Synopsis

SPONSOR	International Extranodal Lymphoma Study Group (IELSG)	
NAME PRODUCTS / INTERVENTION	Lenalidomide and Claritromycin	
NAME OF ACTIVE PRINCIPLE	Lenalidomide and Claritromycin	
PROTOCOL CODE	IELSG40	
PROTOCOL TITLE	A phase II trial addressing feasibility and activity of clarithromycin + lenalidomide combination: a full oral treatment for patients with relapsed/refractory extranodal marginal zone lymphoma	
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STUDY SITES	Three countries were involved: Italy, Austria, and Spain, and a total of 10 enrolling sites.	
STUDY PERIOD	First Patient Enrolled - 17 March 2017 Last Patient Enrolled – 11 October 2019	
DEVELOPMENT PHASE	II	
OBJECTIVES	<u>Primary Objective</u> To assess the overall response rate (complete and partial responses) of the combination treatment of clarithromycin and lenalidomide (Revlimid) in patients with MALT lymphoma, refractory or relapsing after radiotherapy and/or chemotherapy and/or immunotherapy. <u>Secondary Objectives</u> 1. Adverse events incidence, severity, and relationship to study treatment 2. Time from first investigational medicinal product administration to assessment of disease progression or death due to any cause 3. Time from first investigational medicinal product administration to assessment of disease progression or death due to progression 4. Time from first IMP administration to patient's death	

STUDY DESIGN AND METHODOLOGY	Single-arm, open-label, 2-stage phase II clinical trial according to the Simon Minimax design. At stage 1, 30 patients were evaluated for tumour response: if ≤18 responses were observed, the study would have been stopped, and the combination would have been considered of no interest. If ≥19 responses were observed, the study would have been continued until a total of 62 evaluable patients were included. If ≥44 responses had been observed, the combination would have been considered worthy of further evaluation.
SUBJECT POPULATION	Number of Subjects Planned: 68 Number of Subjects Enrolled: 44 Number of Subjects Randomized: NA Number of Subjects for Efficacy Analysis: 43 subjects Number of Subjects for Safety Analysis: 44 subjects <u>Brief description of demographic and baseline characteristics</u> A total of 43 patients were included in the treated population. The median age was 69 years. The majority of patients were male (56%), and most had an ECOG performance status of 0 (91%), indicating good functional status at baseline. With respect to disease characteristics, 44% of patients had Ann Arbor stage I–II disease, while 56% presented with stage III–IV disease. Elevated serum LDH levels were observed in 19% of patients, and anemia was reported in 12%. According to the MALT-IPI prognostic index, 14% of patients were classified as low risk, 53% as intermediate risk, and 33% as high risk. Most patients had received prior systemic therapy: 54% had one prior line, 23% had two lines, 16% had three lines, and 2% had six prior lines of treatment. Other previous treatments included alkylating agents (42%), lenalidomide (12%), and clarithromycin (16%). In addition, 2 patients (5%) had received radiotherapy only before enrollment. The main sites of relapsed or refractory disease included the stomach (26%), ocular adnexa (19%), lung (14%), salivary glands (9%), and liver (9%). Less common sites were the skin (7%), subcutaneous tissue (5%), breast (5%), kidneys (2%), bone (2%), and muscle (2%). <u>Brief description of subjects excluded from the primary analysis population.</u> Response was not evaluable in five patients: three because of consent withdrawal and two because of early treatment discontinuation after serious adverse events (fever and pulmonary thromboembolism).
ELIGIBILITY CRITERIA	**Inclusion Criteria** 1. Histologically verified diagnosis of MALT lymphoma arising at any extranodal site

