

## 2. SYNOPSIS

Name of Sponsor/Company: LYSARC	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Lenalidomide (Revlimid®)		
Name of Active Ingredient: Lenalidomide		
<b>Title of Study:</b> Study of the efficacy and safety of first line treatment with CHOP and Lenalidomide (Rev-CHOP) in patients aged from 60 to 80 years with previously untreated angioimmunoblastic T-cell lymphoma (AITL).		
<b>Coordinating Investigator:</b> Prof. Corinne HAIOUN, Unité Hémopathies Lymphoïdes, CHU Henri Mondor, Créteil, France <b>Co-coordinating Investigator:</b> Dr. Violaine SAFAR, Service d'hématologie, Centre Hospitalier Lyon Sud, Pierre-Bénite, France.		
<b>Study site(s) and countries:</b> 25 study centers in France and Belgium.		
<b>Publications (reference):</b> Not applicable.		
<b>Studied period (years):</b> Date first subject first visit: 28 Nov 2011 Date last subject completed: 21 Mar 2019 Data cutoff date: 21 Mar 2019	<b>Phase of development: 2</b>	
<b>Trial registry number(s):</b> ClinicalTrials.gov identifier: NCT01553786 EudraCT number: 2011-001356-10		
<b>Objectives:</b> <u>Primary:</u> To evaluate the Complete Metabolic Response (CMR) rate at the end of treatment defined according to Lugano Classification (PET-CT-Based response (Cheson et al, 2014)) <u>Secondary:</u> To evaluate: <ul style="list-style-type: none"> <li>• Complete response (CR) rate at the end of treatment according to the IWC (International Harmonization Project – Cheson 2007) as assessed by site Investigator.</li> <li>• Progression-free survival at 2 years (2y-PFS), events being relapse for complete responders, disease progression, and death from any cause.</li> <li>• Overall survival (OS) and event-free survival (EFS)</li> </ul> <u>Exploratory:</u> <ul style="list-style-type: none"> <li>• To evaluate the role of PET in defining an accurate staging</li> <li>• To evaluate the tumour metabolic activity based on FDG avidity measured by SUV max at baseline and the decrease of SUV max at the end of treatment</li> <li>• To correlate response rate, survival and biological factors (phenotype, EBV status, T/B clonality, circulating cytokine dosages).</li> <li>• Biological studies at diagnosis: <ul style="list-style-type: none"> <li>o Pathological and phenotypical description of the disease at presentation, with a detailed characterization of T-cells (T-cell antigens, CD10, CXCR5, PD1, CXCL13, ICOS, and Bcl6, Tbet, Gata3, RorγT transcription factors), FDC markers and EBV detection with B or T cells colocalization (by combined immunohistochemistry and in situ hybridization). A centralized</li> </ul> </li> </ul>		

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Name of Active Ingredient: Lenalidomide	Page:	

- pathological tissue banking, pathological review by a panel of expert hematopathologists, achievement of Tissue Micro Array and collection of frozen tumour samples (and/or DNA and RNA) will be achieved within the LYSA-P institute.
- o TCR and IgH clonality analyses by PCR on tumour sample and blood
  - o Phenotypic analysis of lymphoid cells in blood, including T antigens, CD10 CXCR5 CXCR3 CCR6 expression on CD4+ T-cells, CD19, CD20, CD27 and CD38 expression on B cell and NK cells numeration, using a 8- color flow cytometry device
  - o Cytokine profiles in serum samples (VEGF, IL4, IL5, IL10, IL13, IL21, IL17A, IL22, IL6, IFN $\gamma$  TNF $\alpha$ , CXCL13, EBI3) using luminex technology
  - o EBV virus load in total blood, in fractionated T and B cells and their impact on treatment response.
  - o Biological studies at the end of induction including same diagnostic flow cytometry and EBV virus explorations.
- Provide purified collection of neoplastic TFH cells for high throughput methods (GEP, mi-RNAs, deep sequencing...). For deep sequencing interpretation, a blood sample will be collected for autologous allelic polymorphism analyses.
  - Derive tumour cell lines and/or lymphoblastoid cell lines from the EBVpos B cells of the microenvironment (to evaluate their capacity to induce TFH commitment from autologous naïve normal CD4pos T cells, in connection with the PAIR INCa program).
  - Define the molecular signature(s) (gene expression and mutations) of AITL entities and correlate these signatures with response to therapy
  - Determine novel molecular predictive factors of response to Lenalidomide-CHOP treatment
  - Determine feasibility and clinical impact of cell free DNA sequencing in AITL
  - For all those purposes, the collection of fresh relapse samples will be encouraged through an oligocentric network integrated to the National TENOMIC PHRC-PAIR program.

