2. SYNOPSIS

Name of Sponsor/Company: Giuliani SpA/Celgene **Name of Finished Product:** GED-0301 **Name of Active Ingredient:** GED-0301	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

Title of Study:

A Phase 2 multicenter, randomized, double-blind, controlled versus placebo, long-term extension study to evaluate the safety and tolerability of 40 mg GED-0301 for the maintenance of Crohn's disease in remission

Principal Investigator:

Prof. Giovanni Monteleone, Fondazione PTV, "Policlinico Tor Vergata," UOC di Gastroenterologia, Viale Oxford 81, 00133 Roma, Italy.

Investigators:

Prof. Gino Roberto Corazza, Policlinico San Matteo, Padiglione 3 – Medicine (Medicina Generale 1) Viale Camillo Golgi 19, 27100 Pavia, Italy.

Prof. Vito Annese, AOU Careggi di Firenze, Gastroenterologia SOD2 Dipartimento di Specialità, Medico Chirurgiche, Via delle Oblate 1, 50141 Firenze, Italy.

Prof. Maurizio Vecchi, Gastroenterologia ed Endoscopia Digestiva, IRCCS Policlinico San Donato, Piazza Edmondo Malan, 20097 San Donato Milanese, Milano, Italy.

Study center(s): 4 sites in Italy

Publications (reference): Not applicable.

Studied period (years): Date first subject enrolled: 14 Jun 2012 Date last subject completed: 11 Apr 2013	**Phase of development:** 2

Objectives:

Primary: Evaluation of safety of GED-0301, oral administration in a long-term study.

Secondary: Evaluation of efficacy of GED-0301 in the maintenance of remission in subjects with Crohn's disease (CD), defined as percentage of subjects in remission (Crohn's Disease Activity Index [CDAI] score < 150) at Week 16 and at Week 36.

Methodology:

This was a Phase 2, multicenter, randomized, double-blind, placebo-controlled, long-term extension study to evaluate the safety and tolerability of GED-0301 in subjects with active CD (ileo-colitis). This study was sponsored and supervised by Giuliani SpA, acting under contract to Nogra Pharma Limited. Celgene was responsible for final report writing.

Eligible male and female subjects who participated in Study GED-301-01-11 and who were still in remission (CDAI score < 150) were randomized into 1 of 2 treatment groups: placebo or GED-0301 40 mg. Subjects received treatment for 7 days at Week 1 and if their remission (CDAI score < 150) was

Name of Sponsor/Company: Giuliani SpA/Celgene	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: GED-0301	Volume:	
Name of Active Ingredient: GED-0301	Page:	

maintained, received treatment for an additional 7 days at Week 16.

Subjects were screened to determine eligibility (Visit 1, Screening/Randomization Visit) on Day 1. Subsequent visits were performed at Week 16 (Visit 2, start of the second 7-day treatment period) and Week 36 (Visit 3, End of Study Visit). Subjects were contacted by telephone at Weeks 4, 8, 12, 20, 24, 28, and 32 to assess general health conditions, CD symptoms, compliance to investigational product (IP), adverse events (AEs), and concomitant medications. Unscheduled visits could have been performed in the case of any suspicion of CD reoccurrence. If reoccurrence is confirmed by a CDAI score > 150, the subject was to be withdrawn from study.

Physical examinations, vital signs, body weight, C-reactive protein (CRP), and CDAI were assessed at Day 1, Weeks 16 and 36, and unscheduled visits (as needed). Pregnancy tests (if necessary); hematology, clinical chemistry, and urinalysis laboratory parameters; and electrocardiograms (ECGs) were assessed at Day 1, Week 36, and unscheduled visits (as needed). Class effects (complement activation and coagulation parameters) were assessed at Week 36 and at unscheduled visits (as needed).

Number of subjects (planned and analyzed):

Planned: approximately 70 subjects

Analyzed: 10 subjects

Diagnosis and main criteria for inclusion:

Subjects must have met all of the following criteria in order to be eligible for inclusion:

1. Written informed consent, personally signed and dated by the subject prior to any study-related procedure being carried out.
2. Subjects in remission of CD at the end (Week 12) of the lead-in study (Study GED-301-01-11).
3. Female subjects not of childbearing potential (women in menopause defined as surgically sterile or one year postmenopausal); female subjects of childbearing potential with a negative pregnancy testing at enrollment and using effective method of birth control during the study.
4. Ability to understand and comply with study procedures and restrictions.

Subjects were excluded from the study if any of the following criteria were met:

1. Pregnant or breast-feeding women.
2. Screening laboratory values within the following parameters:
   - activated partial thromboplastin time > 1.5 upper limit of normal (ULN)
   - platelet count ≤ 100000/mm^3
   - serum creatinine > 1.5 ULN
   - total bilirubin > 1.5 ULN (excluding Gilbert's Syndrome)

Name of Sponsor/Company: Giuliani SpA/Celgene	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: GED-0301	Volume:	
Name of Active Ingredient: GED-0301	Page:	

- aspartate aminotransferase and alanine aminotransferase >1.5 ULN.