	2. Disease refractory to or in first or greater relapse after prior radiotherapy and/or chemotherapy and/or immunotherapy 3. Measurable or non-measurable lesions where the response is nevertheless evaluable by non-imaging means (e.g., gastric or bone marrow infiltrations) 4. Ann Arbor Stage I-IV 5. ECOG performance status of 0, 1, or 2 6. Age ≥ 18 years 7. Life expectancy of at least 3 months 8. Adequate haematological status: ANC (absolute neutrophil count [segmented + bands]) ≥1.0 x 109/L, platelet count ≥ 75 x 109/L, haemoglobin ≥8 g/dL. 9. Adequate cardiac, renal, and liver function tests (LVEF > 40%, serum creatinine < 2.5 mg/dl, ALAT or ASAT < 2.5 x upper limit of normal range, alkaline phosphatase < 2.5 x upper limit of normal range, serum bilirubin < 2.0 mg/dl) 10. Patient must be willing and able to comply with the protocol for the entire study duration 11. Female patients of childbearing potential must agree to use, and be able to comply with, effective contraception and agree to have medically supervised pregnancy tests before starting the study treatment and during therapy 12. Male patients must agree to always use a condom during any sexual contact with females of reproductive potential and agree not to donate sperm while taking lenalidomide 13. Patient must agree to abstain from donating blood while taking the study drug therapy 14. Patient must agree not to share study medication with another person and to return all unused study drug to the investigator 15. Patient must be willing and able to comply with the protocol 16. Patient must be capable of understanding the purpose of the study and have given written informed consent **Exclusion Criteria** 1. Lymphoma histology other than MALT lymphoma or MALT lymphoma 2. with a diffuse large cell lymphoma (“high grade lymphoma”) - component 3. Use of any investigational agent within 28 days before initiation of treatment 4. History of malignancy other than squamous cell carcinoma, basal cell carcinoma of the skin, or carcinoma in situ of the uterine cervix within the last 5 years, unless in complete remission for at least 3 years 5. Dependency on red blood cell and/or platelet transfusions 6. HBsAg positivity 7. Evidence of central nervous system involvement 8. A history of uncontrolled seizures, central nervous system disorders, or psychiatric disability judged by the investigator to be clinically significant and adversely affecting compliance with study drugs 9. Severe peripheral polyneuropathy 10. Clinically significant cardiac disease (e.g., congestive heart failure, symptomatic coronary artery disease, and cardiac arrhythmias not well-controlled with medication) or myocardial infarction within the

	last 6 months and/or long QT syndrome 11. HIV seropositivity 12. Presence of active opportunistic infections 13. Pregnancy or lactation 14. Uncontrolled diabetes mellitus 15. Pre-existing thromboembolic conditions at study entry 16. Known hypersensitivity to thalidomide or lenalidomide, or macrolide antibiotics 17. Presence of any contraindication reported on the Summary of Product Characteristics (SmPC) of Clarithromycin 18. Hypersensitivity to any active principle and/or any excipient according to the contraindications reported in the SmPC of clarithromycin and in the Investigator's Brochure (NS) of lenalidomide
STUDY PRODUCTS / DOSE AND MODE OF ADMINISTRATION/ INTERVENTIONS	Lenalidomide was supplied free of charge by Celgene Corporation as 10, 15, and 20 mg capsules for oral administration. Clarithomycin was supplied free of charge by the Sponsor as 500 mg tablets. Each treatment cycle consisted of: • Oral Lenalidomide (Revlimid) once daily for 21 days at a dose of 20 mg; in case of drug-related adverse events, the dose was reduced to 15 and 10 mg/day. • Oral Clarithromycin 500 mg twice daily for 28 days. Cycles were repeated every 28 days. After the first 3 cycles, patients with stable disease or better response given another three cycles. Patients with complete remission or disease progression after 6 cycles were taken off study, while patients with partial response or stable disease received 3 further cycles of treatment. Again, patients with complete response or disease progression stopped therapy, while patients with partial response/stable disease received 3 further cycles up to a maximum of 12 cycles in total. The assessment of tumour response was performed every 3 cycles while patients were on treatment. Patients with SD, PR or CR at the end of their last treatment cycle repeated the tumour assessment examinations every 4 months after the end of treatment for the first 3 years of follow-up, every 6 months for the following 2 years, and yearly afterwards, until progression, start of a new antitumour therapy, death, or study end, whichever occurs earlier. Patients were followed for a maximum of 10 years after treatment discontinuation.
DURATION OF TREATMENT	12 months
STUDY PRIMARY ENDPOINT	Tumor response was assessed according to the international Revised Response Criteria for Malignant Lymphoma (Cheson et al) and the GELA (Group d'Etude des Lymphomes de l'Adulte) histological scoring system for post-treatment biopsies of patients with gastric MALT lymphoma. The overall response rate was represented by the total number of complete and partial responses.
STATISTICAL METHODS AND	Stage 1: 30 evaluable patients Stage 2: 32 evaluable patients