**Methodology:**

This was a multicenter, open-label, non-randomized, Phase 2 study, to evaluate efficacy and safety of Rev-CHOP in adult subjects with previously untreated, histologically proven AITL. Given the nature of the experimental agent, this study was an open-label study. The study consisted in 3 phases: Screening Phase, Treatment Phase, and Follow-up Phase.

Subjects were to be eligible for screening once the subject had approved and signed the informed consent form. In the Screening Phase, the subject was to undergo baseline assessments of their disease and other assessments up to 14 days before first dose of study drug, except for imaging exams and biopsies (up to 28 days before first dose of study drug). Subject eligibility was based on local pathology diagnosis.

Upon completion of the required assessments in the Screening Phase and fulfillment of the eligibility criteria, subjects were included.

Treatment should start as soon as possible after randomization. A pathological review for diagnosis was mandatory to confirm the AITL histology. Outcome of the central pathology confirmation was not required for entry into the study. Response assessment included review of computed tomography (CT) and [<sup>18</sup>F]-Fluorodeoxyglucose-positron emission tomography (FDG-PET) scans, bone marrow (BM) examination, laboratory tests, and clinical examination according to International Working Group (IWG) response criteria for non-Hodgkin lymphoma (NHL).

All subjects were to be followed in the Follow-up Phase for PFS and OS with clinic visits every 3 months

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<p>for the first 2 years, every 6 months for the next 5 years, and then once a year thereafter. Once the subjects had been discontinued from study drug, they were to be followed for progression of disease or relapse, lymphoma treatments, and death.</p> <p>The first stage analysis was to be performed after 37 evaluable subjects (as defined) had been included. The trial was to be terminated if 16 or fewer subjects respond to treatment and treatment will be considered as ineffective. The probability of early termination was 0.482. All data available at the scheduled time of interim analysis were to be used for these subjects. Otherwise, the trial was to proceed to second stage and include 33 additional evaluable subjects. Thus, a total of 70 evaluable subjects (as defined) were to be studied. At the end of the second stage, if the total number of responder subjects was less than or equal to 38, treatment was to be considered as inefficient. Two analyses were planned at the beginning of the study: the interim analysis on the first 37 patients and the final analysis when all patients will have finished the follow-up period. The analysis of the principal criteria when all included patients will have 6 months of follow-up was also added.</p>		
<p><b>Number of subjects (planned, enrolled, and analyzed):</b> Planned: 80 subjects Enrolled: 80 subjects Analyzed: 78 subjects</p>		
<p><b>Diagnosis and main criteria for inclusion:</b> Male or female adult (aged 60 to 80 years old) subjects with histologically proven AITL not previously treated, with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0, 1, or 2, and life expectancy <math>\geq 90</math> days were eligible for participation in the study. Subjects with other categories of T-cell lymphoma were excluded from the study. Other exclusion criteria included: previous treatment for AITL with immunotherapy or chemotherapy except for short-term corticosteroids (duration of <math>\leq 10</math> days) before randomization, previous radiotherapy for AITL, central nervous system (CNS)-meningeal involvement.</p>		
<p><b>Test product, dose, and mode of administration:</b> Lenalidomide was supplied in labelled blister. Each capsule contains 10mg or 5mg of Lenalidomide. Subjects will be treated with Lenalidomide on an outpatient basis during. Oral Lenalidomide is initiated on day 1 of cycle 1 at a dose of 25 mg daily and continued for in each 14 day cycle, and repeated at day 21. Treatment is to be continued as tolerated for 8 cycles.</p>		
<p><b>Duration of treatment:</b> Subjects were to receive study drugs for up to 8 cycles, or until unacceptable toxicity developed, or progression, or voluntary withdrawal.</p>		
<p><b>Reference therapy, dose, and mode of administration:</b> No reference therapy was used in this study. Lenalidomide was administered in combination with CHOP regimen.</p>		
<p><b>Criteria for evaluation:</b> <u>Efficacy:</u> The primary efficacy endpoint was the CMR rate at the end of treatment according to Lugano 2014 criteria, based on central review. The secondary efficacy endpoints were CMR rate according to Lugano 2014 criteria based on local review, PFS, OS and EFS. <u>Safety:</u> Safety assessments included recording of adverse events, clinical laboratory measurements (hematology and serum chemistry, pregnancy), and vital signs. Adverse events included severity graded</p>		

