CLEAR

CLINICAL STUDY REPORT SYNOPSIS

Investigational Product:	CC-292 and lenalidomide
Protocol No./Study No.:	CLEAR
EudraCT No.:	2012-003316-32
Study Title:	A phase I_B study of the BTKi CC-292 combined with LENALIDOMIDE in adult patients with relapsed/refractory B-cell lymphoma.

Development Phase:	Ib
Indication:	Relapsed/refractory B-cell lymphoma.

Date First Patient enrolled:	01-Mar-2013
Date Last Patient Last Visit:	14-Jan-2018
Report Date:	31-August-2018
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1. SYNOPSIS

Name of Sponsor/Company:	LYSARC	
Name of Finished Product:	CC-292 and lenalidomide	

Title of Study:
A phase I_B study of the BTKi CC-292 combined with LENALIDOMIDE in adult patients with relapsed/refractory B-cell lymphoma

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Study Centers:
Conducted in 6 centers in France.
Program coordinating center: LYSARC, Centre Hospitalier Lyon Sud, Secteur Sainte Eugénie – Pavillon 6D, F-69495 Pierre Bénite Cedex

Publications:
No publications based on this study are currently available (as of the date of this clinical study report).

Studied Period (years):		**Phase of Development:**
Date of first patient enrolled:	01-Mar-2013	Ib
Date of last patient last visit :	14-Jan-2018	

Primary Objective:
The primary objective of this study is to determine the safety and tolerability of the combination of CC-292 when administered in association with lenalidomide (Revlimid®) in patients with relapsed/refractory B-cell lymphoma. The optimal CC-292 and lenalidomide combination will be determined based on the maximum tolerated dose (MTD), the dose limiting toxicities (DLT) and/or the analysis of adverse events, serious adverse events and toxicities observed during the study.

Secondary Objectives:
The secondary objectives of the study are:

-to determine the PK of CC-292 and lenalidomide when used in combination in patients with relapsed/refractory B cell lymphoma;

- to assess the preliminary efficacy signals of the CC-292 + Lenalidomide combination as assessed by best overall response rate and overall response rate at 6 months. Complete and partial response rates, progression free survival, response duration, time to next treatment and overall survival will be also examined

- to assess the pharmacodynamics of CC-292 in combination with lenalidomide on tumor samples collected at baseline and after 21 days of treatment

Methodology:
This study is a multicentre, open-label, phase I_B trial which will be held in two parts:

- A dose escalation part with escalated doses of lenalidomide (Revlimid®) administered orally for 3 weeks during every 28-day cycle, in combination with escalated doses of CC-292 administered orally twice per day during every 28-day cycle.
- An expansion part with 3 cohorts of 12 patients each (cohort A with DLBCL lymphoma; cohort B with Mantle Cell Lymphoma patients; cohort C with patients with any other histological subtypes of B-cell lymphoma)

Number of Patients:
During the dose escalation phase of the study, a standard "3 + 3" dose escalation design will be used to identify initial toxicities of and to determine the MTD of the combination treatment. The final number of subjects needed in dose escalation phase depends on number of DLTs observed within each cohort. After the MTD and preliminary RD have been determined, 36 additional subjects will be enrolled to further evaluate the safety and efficacy of the CC-292 and lenalidomide combination therapy at the preliminary RD.

Finally, 18 patients were included in the study in the dose escalation part. Expansion phase was cancelled by sponsor in accordance with pharmaceutical company decision and no patient was included in this part..