SAMPLE SIZE	Total: 68 patients (62 evaluable patients + 10% dropout) The overall response rate (ORR) observed in the clinical trials of lenalidomide and clarithromycin alone is 61% and 52%, respectively. The hypothesis tested in the CLEO trial is an improvement of the ORR, of 15% with the new regimen relative to an expected ORR of 60% with lenalidomide alone. This hypothesis was based on data available when the study was planned, which proved that clarithromycin is able to overcome resistance to lenalidomide, a common reason for progression or lack of response to this IMiD.Applying the Simon Mini-max design, we therefore assume that the maximum ORR considered of low interest is 60% (null hypothesis, H_0) and the minimum ORR considered of interest is 75% (alternative hypothesis, H_1). With an alpha level of 0.05 and a beta level of 0.20, 62 patients (30 at stage 1 + 32 at stage 2) are needed to assess this difference. Considering an expected 10% dropout rate, we plan to enrol 68 patients in total. All registered patients who started treatment were included in the primary analysis of the overall response rate (primary analysis population). Patients progressing and/or dying during treatment without having achieved a disease stabilization or better response were considered nonresponders. The 95% confidence limits of the proportion of responding patients at the end of the study were computed according to Fleiss (Statistical Methods for Rates and Proportions). Progression-free survival and time to progression were calculated using the Kaplan-Meier method. Patients with no disease progression at study end were censored at the last visit date. Overall survival was calculated using the Kaplan-Meier method, and patients still alive at the study end were censored at the date of their last contact. Adverse Events overall incidence and incidence by intensity (CTCAE grade) and relationship to the trial medications were presented in descriptive frequency tables.
SUMMARY OF RESULTS	<u>Efficacy Results</u> Enrollment was terminated after the first-step analysis in the first 30 patients showed an overall response rate of 44%, which did not meet the predefined threshold, while the patients already recruited continued the study treatment. As a result, it was decided to reduce the follow-up from 10 to 5 years. At a median follow-up of 46 months, the best response was a CR in 6 patients, a PR in 10, and stable disease in 6. Five patients had progressive disease (3 with gastric, 1 with lung, and 1 with salivary gland lymphoma). Response was not evaluable in five patients: three because of consent withdrawal and two because of early treatment discontinuation after serious adverse events (fever and pulmonary thromboembolism). In the intent-to-treat population (n=43), the overall response rate was 44% with a CR rate of 14%, respectively, in the subset of 38 evaluable patients, of whom 29 were assessed by computed tomography scan, and nine (with localized gastric involvement) by repeat endoscopic biopsy only. Twenty-one (49%) patients completed the entire protocol planned treatment program; six of them achieved a CR, and eight had a PR. The median of progression-free survival (PFS) was 40 months with a 5-year PFS rate of 43%, while the median of overall survival (OS) was not reached, and 77% of patients were alive at 5 years.

	Notably, the response quality improved over time: of 11 patients with a PR at 3 months, three achieved a CR at 1 year; of 20 patients with stable disease at 3 months, one achieved a CR and three a PR at 1 year.
	Safety Results During the study, 22 of 43 patients (51%) discontinued treatment, mainly due to lymphoma progression (8), toxicity (4), withdrawal of consent (8), or investigator decision (2). Almost all patients (41 of 43) experienced at least one treatment-emergent adverse event, most commonly rash, neutropenia, asthenia, and dysgeusia, with diarrhea, vertigo, and musculoskeletal pain also frequently reported. Grade 3 or higher adverse events occurred in 31 patients, with neutropenia being the most common. No clarithromycin-related cardiac toxicity was observed. Thirteen serious adverse events were reported, four of which were attributed to lenalidomide: febrile neutropenia, pulmonary thromboembolism, lung infection, and basal cell carcinoma (one patient each). Apart from one pulmonary thromboembolism, no other severe thrombotic or hemorrhagic events occurred, with only one case of superficial venous thrombosis (Grade 1) and two moderate bleeding episodes (Grade 2). All deaths during follow-up were disease-related, with patients aged 51–87 years, and none were linked to treatment. Overall, the data indicate that the therapy was generally well tolerated, with severe adverse events primarily hematologic, and mortality driven by underlying lymphoma rather than the study treatment.
CONCLUSIONS	The efficacy of the clarithromycin-le-nalidomide regimen appears like that observed with clarithromycin alone. Moreover, the overall response rate seems lower than the one reported in the study of lenalidomide alone, which we used for the sample size calculation. Since there are no reasonable grounds to assume that the combination is detrimental, the most likely explanation for these findings is the inclusion of a sizable number (15% to 60%) of untreated patients and the significantly higher proportion of stage I patients (over 70%) in the prior studies. This may also explain a higher lymphoma-related mortality (9%) in the present study than in the prior ones. However, it is worth noting that, despite a lower overall response rate, the duration of response and progression-free survival are not inferior to those observed in the trial that led to approval by the Food and Drug Administration of the lenalidomide-rituximab combination for previously treated patients with indolent lymphoma.
VERSION AND DATE OF THE REPORT	Version 1.0 – 21.11.2025