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according to the Common Terminology Criteria for Adverse Events (CTCAE; Version 4.03), causality; dose interruption, dose adaptation, study treatment discontinuation, and death.		
<p><b>Statistical methods:</b></p> <p><u>Analysis Sets</u></p> <p><i>Efficacy population</i>  Evaluable subjects were defined as all subjects who received at least one cycle of Rev-CHOP  - with complete treatment and with central review of PET scans at baseline and at the end of treatment  - prematurely withdrawn before C8  This population was to be used for all efficacy analyses.</p> <p><i>Safety population</i>  The safety population included all subjects who received at least one dose of Lenalidomide.  This population was to be used for all safety analyses.</p> <p><u>Efficacy analyses</u>  A 2-stage statistical analysis following Simon's two-stage design was conducted to assist with making decisions about the utility of continuing the study. The analysis was based on complete metabolic response (CMR) rate (according to Lugano classification (PET-CT-Based response).  Continuous variables were summarized in tables displaying sample size, mean, standard deviation, median, range; quartiles were also be presented when considered relevant. Categorical data were described in counts and percentages (of non-missing data).  Censored data were presented as Kaplan-Meier plots of time to first event and summary tables of Kaplan-Meier estimates for criterion rates at fixed time points, with 95% CIs. The median time to event was calculated (if reached) with 95% confidence intervals.  The number and percent of subjects falling into each category of response according to the Lugano Classification were provided. Deaths were also included as a category, if patients died during the corresponding period. Response rates were expressed with 95% confidence limits according to Pearson-Clopper method.</p> <p><u>Safety analyses:</u> The number and percentage of subjects who reported any TEAEs were tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). Summaries were provided for all TEAEs, treatment-related TEAEs, serious TEAEs, Grade 3 or 4 TEAEs, TEAEs leading to dose reduction, dose interruption, and study drug discontinuation. Clinical laboratory, vital signs, and ECG data were summarized using descriptive statistics.</p>		

