.1. TITLE PAGE

FINAL CLINICAL STUDY REPORT

Study title: **Bortezomib (Velcade®): A feasibility and phase II study in childhood relapsed acute lymphoblastic leukemia**

Name of investigational product: **Bortezomib (Velcade®)**

Indication studied: **relapsed/refractory childhood relapsed acute lymphoblastic leukemia**

Description: **Multicenter, multinational, open label, comparative and randomized phase II study on the antileukemic activity of bortezomib (1.3 mg/m2/dose twice weekly) with conventional combination chemotherapy in relapsed/refractory ALL in children and adolescents. The patients were randomized to receive bortezomib 'early', on days 1, 4, 8 and 11, or 'late', on days 8, 11, 15 and 18.**

Name of the sponsor: **Erasmus MC, Rotterdam, The Netherlands**

Protocol identification: **EudraCT number 2009-014037-25**

Development phase of study: **Phase 2**

Study initiation date / first subject visit: **October 8, 2010**

Study completion date / last subject completed: **October 21, 2014**

Name and affiliation of PI: **prof. dr. GJL Kaspers, Department of Pediatric Oncology/Hematology, VU University Medical Center, Amsterdam, Netherlands**

Name of sponsor signatory: **prof. dr. CM Zwaan, Erasmus MC, Dept of Pediatric Oncology, Sophia Children's Hospital, Rotterdam, The Netherlands. Phone: +31 (0) 10 703 6691/6130; fax: +31 (0) 10 703 1134**

The study was performed in compliance with the principles of Good Clinical Practice, including the archiving of essential documents.

Date of the report: May **23rd, 2017**

2. SYNOPSIS

Name of sponsor: Erasmus MC Name of investigational product: Bortezomib Name of active ingredient(s): Bortezomib	Individual Study Table Referring to Part of the Dossier: Volume: Page:	*(For National Authority Use only)*
Title of Study: Bortezomib (Velcade®): A feasibility and phase II study in childhood relapsed acute lymphoblastic leukemia		
Investigator(s): Prof. dr. GJL Kaspers (principal investigator, Prof. dr. CM Zwaan (co-investigator, sponsor)		
Study center(s): VU University Medical Center, Amsterdam, the Netherlands		
Publication: In preparation		
Study period: 4 years From: October 8, 2010 To: October 21, 2014	Phase of development: Phase 2	
Objectives: <u>Main study objective:</u> Determine the antileukemic activity of combination chemotherapy including bortezomib as reinduction therapy in childhood relapsed/refractory ALL. <u>Secondary study objectives:</u> 1. Determine the feasibility and safety of combining bortezomib with conventional combination chemotherapy in children and adolescents with relapsed/refractory ALL. 2. Evaluate bortezomib levels and proteasome inhibition in cerebrospinal fluid, bone marrow and peripheral blood in patients with relapsed/refractory ALL, and assess the relationship to the efficacy and toxicity of bortezomib.		
Methodology A total of 24 patients had to be randomized (12 patients in each arm) to provide the endpoints. The patients were treated with bortezomib (1.3 mg/m2/dose twice weekly (days 1 and 4 of each week) for a total of 2 weeks. Arm A received bortezomib on days 1, 4, 8 and 11, while Arm B on days 8, 11, 15 and 18. Bortezomib was administered as i.v. push. In addition, patients received standard reinduction chemotherapy consisting of dexamethasone and vincristine. Dexamethasone was given from day 1 onwards for 2 weeks at 10 mg/m2/day in 3 doses, orally. In addition, patients received vincristine on days 8 and 15, at 1.5 mg/m2/dose (maximum 2.0 mg /dose), in a 60 minutes i.v. infusion (which is potentially less neurotoxic than i.v. push). Finally, intrathecal methotrexate was given on days 1 and 22 with age-adjusted dosing (figures 1 and 2; <2 yrs 8 mg, 2 yrs 10 mg, 3 yrs and above 12 mg). Further therapy for good responders (bone marrow (BM) M1 or M2 on day 22) consisted of an additional cycle of bortezomib, but this decision is left to the discretion of the treating physician. A next cycle should start >11 days after the previous administration of bortezomib. Then, bortezomib was again combined with 2 weeks of dexamethasone (same dose and schedule) and vincristine twice (same dose and schedule; figures 3 and 4). Such cycles could be repeated if justified by efficacy and (lack of) toxicity, which again was left to the discretion of the treating physician. Patients with a BM M3 on day 22 and/or those with progressive disease will go off study.		
Number of patients (planned and analysed): 24 subjects planned; 29 subjects enrolled; 29 subjects completed and analyzed.		

