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Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment report for VELCADE

International Nonproprietary Name: bortezomib

Procedure No.: EMEA/H/C/000539/II/0055

This withdrawal Assessment Report is based on the latest assessment report adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Questions and Answers" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7129
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1. RECOMMENDATION

Based on the review of the data on safety and efficacy and the MAH response to the CHMP Request for Supplementary Information, the CHMP considers that the application for the extension of indication of Velcade, in combination with rituximab "in the treatment of adult patients with relapsed follicular non-Hodgkin lymphoma whose time since last antilymphoma therapy was greater than one year", **is not approvable** since major objections still remain, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the 2nd Request for Supplementary Information (Section VI)

Questions to be posed to additional experts

None.

Inspection issues

None.

2. EXECUTIVE SUMMARY

In the present submission, the MAH presented clinical efficacy and safety data to support the addition of a weekly VELCADE 1.6 mg/m2 regimen to rituximab (Vc-R) as combination therapy for the treatment of patients with relapsed follicular non-Hodgkin lymphoma (initially claimed indication) or, as modified by the MAH in response to the CHMP Request for Supplementary Information, in the treatment of adult patients with relapsed follicular non-Hodgkin lymphoma whose time since last antilymphoma therapy was greater than one year.

This application is supported primarily by efficacy and safety results from a large, pivotal, **Phase 3**, randomized, open-label, active-controlled, multicenter, international, prospective study (Study JNJ-26866138-LYM-3001; hereafter referred to as Study LYM-3001) comparing the Vc-R combination with rituximab alone in 676 subjects with relapsed or refractory, rituximab-naïve or -sensitive FL. The study is co-sponsored J&JPRD and MPI. A biomarker study performed in patients enrolled in the pivotal LYM-3001 study aimed at identifying patients who would be predicted to be sensitive to the Vc-R combination drug treatment was presented as exploratory.

Study LYM-3001 was designed (in 2005) and initiated (in 2006) in accordance with the regulatory advice received from the Committee for Medicinal Products for Human Use (CHMP) in 2005 (REF: EMEA/386156/005). At that time, single-agent rituximab was considered an acceptable standard treatment option for relapsed NHL and therefore, Study LYM-3001 was designed to determine if the Vc-R combination provides clinical benefit to these subjects relative to treatment with rituximab alone, as assessed by prolongation of PFS.

A **Phase 2**, randomized, open-label, non-comparative, 2-stage, multicenter, prospective study (Study M34103-061) using the Vc-R combination in patients with relapsed or refractory indolent B-cell lymphoma (including follicular and marginal zone lymphoma), testing two VELCADE dosing regimens (twice-weekly and weekly) in combination with rituximab, was carried out to determine the dosing regimen for subsequent phase 3 development. Safety and efficacy data from Study M34103-061 were considered as supportive.

2.1. Problem statement

Non-Hodgkin lymphomas (NHL) encompass several unique malignant lymphoid disease entities that vary in clinical behaviour, morphologic appearance, immunology, and molecular phenotype. In the 27 countries comprising the EU, the total number of new NHL cases in 2008 was estimated at 73,700.

Non-Hodgkin lymphoma is primarily an adult disease with a median age at onset of 67 years. NHLs can be clinically classified as indolent and aggressive. The majority of patients with indolent (slow-growing) NHL present with advanced disease. For these patients, the disease is incurable with standard treatment and the clinical course is characterized by a pattern of multiple, often symptomatic, relapses and remissions over a median survival period of up to 10 years.

Follicular lymphomas (FL), is the most common type of indolent lymphoma, comprising approximately 30% of all indolent NHL. Follicular lymphoma is a neoplasm of follicle centre B cells and is characterized by follicular growth patterns, at least partially accompanied by diffuse areas of growth.

Relapsed NHL is an incurable disease, characterized by multiple relapses and remissions of increasingly shorter duration. The neoplastic B cells express the pan-B-cell markers CD19, CD20, CD22, CD79a, and CD79b. Follicular lymphoma cells express antigens from the germinal centre including CD10 and Bcl-2. The cytogenetic hallmark of NHL is t(14;18)(q32;q21) and is present in approximately 85% of Grade 1 and 2 FL. The translocation results in the juxtaposition of the Bcl-2 oncogene into the IgH heavy chain locus on chromosome 14, leading to constitutive expression of chimeric Bcl-2/IgH mRNA with subsequent inhibition of apoptosis.