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<b>SUMMARY – CONCLUSION</b>		
<b>Study Disposition</b>		
In total, 80 subjects were enrolled between 28 November 2011 and 9 March 2017 in 23 centers in France and two in Belgium. The clinical database was locked on 10 May 2019. Two subjects did not receive at least one dose of treatment (one because of withdrawal of consent and one because of a rapid change in his/her general condition) and were excluded from the safety and efficacy analyses.		
<b>Study Population</b>		
Seventy-one subjects who received at least one dose of Lenalidomide and one cycle of CHOP had a confirmed diagnosis of AITL (N = 67) or nodal PTCL with a TFH phenotype (N = 4). These were included in the sensitivity analysis and ancillary studies and are subsequently referred to as the AITL/TFH set.		
<b>Efficacy Results</b>		
<u>Primary Endpoint:</u>		
At the end of treatment, 73 subjects were evaluated by PET CT, whereas one subject, in complete radiological response, was evaluated by CT. This subject, without residual disease by CT and with normal BM by BM trephine, was considered to be in CMR. CMR was achieved for 32 (41.0%) (CI 95%: 30.0%-52.7%) subjects from the efficacy set (N=78) and a partial response for 12 (15.4%), representing an overall response rate of 56.4%. The prespecified efficacy success criteria of 55.1% CMR at the end of treatment was not reached. The sensitivity analysis performed on the population of subjects with a confirmed diagnosis of AITL/nodal PTCL with TFH phenotype by central pathology review confirmed the robustness of the primary analysis and reached the same conclusion (CMR 42.3%).		
<u>Secondary Efficacy Endpoints</u>		
At a median follow-up of 45 months, the secondary endpoint of PFS rate at 2 years was 42.1%, EFS rate at 2 years was 35.5% and OS rate at 2 years was 59.2%, consistent with the conclusion of the primary analysis.		
<b>Safety Results</b>		
<u>Treatment Exposure</u>		
The mean dose intensity was 89.11% ( $\pm$ 13.3%) for the induction phase (N=78) and 83.56 % ( $\pm$ 17.5%) for the consolidation phase (N=54). Overall, the dose intensity was lower than 75% for 21.8 % of subjects (17.9% for induction phase and 24.1% for consolidation phase). None of the subjects received more than 110% of the prescribed dose.		
<u>Treatment-emergent Adverse Events</u>		
At least one TEAE was reported in 78 (100%) subjects during treatment.		
At least 1 TEAE assessed by the investigator as related to Lenalidomide was reported in 77 (98.7%) subjects. At least 1 TEAE assessed as related to any component of CHOP was reported in 78 (100%) subjects.		
Treatment-emergent AEs with severity Grade 3 or more (i.e., severe or life-threatening or resulting in death) were reported in 96.2% of subjects.		
Treatment-emergent AEs leading to death were reported in 5 (6.4%) subjects.		
At least one SAE was reported in 36 (46.2%) subjects. At least one SAE assessed as related to Lenalidomide was reported in 25 (32.1%) subjects. At least 1 SAE assessed as related to CHOP was		

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reported in 23 (29.5%) subjects.

At least 1 TEAE leading to premature withdrawal occurred in 15 (19.2%) subjects.

#### Deaths

For the entire study, including follow-up, the overall number of deaths was 42 (53.8%). The majority of deaths occurred after treatment and were reported to be due to progression of lymphoma. Death was reported due to AEs in 3 subjects during treatment. Death after treatment was reported as due to toxicity of study treatment in one case, concurrent illness in 2 cases, toxicity of additional treatment in 2 cases, and unknown causes (not assessable or insufficient data) in 4 subjects. Death was reported as due to other causes in 1 subject, specified as ischemic stroke.

For the deaths due to toxicity of study treatment, the deaths during treatment were due to septic shock (2 subjects), and myocardial infarction (1 subject), and one death after treatment was due to septic shock.

#### Commonly reported Adverse Events

The most commonly reported TEAEs ( $\geq 20\%$  of subjects) were in the blood and lymphatic system disorders SOC,: neutropenia including neutrophil count decreased (96.2%), leukopenia including white blood cell count decreased (92.3%) anemia (71.8%), lymphopenia including lymphocyte count decreased (67.9%) and thrombocytopenia including platelet count decreased (61.5%). At least one TEAE in the SOC of infections and infestations was reported for 51.3% of subjects.

TEAES occurring in  $> 10\%$  but less than 20% of subjects were febrile neutropenia (14.1%), asthenia (16.7%), nausea (17.9%), constipation (12.8%), diarrhea (11.5%), peripheral neuropathy (14.1%) and weight decreased (16.7%).

As expected the most frequent reported grade 3 or 4 adverse events were belonging to the Blood and Lymphatic System Disorders SOC, with 75.6 % of subjects experiencing grade 4 events in that category, including 70.5 % with grade 4 neutropenia and 30.8 % with grade 4 thrombocytopenia. The Infections and Infestations SOC included grade 4 events for 9% of subjects, and 4 grade 5 events (2 Septic shocks, 2 Sepsis).

#### Other Serious Adverse Events

At least one SAE was reported in 40 (51.3%) subjects, in 36 subjects during treatment, and 6 post treatment. Of those 73 SAEs occurred during treatment period, 39 (53.4%) were deemed related to Lenalidomide, 37 (50.7%) were deemed related to CHOP. The outcome was recovery without sequelae for 61 (83.6%), death for 8 (11.0%).

