Clinical Summary

Title of the study

A PHASE 2, RANDOMIZED, PLACEBO-CONTROLLED, MULTICENTER STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF GED-0507-34-LEVO (GED0507) FOR TREATMENT OF SUBJECTS WITH ACTIVE ULCERATIVE COLITIS

Publication (reference)	***Clinical phase***
Unpublished to date (2017)	Phase 2
Date of first enrolment	***Date of last completed***
28 November 2016 (first patient enrolled)	31 July 2017 (last visit of the last patient)

Objectives

Primary Objective:
To evaluate the clinical efficacy of GED-0507-34-Levo (80 mg twice daily [BID] and 160 mg BID), compared
with placebo, in subjects with active UC.

Secondary Objective:
To evaluate the safety and tolerability of GED-0507-34-Levo (80 mg BID and 160 mg BID), compared with
placebo, in subjects with active UC.

Exploratory Objective:
To evaluate the onset of clinical effect of GED-0507-34-Levo (80 mg BID and 160 mg BID), compared with
placebo, in subjects with active UC.

Pharmacokinetic Objective:
- To characterize the pharmacokinetics (PK) of GED-0507-34-Levo in subjects with active UC.
- To evaluate the change in biomarkers such as C-reactive protein (CRP) and fecal calprotectin (FCP) in response to GED-0507-34-Levo (80 mg BID and 160 mg BID), compared with placebo, in subjects with active UC.
- To explore the histological effects of GED-0507-34-Levo (80 mg BID and 160 mg BID) such as inflammatory cell infiltration and tissue destruction in colonic mucosal biopsies from subjects with active UC (Geboes Index).

Study design

This was a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of 2 doses of GED-0507-34-Levo in subjects with active, mild-to-moderate UC (defined as a Modified Mayo score [MMS] of ≥ 4 to ≤ 8, with a Stool Frequency sub-score [SFS] ≥ 1, a Rectal Bleeding sub-score [RBS] = 1 or 2 and an endoscopic sub-score > 1 and < 3).

The study has been designed to randomize 207 subjects included in three treatment groups: 80 mg BID, 160 mg BID, or identically appearing placebo BID for up to 8 weeks. Treatment was assigned via an Interactive Web Response System (IWRS) in 1:1:1 ratio.

The study consisted of 3 phases:

- Screening Phase – up to 4 weeks
- Double-blind Placebo-controlled Phase – Weeks 0 to 8

- Follow-up Phase – Week 9

An interim safety evaluation for the first 24 patients randomized (8 patients into each treatment group) has been foreseen to evaluate the safety of investigational product at 320 mg dose arm.

Patient population

The study population has been designed to recruit approximately 207 patient of female and male subjects over 18 years and older.

Main inclusion criteria

1. Subjects must satisfy the following criteria to be enrolled in the study:
2. Male or female aged 18 and over at the time of signing the informed consent.
3. Must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.
4. Must be able to adhere to the study visit schedule and other protocol requirements.
5. Diagnosis of UC with a duration of at least 3 months prior to the Screening Visit.
6. MMS ≥ 4 to ≤ 8 (range: 0 - 9) prior to randomization in the study
7. SFS ≥ 1 and RBS = 1 or 2
8. Mayo endoscopic sub-score > 1 and < 3 prior to randomization in the study
9. Subjects are required to have a colonoscopy if one has not been performed within 12 months prior to the Screening Visit.
10. Subjects who have relapsed on maintenance therapy with doses of 5-ASA ≤ 2.4 g/day.
11. Must meet the following laboratory criteria:
12. WBC count ≥ 3000/mm3 (≥ 3.0 × 109/L) and < 14,000/mm3 (< 14 × 109/L)
13. Platelet count ≥ 100,000/mm3 (≥ 100 × 109/L)
14. Serum creatinine ≤ 1.5 mg/dL (≤ 132.6 µmol/L)
15. AST (SGOT) and ALT (SGPT) ≤ 2 upper limit of normal (ULN). If initial test shows ALT or AST > 2 ULN, 1 repeat test is allowed during the screening period
16. Total bilirubin ≤ 2 mg/dL (≤ 34 mol/L) and albumin > lower limit of normal (LLN). If initial albumin test result is < 2 g/dL, 1 repeat test is allowed during the screening period
17. Hemoglobin ≥ 9 g/dL (≥ 5.6 mmol/L)
18. FCBP must have a negative pregnancy test at screening and the Baseline Visit. While on IP and for at least 28 days after taking the last dose of IP, FCBP who engage in activity in which conception is possible must use one of the approved contraceptive options2 described below:
19. Option 1: Any one of the following highly effective methods: hormonal contraception (oral, injection, implant, transdermal patch, vaginal ring); intrauterine device (IUD); tubal ligation; or partner's vasectomy
    OR
    Option 2: Male or female condom (latex condom or nonlatex condom NOT made out of natural [animal] membrane [for example, polyurethane]); PLUS one additional barrier method: (a) diaphragm with spermicide; (b) cervical cap with spermicide; or (c) contraceptive sponge with spermicide
20. Male subjects (including those who have had a vasectomy) who engage in activity in which conception is possible must use barrier contraception (male latex condom or nonlatex condom NOT made out of natural [animal] membrane [for example, polyurethane]) while on investigational product and for at least 28 days after the last dose of investigational product.

