1. TITLE PAGE

Investigational Product:	**FL05-1** - Velcade™ (bortezomib) for Injection
Protocol No. / Study No.:	28866138-LYM-2003
EudraCT No.:	2005-000734-21
Study Title:	A Phase 2 Study of Velcade™ in Patients with Relapsed or Refractory follicular B-cell Lymphoma

Development Phase:	II
Indication:	Previously treated follicular B-cell lymphoma
GCP Statement:	

Date First Patient First Visit:	30/08/2005
Date Last Patient Last Visit:	28/01/2010
Report Date:	15/02/2011
Report Written by:	
Sponsor:	**GELA** : **G**roupe d'**E**tude des **L**ymphomes de l'**A**dulte ✉ : CHU Saint Louis – Centre Hayem – 75475 Paris cedex 10 - France ☎ : +33(0)1 42 49 98 11 Fax : +33(0)1 42 49 99 72
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2. SYNOPSIS

Name of Sponsor/Company: GELA	Individual Study Table Referring to Module x.x.x	*(For National Authority Use only)*
Name of Finished Product: Velcade™	Volume:	
Name of Active Ingredient: bortezomib	Page:	

Title of Study: A phase 2 study of Velcade™ in patients with relapse or refractory follicular B-cell lymphoma

Coordinating Investigators: Pr. Bertrand COIFFIER, Dr Vincent RIBRAG

Study Center: see list in Appendix 1.1.1

Publication: N/A

Studied Period (years):	**Phase of Development:** II
Date of first patient first visit: 30-Aug-2005	
Date of last patient last visit : 28-Jan-2010	

Objectives:

Primary Objective:

To determine the **response rate (complete response [CR] + complete response unconfirmed [CRu] + partial response [PR])** to Velcade™ as single agent, according to criteria based on those developed by Cheson at al.

Secondary Objectives:

- To determine the overall CR rate (CR + CRu)
- To determine time to progression (TTP)
- To determine overall survival
- To determine duration of response
- To determine the time to best response
- To evaluate the safety and tolerability of Velcade™
- To evaluate the effects of Velcade™ given bis weekly at 1.5 mg /m^2 versus 1.6 mg/m² weekly

Methodology:

Prospective, randomized, sequential, international, multicentre, 2-arm, non-comparative, open-label, 2-stage clinical study

Number of Patients:

120 enrolled patients, 110 evaluable patients, 55 per treatment arm.

Patients non evaluable for response were replaced, up to 120 patients.

	Velcade™ 1.5mg/m² N (%)	Velcade™ 1.6mg/m² N (%)	All N (%)
All-included Patients (AIP)	50 (100)	37 (100)	87 (100)
ITTEfficacy population (ITTE)	47 (94)	35 (95)	82 (94)
Safety	50 (100)	37 (100)	87 (100)

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Diagnosis and Main Criteria for Inclusion:
Male or female patient 18 years or older, with initial diagnosis of follicular B-cell lymphoma (CD20+) (grades 1, 2, and 3 based on the World Health Organization 1997 classification), in first or subsequent relapse or progression after prior anti-neoplastic treatment including previous rituximab treatment. Relapse or progression since previous anti-neoplastic therapy must have been documented by new lesions or objective evidence of progression of existing lesions; at least 1 measurable lymph node mass that is >1.5 cm in 2 perpendicular dimensions, and has not been previously irradiated or has grown since previous irradiation; no active CNS lymphoma and KPS ≥ 50% (Eastern Cooperative Oncology Group [ECOG] 0-2).

Test Product:	**Dose and Mode of Administration:**	**Batch Number:**
Arm A - Velcade™ Arm B - Velcade™	21-day cycle: 1.5 mg/m² twice a week for 2 weeks. Days 1, 4, 8, and 11 35-day cycle: 1.6 mg/m² once a week for 4 weeks. Days 1, 8, 15, and 22	R13184 R13884 R13993 6DBS1 R13884 6GZSN-1

Duration of Treatment:
Arm A: Patients received a total of **8 cycles** of treatment, approximately 24 weeks. Two additional cycles were administered for patients showing improvement to PR after 8 cycles.
Arm B: Patients received a total of **6 cycles** of treatment, approximately 30 weeks. Two additional cycles were administered for patients showing improvement to PR after 6 cycles.

Criteria for Evaluation:
Efficacy:
Primary efficacy variable:
The primary efficacy endpoint was disease response rate (CR + CRu + PR).
The secondary efficacy variables were the following: overall CR rate (CR + CRu), Time To Progression (TTP), duration of response, time to best response, and overall survival. Additional secondary endpoints included tumor measurements and Karnofsky performance status (KPS) assessments
Safety:
AEs, physical examination findings, vital signs, weight and clinical laboratory results.

Statistical Methods: An intent-to-treat analysis was applied to all endpoints. Qualitative comparisons of the Two treatment arms based on safety, efficacy, and dosing convenience were performed in order to recommend a dose schedule for further clinical study
Primary Efficacy Analysis:
DISEASE RESPONSE RATE (CR + CRU+ PR). i.e the response at the end of treatment on evaluable patients using the patient's last response assessment in case of premature discontinuation. The analysis was performed on the ITTE
Analysis of Safety:
Descriptive statistics

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SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

Overall response rate was 31.9% when Velcade™ was administered at 1.5mg/m² Day 1, 4, 8 and 11 every 21 days (arm A) and 22.9% in the weekly regimen (arm B). The median duration of response was 7 months with a median duration greater than 12 months in more than 50% of patients.

Complete response rate was achieved in 4 patients out of 47 in treatment arm A and 5 patients out of 35 in treatment arm B. The time to best response was achieved in 15 patients in treatment arm A and 9 patients in treatment arm B. Progression-free survival, overall survival and duration of response appeared to be slightly better for patients in treatment arm A.

SAFETY RESULTS:

The number and percent of adverse events per treatment group are presented in the following table.

Adverse Events (Safety Population)	**Velcade™ 1.5 mg/m²** N=50	(%)	**Velcade™ 1.6 mg/m²** N=37n	(%)
Patients with at least one Serious Adverse Event (SAE)	16	32	11	30
AEs leading to permanent study drug discontinuation	26	2	18	2
Deaths	17	34	21	57

All AEs reported in this study were known and most of them were related to the study treatment in both treatment arm s: the most common being blood and lymphatic system disorders.

Thirty-eight SAEs occurred during the study whose 4 deaths and 10 SUSARs which were judged related to the study drug.

Overall safety was in accordance with the SCP apart of the occurrence of the 10 SUSARs.

CONCLUSIONS:

Overall response rate was 31.9% when Velcade™ was administered at 1.5mg/m² Day 1, 4, 8 and 11 every 21 days (arm A) and 22.9% in the weekly regimen (arm B). The median duration of response was 7 months with a median duration greater than 12 months in more than 50% of patients. It was not possible to conclude that the overall response rate (CR, Cru and PR) as defined by the protocol was greater than 30% either in the treatment arm A or in the treatment arm B.

Complete response rate was achieved in 4 patients out of 47 in treatment arm A and 5 patients out of 35 in treatment arm B. The time to best response, progression-free survival, overall survival and duration of response appeared to be slightly better for patients in the treatment arm A.

Overall safety was in accordance with the SCP apart the occurrence of the 10 SUSARs. The occurrence of AEs in the blood and lymphatic system disorders appeared to be more frequent than AEs in the nervous system disorders compared to the SCP. Safety was acceptable in both treatment arms and looked similar in terms of frequency and intensity for both treatment arms.

Report Date:

11-Apr-2011