#### Second Primary Malignancies

There were 4 events reported, each in one subject. One subject with myelodysplastic syndrome deemed possibly related to Lenalidomide died of cardiac insufficiency and acute pulmonary oedema due to allograft. One subject with acute myeloid leukemia deemed related to Lenalidomide died of unknown cause. One subject with marginal zone lymphoma deemed unrelated to Lenalidomide recovered with sequelae (partial response), and one subject with neuroendocrine tumor deemed related to Lenalidomide recovered without sequelae.

#### **Conclusions**

The results of this study do not support the addition of Lenalidomide to CHOP in untreated elderly AITL subjects. The primary endpoint based on the hypothesis of an increase of the CMR rate from 45% to 60% was not reached, the CMR being 41% (CI 95%: 30%-52.7%). Another trial assessing the combination of Lenalidomide with CHOEP in nodal PTCL showed a CR rate of 48% and a high rate of early discontinuation (Lunning, 2019) in line with those results. Altogether these data indicate the lack of

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<p>benefit from the addition of Lenalidomide to chemotherapy in upfront treatment of AITL. AITL remains a hard-to-treat lymphoma and no significant therapeutic progress has been made in years. The standard of care remains CHOP in first line, and there are no extensive series focused on AITL. No positive signal of efficacy was seen in the previous LYSA phase 2 trial RAIL, in which 27 previously untreated subjects with AITL, aged from 60 to 80 years, were treated with a combination of rituximab and CHOP between 2005 and 2008 (Delfau, 2012). The CR rate was 44%, median PFS 16 months, and median OS 28 months, similar to the results of the REVAIL trial, for which the CR rate was 43.6%, median PFS 14 months, and OS 32 months, confirming the absence of any benefit from the addition of rituximab or Lenalidomide to CHOP in elderly subjects with AITL and the absence of improvement of AITL subject survival over the last few decades. In the REVAIL trial, most subjects were treated in the second line by chemotherapy (platin based chemotherapy N = 15/37, 41%, or bendamustin N = 11/37, 30%) with an overall response rate of 10/37 (27%), showing that, although widely used, chemotherapy that has activity in B-cell lymphoma has limited efficacy in AITL and that alternative treatments are needed.</p> <p>Lenalidomide has been combined with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy in diffuse large B-cell lymphoma (Nowakowski 2015, Castellino 2018, Vitolo 2019) and follicular lymphoma (Tilly 2018) showing an acceptable safety profile, but variable efficacy. Furthermore, lenalidomide has demonstrated anti-lymphoma efficacy in relapsed-refractory PTCL as a single agent (Morschhauser 2018, Fabbri 2013, Dueck 2010, Toumishey 2015) especially in AITL (Morschhauser 2018).</p> <p>A higher frequency and severity of hematological TEAEs in this trial compared to R-CHOP combinations in B -cell lymphoma may be related to disease characteristics of the trial population of elderly AITL with large proportion of BM involvement. The substantial proportion of subjects discontinuating treatment for toxicity (19.2%) may have contributed to the lack of benefit of this combination.</p> <p>An IPI score 3 to 5 was associated with a lower CMR rate and a shorter OS, confirming the value of this prognostic index in this disease. Apart from the IPI, a detectable phenotypically aberrant population in the blood was associated with a lower CMR rate, although it did not affect PFS or OS,. More than one extranodal site, BMI, albumin levels inferior to normal, <math>\beta</math>2 microglobulin &gt; 3.5g/L, and DNMT3A mutation were associated with shorter PFS, whereas male sex, BMI, low albumin levels, and <math>\beta</math>2 microglobulin &gt; 3.5g/L were associated with shorter OS.</p> <p>This trial was one of the largest dedicated to AITL and TFh lymphoma and allowed to prospectively study the mutational landscape of AITL and its association with clinical features and outcome, which are the object of publications (Lemonnier 2020).</p> <p><b>Date of the report:</b> Draft 1.0, 30 Jul 2020.</p>		