The Follicular Lymphoma International Prognostic Index (FLIPI; Solal-Celigny 2004) can successfully discriminate between patients with a good prognosis (low FLIPI score, 0 to 1 factor) with 91% 5-year overall survival (OS); intermediate prognosis (intermediate FLIPI score; 2 factors) with 78% 5-year OS; and with poor prognosis (high FLIPI score; 3 factors) with only a 53% 5-year OS.

Patients with bulky disease or high tumor burden also have poor prognoses with a lower probability of response to treatment and a higher probability of relapse. Patients with high FLIPI score and high tumor burden are therefore poor prognosis high-risk patients.

FLIPI Factors and Criteria

Factor	Criteria
Age	≥60 years
Ann Arbor stage	III-IV
Hemoglobin level	<12 g/dL
Serum LDH level	>ULN (upper limit of normal)
Number of nodal sites	≥5

Each criterion receives 1 point on the score.
The World Health Organization (WHO, 1997) has classified FLs as
Grade 1 (follicular small cleaved),
Grade 2 (follicular mixed),
Grades 3a and 3b (follicular large cell).

Grades 1 and 2 FLs (indolent) are similar in natural history with fewer relapses than Grade 3 lymphomas (aggressive), which have the potential for early relapse. Grades 1 and 2 FLs are treated similarly, while Grade 3 NHL is treated more similarly to aggressive NHL using anthracycline-based therapy.
As different approaches are used to treat Grade 3 FL, Study LYM-3001 only enrolled subjects with documented Grade 1 and 2 NHL who would be suitable for treatment with rituximab or Vc-R at time of relapse.

FL treatment

Despite the number of available therapies for relapsed FL, there is still an unmet medical need for newer treatment options that provide clinical benefit (i.e., treatments that provide a longer time without progression, delay the need for additional therapy, and delay treatment-related toxicity).

Standard modalities of treatment include watchful waiting, radiation, single-agent or combination chemotherapy (alkylating agents, anthracyclines, nucleoside analogues, vinka alkaloids), anti-CD20 monoclonal antibodies, radioimmunotherapy, autologous stem cell transplant, or allogenic stem cell transplant, or any combinations thereof.

Commonly used treatments for relapsed NHL include single-agent rituximab, single-agent bendamustine, R-CHOP, R-CVP and fludarabine-based regimens.

The most commonly used alkylator-based regimens include chlorambucil (as monotherapy or in combination with prednisone;) and cyclophosphamide (as a single agent or in combinations such as CVP [cyclophosphamide, vincristine, and prednisone], CHOP [cyclophosphamide, doxorubicin, vincristine and prednisone], C-MOPP [cyclophosphamide, vincristine, procarbazine, prednisone]).

The most commonly used purine analogue is fludarabine, which has demonstrated activity as a single agent in the treatment of relapsed and untreated FL. Based on the demonstrated synergism of purine analogues, fludarabine has been incorporated into several NHL regimens including FC (fludarabine-cyclophosphamide), FND (fludarabine, mitoxantrone, and dexamethasone), and FCM (fludarabine, cyclophosphamide, and mitoxantrone).

Bendamustine is a mechlorethamine derivative approved in the EU for the treatment of CLL, for the treatment of rituximab-refractory, indolent B-cell NHL, and for the frontline treatment of multiple myeloma (Levact, approved in 2010). Studies of bendamustine for the treatment of NHL have been conducted in various NHL subtypes including FL. The recent approval of bendamustine in NHL was based on a Phase 3, open-label, single-arm study of bendamustine monotherapy in patients who were unresponsive to rituximab or whose disease had progressed within 6 months of rituximab therapy.

Given the similarity and outcomes of the R-CHOP and R-CVP regimens, as well as limitations on cumulative exposure to doxorubicin, physicians use different classes of drugs for second and subsequent lines of treatment for FL.

Although allogeneic bone marrow transplantation has a very limited role in the management of NHL due to the high transplant-related mortality, high dose chemotherapy and autologous stem cell support is an option in select patients with chemosensitive relapse, but there is no survival advantage compared with conventional treatment and therefore its use in the management of NHL has been limited and is not a common practice.