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Inclusion criteria:
Histology:

- Patients with any type of B-cell Lymphoma except CLL, SLL and Waldenström disease will be eligible during the dose escalation phase
- During the expansion phases, patients with DLBCL for cohort A, mantle cell lymphoma for cohort B and any other type of B-cell lymphoma except CLL, SLL and Waldenström disease for cohort C

Other criteria:

- Signed inform consent
- Patients should be relapsed or refractory NHL after ≥1 prior Rituximab-containing regimen for which no other type of therapy is of higher priority
- Aged 18 years or more
- ECOG performance status 0-2
- Measurable disease defined by at least one single node or tumor lesion > 1.5 cm,
- Life expectancy of ≥ 90 days (3 months).
- Patients must be eligible and willing to undergo excisional biopsies of tumor sites with a lymph node minimum measurement of 1 cm at baseline and after 21 days of treatment.
- Females of childbearing potential (FCBP)† must have two negative serum or urine pregnancy tests with a sensitivity of at least 25 mIU/mL before starting lenalidomide – the first test must be performed within 10- 14 days before starting lenalidomide treatment and the second test must be performed within 24 hours before starting lenalidomide
- FCBP must either commit to continued abstinence from heterosexual intercourse or begin two methods of birth control, at least 4 weeks before she starts taking lenalidomide. FCBP must also agree to monthly pregnancy testing and must be counseled at a minimum of every 4 weeks about pregnancy precautions and risks of fetal exposure.
- Men must agree not to father a child and agree to use a condom if his partner is of child bearing potential. Men must also be counseled at a minimum of every 4 weeks about pregnancy precautions and risks of fetal exposure.

† A female patient is considered to have childbearing potential if she 1) has not undergone a hysterectomy or bilateral oopherectomy or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e. has had menses at any time in the preceding 24 consecutive months).

Exclusion criteria:

- Previous treatment with lenalidomide or a BTK inhibitor
- Central nervous system or meningeal involvement
- Contraindication to any drug contained in this regimen
- Concomitant use of medicines known to cause QT prolongation or torsades de pointes (see Appendix 7)
- HIV disease, active hepatitis B or C
- Any serious active disease or co-morbid medical condition (according to investigator's decision)
- Any of the following laboratory abnormalities.
    - Absolute neutrophil count (ANC) < 1,500 cells/mm3 (1.5 x 109/L).
    - Platelet count < 80,000/mm3 (80 x 109/L)
    - Serum SGOT/AST or SGPT/ALT ≥ 3.0 x upper limit of normal (ULN).

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- Serum total bilirubin > 1.5 ULN except in case of hemolytic anemia and Gilbert's syndroma.
- Calculated creatinine clearance (Cockcroft-Gault formula or MDRD) of < 50 mL /min

- Prior history of malignancies other than lymphoma (except for basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the cervix or breast or Incidental histological finding of prostate cancer [TNM stage of T1a or T1b]) unless the subject has been free of the disease for ≥ 5 years
- Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form.
- Pregnant or lactating females.
- Prior ≥ Grade 3 allergic reaction/hypersensitivity to thalidomide and/or pomalidomide.
- Prior ≥ Grade 3 rash or any desquamating (blistering) rash while taking thalidomide and/or pomalidomide.
- Subjects with ≥ Grade 2 neuropathy.
- Use of any standard or experimental anti-cancer drug therapy within 28 days of the initiation (Day 1) of study drug therapy.
- Chronic use of proton pump inhibitors, H2 antagonists or antacids or their use in the last 7 days prior to the first CC-292 dose. Patients with chronic gastroesophageal reflux disease, dyspepsia, and peptic ulcer disease, should be carefully evaluated for their suitability for this treatment prior to enrollment in this study. These medications should be avoided throughout the study.
- Patients taking corticosteroids during the 4 weeks prior to inclusion, unless administered at a dose equivalent of ≤ 10 mg/day prednisone (over these 4 weeks).

Investigational Product:

Lenalidomide and CC-292: provided by Celgene.

Lenalidomide is provided in capsules of 5mg, 10mg, 15mg, 20mg or 25mg of lenalidomide.

CC-292 was supplied as 125 mg capsules for oral administration in dosage strength of 125 mg. It was packaged in high density polyethylene (HDPE) bottles fitted with an induction seal and child-resistant plastic closure.

