

2. SYNOPSIS

Name of Sponsor/Company: LYSARC	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use Only)</i>
Name of Finished Product: Entospletinib	Volume:	
Name of Active Ingredient: Entospletinib	Page:	
Title of Study: A phase IB-II study of Entospletinib (ENTO) in newly diagnosed diffuse large B cell lymphoma (DLBCL) patients with aalPI ≥ 1 treated by R-CHOP.		
Coordinating Investigator: Dr Emmanuelle Tchernonog, Service d’Hématologie, Hôpital Saint Eloi, Montpellier, France. Co-coordinating Investigator: Dr. Julien Depaus, Service d’Hématologie, Dinant Godinne UCL Namur, Yvoir, Belgique.		
Study site(s) and countries: 27 study centers from France and Belgium.		
Publications (reference): Not applicable.		
Studied period (years): Date first subject first visit: 26 Jul 2017 Date last subject completed: 18 Oct 2019 Data cutoff date: 18 Oct 2019	Phase of development: IB-II	
Trial registry number(s): ClinicalTrials.gov identifier: NCT03225924 EudraCT number: 2016-003103-56		
Objectives: <u>Primary:</u> Phase Ib: <ul style="list-style-type: none"> to determine the recommended phase 2 dose (RP2D) for ENTO in patients treated with R-CHOP 21 Phase II: <ul style="list-style-type: none"> to determine the Complete Metabolic Response (CMR) rate by the Lugano classification 2014 (Deauville scale 1-3) at the end of treatment <u>Secondary:</u> Phase Ib: <ul style="list-style-type: none"> to evaluate the safety of ENTO in patients treated with 8 cycles of R-CHOP 21 to evaluate the preliminary anti-tumor activity of ENTO in patients treated with R-CHOP 21 as assessed by CMR rate by the Lugano classification 2014 at the intermediate evaluation (i.e., after 4 		

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cycles or at treatment discontinuation) and at the end of treatment (i.e., after 8 cycles or at treatment discontinuation)		
<p>Phase II:</p> <ul style="list-style-type: none"> to evaluate the safety of 8 cycles of ENTO in patients treated with R-CHOP 21 to evaluate the complete metabolic response rate at the intermediate evaluation, the Overall Metabolic Response Rate (OMRR) at the intermediate evaluation and at the end of treatment, duration of response (DOR), Progression-Free Survival (PFS) and Overall Survival (OS) at 24 and 52 weeks, and OS. 		
<p>Methodology:</p> <p>This study was a phase Ib/II, open label, multi-center, dose escalation study of ENTO. Initially three patients were treated with ENTO 200mg BID from day -4 to day 3 (for 7 days) in combination of R-CHOP (at day 1) given a pre-clinical hypothesis that starting ENTO before vincristine would have optimized the synergistic activity of ENTO and vincristine.</p> <p>ENTO was administered orally BID from day 1 (D1) until day 7 (D7) in combination with fixed doses of rituximab (R), cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) administered every 21 days (R-CHOP 21) for a total of 8 cycles.</p> <p>Patient were followed until 30 days after the last study drug administration of the last patient; no additional study visit was performed after this date.</p>		
<p>Number of subjects (planned, enrolled, and analyzed):</p> <p>Planned: 15 patients for the phase IB / 121 patients for the phase II Enrolled: 9 patients for the phase IB / 16 patients for the phase II Analyzed: 9 patients for the phase IB / 16 patients for the phase II</p>		
<p>Diagnosis and main criteria for inclusion:</p> <p>Eligible patients were 60 to 80 years old with newly diagnosed untreated histologically proven CD20+ DLBCL (2008 WHO classification), aaIPI\geq1, at least one bi-dimensionally measurable lesion defined as at least one node or tumor lesion on CT-Scan \geq 1.5 cm and had a life expectancy of \geq3 months.</p> <p>Patients were required to have normal liver, renal and hematological functions unless abnormalities were related to DLBCL. Patients with altered cardiac function or uncontrolled diabetes mellitus interfering with normal application of protocol treatment were not eligible for inclusion. Patients presenting a central nervous system involvement at diagnosis were excluded.</p>		
<p>Test product, dose, and mode of administration:</p> <p>Except ENTO, all drugs composing the regimens of the study were registered and were available at the hospital pharmacy. R-CHOP was administered according to the standard preparation and infusion procedures of each investigational site.</p>		