Main Exclusion Criteria

The presence of any of the following excluded a subject from enrolment:

1. Diagnosis of Crohn's disease, indeterminate colitis, ischemic colitis, microscopic colitis, radiation colitis, or diverticular disease-associated colitis.
2. UC restricted to the distal 15 cm or less (eg, ulcerative proctitis).
3. Subjects, who have had surgery as a treatment for UC or who, in the opinion of the Investigator, are likely to require surgery for UC during the study.
4. Clinical signs suggestive of fulminant colitis or toxic megacolon.
5. Evidence of pathogenic enteric infection.
6. History of colorectal cancer or colorectal dysplasia.
7. Prior use of any TNF inhibitor (or any biologic agent).
8. Prior use of mycophenolic acid, tacrolimus, sirolimus, cyclosporine, or thalidomide.
9. Subjects who have relapsed on maintenance therapy with doses of 5-ASA > 2.4 g/day were excluded from the study. If a subject had a recent 5-ASA dose reduction from > 2.4g/day to ≤ 2.4 g/day and relapsed within 2 weeks of that dose reduction.
10. Oral aminosalicylates are not permitted during the study treatment period (from visit 2 until visit 7 or ET visit)'.
11. Use of budesonide-MMx within the last 8 weeks.
12. Use of oral and/or IV corticosteroids within 2 weeks of the Screening Visit.
13. Use of immunosuppressants (azathioprene [AZA], 6-mercaptopurine [6-MP] or methotrexate [MTX]) within 8 weeks of the Screening Visit.
14. Use of topical treatment with 5-ASA or corticosteroid enemas or suppositories within 2 weeks of the Screening Visit.
15. History of any clinically significant neurological, renal, hepatic, GI, pulmonary, metabolic, cardiovascular, psychiatric, endocrine, hematological disorder or disease or any other medical condition that, in the Investigator's opinion, would preclude participation in the study.
16. Prior history of suicide attempt at any time in the subject's lifetime prior to randomization in the study or major psychiatric illness requiring hospitalization within 3 years of study randomization.
17. Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she was to participate in the study or confounds the ability to interpret data from the study.
18. Pregnant or breast-feeding.
19. History of any of the following cardiac conditions within 6 months of screening: myocardial infarction, acute coronary syndrome, unstable angina, new onset atrial fibrillation, new onset atrial flutter, second- or third-degree atrioventricular block, ventricular fibrillation, ventricular tachycardia, heart failure, cardiac surgery, interventional cardiac catheterization (with or without a stent placement), interventional electrophysiology procedure, or presence of implanted defibrillator.
20. Known active current or history of recurrent bacterial, viral, fungal, mycobacterial, or other infections (including but not limited to tuberculosis, atypical mycobacterial disease, and herpes zoster), human immunodeficiency virus (HIV), or any major episode of infection requiring hospitalization or treatment with IV or oral antibiotics within 4 weeks of screening.
21. Subjects with active hepatitis B infection, as described in Appendix D, are ineligible for the study. Subjects without current hepatitis B infection, as described in Appendix E, may participate in the study.
22. Subjects who are positive for the hepatitis C antibody are not eligible for the study.