Product	Mode of administration	Dose	Lot Numbers
Lenalidomide	Oral	5 mg	12F0764; 13F0189; 13F0906; 14F0413
Lenalidomide	Oral	10 mg	12F0763; 13F0188; 13F0904
Lenalidomide	Oral	15 mg	12F0762; 13F0187
Lenalidomide	Oral	20 mg	12F0765; 13F0190; 13F0326
Lenalidomide	Oral	25 mg	12F0761; 13F0186
CC-292	Oral	125 mg	12F0732; 13F0432; 14F0787

Criteria for Evaluation:

For the part 1 of the study, the primary endpoint of the study is the determination of the safety and tolerability of the combination of CC-292 when administered in association with lenalidomide (Revlimid®) in patients with relapsed/refractory B-cell lymphoma. The optimal CC-292 and lenalidomide combination will be determined based on the maximum tolerated dose (MTD), the dose limiting toxicities (DLT) and/or the analysis of adverse events, serious adverse events and toxicities observed during the study. DLT is a clinically significant toxicity that is assessed by the investigator as related to the study drug (CC-292 and/or lenalidomide) that occurs during the first treatment cycle (ie, Cycle 1, days 1-28).

Hematologic Dose-Limiting Toxicity:

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- Grade 4 neutropenia ≥ 7 days or neutropenia grade 3 associated with fever (temperature >38.5°C more than 48h)
- Grade 3 thrombocytopenia (platelet count < 50,000 cells/mm³[50x109/L]) more than 7 days
- Grade 4 thrombocytopenia more than 3 days
- Grade 4 anemia

Non-Hematologic Dose-Limiting Toxicity

- Any Grade ≥ 4 non-hematologic toxicity of any duration during Cycle 1
- Grade 3 total bilirubin elevation, whether symptomatic or asymptomatic:
    - Subjects with elevated bilirubin at screening due to Gilbert's syndrome or hemolysis will be considered to meet the DLT threshold for bilirubin if the total bilirubin increases to 2 × the highest study-recorded screening pre-treatment value or meets criteria for Grade 3 CTCAE (version 4.03).
    - Subjects with AST/ALT ≥3xULN and total bilirubin > 2x ULN and no other medical reason or concomitant medication can be found as a reason for the combination of these abnormalities will be considered to meet the DLT threshold (potential indicator of drug induced liver injury (DILI) or Hy's law).
- Any Grade 3 non-hematologic toxicity except:
    - Nausea, vomiting, or diarrhea lasting less than 24 hours following initiation of medical therapy;
    - Tumor lysis syndrome which does not progress to Grade 4 and resolves in less than 7 days with medical management;
    - A non-hematologic Grade 3 clinical laboratory AE (see separate rule for total bilirubin above) that is asymptomatic and rapidly reversible (returns to baseline or to ≤ Grade 1 within 7 days).

Secondary efficacy endpoints will include Response Rate at 6 months according to Cheson 2007, Best Response Rate at 6 months according to Cheson 2007, Progression-Free Survival (PFS), Duration of response (DoR), Time to Next Anti-Lymphoma Treatment (TTNLT) and Overall Survival (OS).

Sample Size Determination:

During the dose escalation phase of the study, a standard "3 + 3" dose escalation design will be used to identify initial toxicities of and to determine the MTD of the combination treatment. The final number of subjects needed in dose escalation phase depends on number of DLTs observed within each cohort. Non-DLT evaluable subjects withdrawn prior to completion of Cycle 1 due to reasons other than DLT may be replaced with the approval of the Dose Escalation Committee. After the MTD and preliminary RD have been determined, 36 additional subjects will be enrolled to further evaluate the safety and efficacy of the CC-292 and lenalidomide combination therapy at the preliminary RD. The sample size of 36 subjects for the expansion cohort is not based on formal statistical calculation to have adequate power for hypothesis testing. Rather it is to provide additional efficacy and safety information beyond the limited number of subjects in the dose escalation phase.

CONCLUSIONS:

Eighteen patients were enrolled in the phase Ib part of CLEAR trial. There was no major safety issue. At the end of dose escalation part, given the first disappointing results available and decision taken by Celgene to stop CC-292 development, the LYSARC, as study Sponsor decided not to implement the expansion part of the study.

Report Date:

31-August-2018