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Diagnosis and main criteria for inclusion:
Inclusion criteria: Age between 6 months and 19 years, patients with a second or subsequent relapsed ALL, patients with first relapsed ALL after prior allogeneic stem cell transplantation in first complete remission, patients with refractory first relapse of ALL refractory, as defined by the ALL relapse protocol these patients were enrolled in, circulating leukemic blasts of at least 100/ul peripheral blood (i.e. at least 0.1x109/l), patients must take adequate contraceptives when of childbearing potential, written informed consent.
Exclusion criteria: Relapse not involving bone marrow**, s**ymptomatic CNS leukemia**, a**ctive uncontrolled infection, performance status (Lansky or Karnofsky score) of 60% or less, life expectancy of less than 6 weeks, existing peripheral neuropathy NCI grade 2 or higher, presence of acute diffuse infiltrative myocardial and/or pericardial disease, clinical signs of cardiotoxicity, previous allogeneic stem cell transplantation within 100 days, pregnant (requiring a pregnancy test in post-pubertal females) or breastfeeding, other contra-indications for chemotherapy, including no recovery from previous treatment, previous exposure to bortezomib, other experimental or conventional antileukemic treatment within 7 days from start of bortezomib, allergy to boron and its metabolites (present in vials of bortezomib), concomitant anti-leukemic therapy other than according to this protocol.

Test product, dose and mode of administration: bortezomib (1.3 mg/m2/dose twice weekly, days 1 and 4 of each week) for a total of 2 weeks, administered as i.v. push.

Duration of treatment: 22 days, of which bortezomib for 4 doses in 2 weeks.

Criteria for evaluation
Primary: The absolute peripheral blood (PB) blast count on day 8 of treatment.
Secondary: The absolute bone marrow (BM) blast percentage on day 8, and BM and PB analysis on day 22 of treatment

Statistical methods: Statistical comparison of response and toxicity data in both arms was done using Pearson chi-square statistics for differences in the distribution of categorical variables (Fisher exact test in case of sparse data), and the Mann-Whitney-U test for differences in continuous variables. For differences in continuous variables in paired samples, Wilcoxon's signed-rank test was used. The number of 12 patients in each group provides a power of 80% to detect a statistically significantly lower absolute number of circulating leukemic blasts on day 8 of treatment in patients exposed to 'BTZ early' as compared to patients not yet exposed to BTZ ('BTZ late') of at least 30% (2-sided test, alpha <0.05).

Summary – Conclusions

Efficacy Results:

Both treatment groups did not differ regarding the primary endpoint.

Out of 25 patients with data on response after cycle 1, 8 (32%) achieved complete remission with incomplete hematologic recovery (CRi), 7 (28%) a partial remission (PR), and 10 (40%) had a treatment failure, for a total response rate of 60%.

Safety Results:

Most common grade 3-4 neurotoxicities in cycle 1 were pain, (5 patients; 17%) and peripheral neuropathy,(2 patients; 7%) The amount and severity of toxicities was BTZ schedule independent. BTZ did not or hardly penetrate the cerebrospinal fluid and pharmacokinetic and –

dynamic parameters did not correlate with response. **Conclusion:** No demonstrable early antileukemic effect of BTZ was noted. However, BTZ in combination with vincristine, dexamethasone and intrathecal methotrexate is effective in a significant subset of pediatric rrALL.
Date of report: May 23rd 2017