23. History of congenital or acquired immunodeficiency (eg, Common Variable Immunodeficiency Disease).
24. History of malignancy, except for:
25. Treated (ie, cured) basal cell or squamous cell in situ skin carcinomas
26. Treated (ie, cured) cervical intraepithelial neoplasia (CIN) or carcinoma in situ of the cervix with no evidence of recurrence within the previous 5 years
27. Any condition that could affect oral drug absorption, including gastric resections, gastroparesis, or bariatric surgery, such as gastric bypass.
28. Subjects who have received any investigational drug or device within 3 months of study randomization.
29. History of alcohol, drug, or chemical abuse within the 6 months prior to screening.
30. Known hypersensitivity to GED-0507-34-Levo or any excipients in the formulation.

Test product, dose and mode of administration

The chemical name of GED-0507-34-Levo (GED0507) is (S)-(-)-3-(4-aminophenyl))-2 Methoxypropionic acid.GED-0507-34-Levo was provided as 80 mg tablets and the Placebo was also provided as tablets identical in appearance. Tablets were taken by mouth BID, in the morning (AM) and in the evening (PM), approximately 12 hours apart, on an empty stomach (ie, at least 3 hours after eating and at least 1 hour prior to eating breakfast or dinner).

Treatment group:

80 mg BID group: 2 tablets AM (1 placebo + 1 active 80 mg) and 2 tablets PM (1 placebo + 1 active 80 mg).

160 mg BID group: 2 tablets AM (2 active 80 mg) and 2 tablets PM (2 active 80 mg).

Placebo BID Group: 2 tablets AM and 2 tablets PM.

Statistical methods

The study, designed to enroll 207 patients, was terminated by the sponsor earlier due to a low recruitment rate.

Since only 19 patient were recruited, it has been decided to perform only a descriptive statistics related to safety. No efficacy parameters or endpoints have been assessed.

SUMMARY OF THE RESULTS

A total of 50 patients were enrolled, when the study has been terminated, 25 males and 25 females. However, 16 patients of the males group and 15 patients of the females group resulted as screened failures.

Only 19 patients were randomized to receive the investigational product. A total of 8 patients completed the study treatment, 4 patients discontinued the treatment and 7 patients were in treatment when the study has been stopped.

Among the 8 patients who completed the study treatment: 4 patients were included in placebo BD group, 2 patients in the 80 mg BD group, 2 patients in 160 mg BD group.

Among the 4 patients who discontinued the treatment:
1 patients in the placebo BD group
104101 patient discontinued the treatment after 6 weeks
3 patients were included in the 160 mg BD group:
402101 patient discontinued the treatment after 4 weeks
308101 patient discontinued the treatment after 4 weeks
451101 patient discontinued the treatment after 2 weeks
All patients interrupted the treatment due to a worsening of disease (Ulcerative Colitis), but only one was hospitalized (104101).

Among the 7 patients still in treatment when the study has been stopped:
3 patients were included in the 160 mg BD group:
613102 patient interrupted the treatment after 1 week
351101 patient interrupted the treatment after 3 weeks
605103 patient interrupted the treatment after 1 week
2 patients in the placebo BD group:
613103 patient interrupted the treatment after 2 week
257101 patient interrupted the treatment after 3 week
2 patients in 80 mg BD group:
702101 patient interrupted the treatment after 2 week
611102 patient interrupted the treatment after 4 weeks

The 7 patients above who discontinued the investigational product, were then treated with the standard treatment for Mild-to-Moderate Ulcerative colitis, according to the Principal Investigator decision.

During the study, only one Serious ADR was reported and defined as worsening of ulcerative colitis. The patient discontinued the treatment, was hospitalized and the event has been resolved.
The patient was included into the placebo treatment group
The event is listed as per current RSI (Investigator's Brochure) and does not modify the benefit/risk profile of the IMP.
The event has been judged by the Sponsor as unlikely related to the study drug.

No SUSARs were reported during the study.
No safety concerns that could modify the safety profile of the IMP arose from the study.
Regarding the physical examination and the laboratory tests results, not clinically significant changes have been reported.

Conclusions

Overall, within the limited number of exposed patients, GED-0507-34-Levo 80 mg and 160 mg appeared to be safe and well tolerated in subjects with UC from mild to moderate.

Date of the report

06th November 2017

Company's Medical Officer Responsible

15/11/2017

Signature ***Date***