*s ability to comply with study procedures
14) Co-infection with chronic HIV, hepatitis B or hepatitis C
15) Active tuberculosis or history of latent tuberculosis that has not been treated
16) History of malignancy in the last 5 years except for subjects who have been successfully treated for non-melanoma skin cancer or cervical carcinoma in situ
17) Any other investigational medicinal therapy or investigational biologics use 4 weeks prior to screening (and at least 8 weeks prior to randomization)
18) Any chronic medical condition (including, but not limited to, cardiac or pulmonary disease, alcohol or drug abuse) that, in the opinion of the Investigator, would make the subject unsuitable for the study or would prevent compliance with the study protocol procedures
19) Females who may wish to become pregnant and/or plan to undergo egg donation or egg harvesting for the purpose of current or future fertilization during the course of the study and up to 30 days of the last dose of the study drug
20) Male subjects unwilling to refrain from sperm donation for at least 90 days after the last dose of study drug
21) Treatment with tacrolimus
22) Treatment with apheresis

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)

Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-07-2016
Enrollment:	12
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	26-10-2015
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-12-2015
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-05-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-05-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-07-2016

Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-07-2016
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	EUCTR2014-005217-24-NL
CCMO	NL54857.028.15