3. QTc interval > 450 msec for males and > 470 msec for females.
4. Any medical disorder that emerged during/after the participation in Study GED-301-01-11 and may have required treatment (eg, renal or hepatic impairment), or that made the subject unlikely to fully complete the study, or any condition that presented undue risk from the study medication or procedures.

Test product, dose and mode of administration, batch number:

GED-0301 was administered orally as 40 mg tablets (batch number PD11249).

Duration of treatment:

Subject were treated with placebo or GED-0301 40 mg/day for 7 days at Week 1 and if their remission was maintained (CDAI score < 150), were treated for an additional 7 days at Week 16.

Reference therapy, dose and mode of administration, batch number:

Placebo administered orally as tablets (batch number PD11066).

Criteria for evaluation:

Efficacy:

Efficacy was the secondary objective of this study and was defined as the percentage of subjects in remission (CDAI score < 150) at Week 16 and at Week 36.

Safety:

Safety was assessed by physical examinations, body weight, vital signs, ECGs, AEs and serious AEs (SAEs), pregnancy test (as appropriate), and hematology, biochemistry, and urinalysis laboratory values.

Statistical methods:

Efficacy:

Statistical analysis was based on the intention-to-treat principle; all subjects were therefore analyzed in the group allocated by randomization. The primary analysis was conducted on the modified intent-to-treat (mITT) population and was defined as all randomized subjects who received at least one dose of the study medication, excluding those who withdrew from the study due to a reason clearly documented as independent of treatment or remained on study for less than 3 days.

The Pearson's chi-square test (and/or Fisher's exact test) was used to evaluate the difference in the proportion of subjects in clinical remission at Month 4 among subjects receiving GED-0301 40 mg or placebo. Those with missing primary endpoint data at Week 36 were classified as a failure ("no maintenance of clinical remission" category). Additionally, the single items of the CDAI scale were also considered for the efficacy assessment on the basis of the change versus baseline at Week 36.

Pearson's chi-square test, Fisher's exact test, and analysis of covariance were used as appropriate.

Safety:

All randomized subjects who received at least 1 dose of IP were included in the safety analysis.

Name of Sponsor/Company: Giuliani SpA/Celgene	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: GED-0301		
Name of Active Ingredient: GED-0301		

Treatment-emergent adverse events (TEAEs), including AEs with onset after administration of the first dose of IP, as well as baseline conditions worsened in severity while the subject was on treatment, were summarized using frequency tables. Coding of adverse events was done using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events were summarized for each treatment group by MedDRA system organ class and preferred term (PT). Adverse events considered to be related to IP, SAEs, and AEs leading to discontinuation were also to be tabulated by treatment group.

Descriptive statistics were provided for vital signs at each assessment for subjects with a baseline and at least 1 postbaseline value. Physical examination abnormalities and global tolerability according to the investigator were described using frequency tables. For laboratory data (hematology, biochemistry, urinalysis, and coagulation assessment), descriptive statistics (number of observations, mean, standard deviation, minimum, median and maximum values) were used for continuous variables for subjects with a baseline and at least 1 postbaseline value. Categorical values were summarized using frequencies and percentages.

SUMMARY – CONCLUSIONS

After further consideration of the study design in the context of the overall development plan, Nogra decided to terminate the trial early. A total of 10 subjects were randomized and treated in this study. Seven subjects completed the study and 3 subjects were discontinued due to early trial termination.

EFFICACY RESULTS:

All 7 subjects in the mITT population, 3 placebo subjects and 4 GED-0301 subjects, maintained remission (CDAI score < 150) at Week 16 and at Week 36.

SAFETY RESULTS:

A total of 11 AEs were reported in 4 out of 10 subjects: 9 AEs in placebo subjects and 2 AEs in GED-0301 subjects. No AE preferred term was reported in more than 1 subject. Six out of 11 AEs were mild in severity (the rest were moderate in severity) and 9 out of 11 AEs resolved. One placebo subject reported an SAE of subileus. There were no deaths reported and there were no AEs that led to discontinuation of IP.

No clinically meaningful changes were observed in any hematology or clinical chemistry test during the study. No treatment-emergent liver function abnormalities occurred. There was no evidence suggestive of a treatment-related effect of GED-0301 on vital signs, physical findings, ECGs, or complement activation and coagulation parameters.

CONCLUSION:

After further consideration of the study design in the context of the overall development plan, this Phase 2 extension study was terminated early. Data from 10 enrolled subjects, and data on 7 subjects followed for 36 weeks, revealed no newly identified safety concerns.

Date of the report:

19 Nov 2014.

Celgene Signing Page

This is a representation of an electronic record that was signed electronically in Livelink. This page is the manifestation of the electronic signature(s) used in compliance with the organizations electronic signature policies and procedures.

UserName: Usiskin, Keith (kusiskin)
Title: Exec Dir, Clin R&D (MD)
Date: Wednesday, 19 November 2014, 05:59 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
==========