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<p>ENTO 100 mg or 200 mg tablets were packaged in white, high-density polyethylene (HDPE) bottles. Each bottle contained 60 tablets. ENTO was taken twice a day and administered approximately 12 hours between doses.</p> <p>ENTO was taken under fasting conditions. Fasting was defined as no food or liquids other than water for 2 hours pre- and 1-hour post-dose. Subjects were instructed not to bite or chew the tablets. In case of breakage of the tablets in the oral cavity, additional water was taken as a rinse.</p>		
<p>Duration of treatment:</p> <p>All patients were treated with ENTO-R-CHOP at a three-week interval for a maximum of 8 cycles. ENTO started at day 1 of each cycle before R-CHOP and stopped on Day 7 of the 8th cycle.</p>		
<p>Criteria for evaluation:</p> <p>For phase IB, evaluation was assessed by CMR rate by the Lugano classification 2014 at the intermediate evaluation (i.e., after 4 cycles or at treatment discontinuation) and at the end of treatment (i.e., after 8 cycles or at treatment discontinuation).</p> <p>For phase II, evaluation to determine the Complete Metabolic Response (CMR) rate by the Lugano classification 2014 (Deauville scale 1-3) at the end of treatment.</p>		
<p>Statistical methods:</p> <p><u>Enrolled Set</u></p> <p>The Enrolled set included all patients having signed their informed consent.</p> <p><u>Full analysis set (FAS)</u></p> <p>The Full Analysis set included all patients having signed their informed consent and who received at least one dose of ENTO.</p> <p>This set was used for demographic and baseline characteristics as well as for efficacy and safety analyses.</p>		

SUMMARY – CONCLUSION**Study Disposition**

Between July 2017 and March 2019, twenty-six patients were enrolled in the phase Ib-II part of ENTO-R-CHOP trial. Among the 26 patients, 23 patients received at least one dose of ENTO. Three were treated with ENTO 200 mg BID from day-4 to day 3 (for 7 days) (dose level 1) and twenty were treated with ENTO 400 mg BID from day 1 to day 7 (for 7 days) (dose level 2). Three patients were excluded from Full Analysis Set (FAS). Two patients (one treated with ENTO 200 mg BID and one treated with ENTO 400 mg BID) had an inclusion criterion not fulfilled (one for No adequate tissue for central retrospective testing for cell of origin (10-15 slides of tumor biopsy must be available at baseline) and one for No adequate liver function). Among the 23 patients from the FAS, five patients had permanently discontinued treatment due to adverse event (n=2), Progressive disease (n=1), Physician decision (n=1) and patient's choice (n=1). One patient permanently discontinued treatment after cycle 1 and 4 after cycle 5.

Efficacy Results

The complete metabolic response rate **at the end of treatment** was 83% (90%CI: 61.2-95) and 87% (90%CI: 66.4-97.2) according to central review and investigator assessment respectively. The overall metabolic response was 87% (90%CI: 66.4-97.2) and 91% (90%CI: 72.0-98.9) respectively.

The complete metabolic response rate **after cycle 4** was 83% (90%CI: 61.2-95) according to central review and investigator assessment. The overall metabolic response was 91% (90%CI: 72.0-98.9) according to central review and investigator assessment.

Among the 21 patients with PMR/CMR, the median duration of response was not reached (range: 2.2-15.0 months).

Among the 23 patients, 2 PFS events (8,7%) and 1 OS event (4,3%) were observed. The 1y-PFS was 85% (95%CL: 48-97) and the 1y-OS was 100%.

Safety Results

For phase IB, no DLT was observed and the recommended phase 2 dose (RP2D) for ENTO in patients treated with R-CHOP 21 was ENTO 400 mg BID from day 1 to day 7.

In general, AEs were manageable during the treatment phase. The main reason was gastrointestinal disorders (57%) followed by nervous system disorders (48%) mainly due to neuropathy peripheral and headache. Same observations were made for SAEs, as mainly due to gastrointestinal disorders (17%). 86% of AEs were recovered/resolved. Only one patient had permanently discontinued treatment due to adverse event (which is decreased left ventricular ejection fraction related to R-CHOP). No other malignancy was reported and only one death occurred during the study.

Due to stop of the inclusion and the limitation of the follow-up period, the small amount of data cannot permit to conclude for any safety items.

Conclusions

The primary objective of the phase 1b, defined as the determination of the recommended phase 2 dose for ENTO in patients treated with R-CHOP 21, was achieved and phase II of the ENTO-R-CHOP started.

Following the cessation of development of Entospletinib in DLBCL area decided by Gilead, inclusions stopped on March 15, 2019. The patients already included continued their treatment and follow-up period was limited to 30 days after the last treatment for the last patient included instead of 30 months after the last patient included.

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Due to the limited amount of data collected during this period, primary objective of the phase II as well as secondary objectives for both phase Ib and phase II cannot be attained. We also cannot conclude to the input of ENTO associated with the standard of care for newly diagnosed DLBCL. Date of the report:		