The EU approved medicinal products in the treatment of NHL specifically (as indicated in SmPC section 4.1) are:

-Interferon alfa-2b (IntronA, approved in 2000)

Follicular lymphoma

Treatment of high tumour burden follicular lymphoma as adjunct to appropriate combination induction chemotherapy such as a CHOP-like regimen. High tumour burden is defined as having at least one of the following: bulky tumour mass (> 7 cm), involvement of three or more nodal sites (each > 3 cm), systemic symptoms (weight loss > 10 %, pyrexia > 38°C for more than 8 days, or nocturnal sweats), splenomegaly beyond the umbilicus, major organ obstruction or compression syndrome, orbital or epidural involvement, serous effusion, or leukaemia.

-Ibritumomab tiuxetan (Zevalin, approved in 2004) Radio-immunotherapy

[90Y]-radiolabelled Zevalin is indicated as consolidation therapy after remission induction in previously untreated patients with follicular lymphoma. The benefit of Zevalin following rituximab in combination with chemotherapy has not been established.

[90Y]-radiolabelled Zevalin is indicated for the treatment of adult patients with rituximab relapsed or refractory CD20+ follicular B-cell non-Hodgkin's lymphoma (NHL).

Rituximab (Mabthera, approved in 1998) is a chimeric anti-CD20 monoclonal antibody. It binds to CD20-positive B-cells and causes antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and apoptosis.

-MabThera is indicated in adults for the following indications:

Non-Hodgkin’s lymphoma (NHL)

MabThera is indicated for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy.

MabThera maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy.

MabThera monotherapy is indicated for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy.

MabThera is indicated for the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin’s lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy.

Posology

Follicular non-Hodgkin's lymphoma

Combination therapy

The recommended dose of MabThera in combination with chemotherapy for induction treatment of previously untreated or relapsed/ refractory patients with follicular lymphoma is: 375 mg/m2 body surface area per cycle, for up to 8 cycles.

MabThera should be administered on day 1 of each chemotherapy cycle, after intravenous administration of the glucocorticoid component of the chemotherapy if applicable.

Maintenance therapy

Previously untreated follicular lymphoma

The recommended dose of MabThera used as a maintenance treatment for patients with previously untreated follicular lymphoma who have responded to induction treatment is: 375 mg/m2 body surface area once every 2 months (starting 2 months after the last dose of induction therapy) until disease progression or for a maximum period of two years.

Relapsed/refractory follicular lymphoma

The recommended dose of MabThera used as a maintenance treatment for patients with relapsed/refractory follicular lymphoma who have responded to induction treatment is: 375 mg/m2 body surface area once every 3 months (starting 3 months after the last dose of induction therapy) until disease progression or for a maximum period of two years.

Monotherapy

Relapsed/refractory follicular lymphoma

The recommended dose of MabThera monotherapy used as induction treatment for adult patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy is: 375 mg/m2 body surface area, administered as an intravenous infusion once weekly for four weeks.

For retreatment with MabThera monotherapy for patients who have responded to previous treatment with MabThera monotherapy for relapsed/refractory follicular lymphoma, the recommended dose is: 375 mg/m2 body surface area, administered as an intravenous infusion once weekly for four weeks (see section 5.1).

Diffuse large B cell non-Hodgkin's lymphoma

MabThera should be used in combination with CHOP chemotherapy. The recommended dosage is 375 mg/m2 body surface area, administered on day 1 of each chemotherapy cycle for 8 cycles after intravenous infusion of the glucocorticoid component of CHOP. Safety and efficacy of MabThera have not been established in combination with other chemotherapies in diffuse large B cell non-Hodgkin's lymphoma.

FL Prognosis

Progression-free survival (PFS) in patients with relapsed and refractory NHL is frequently less than 10 months using conventional chemotherapeutic regimens. Subsequent remissions occur, but with progressively shorter durations. Despite the increase in overall survival (OS) over time, the overall pattern of the illness has not changed. Repeated responses are usually incomplete and almost always followed by recurrence, with a median OS of up to 10 years.

2.2. About the product

Mechanism of action

Velcade (bortezomib) is a proteasome inhibitor used in the treatment of Multiple Myeloma (MM). It is specifically designed to inhibit the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades poly-ubiquitinated proteins. The catalytic core of the 26S proteasome is the 20S proteasome. The ubiquitin-proteasome pathway plays an essential role in orchestrating the turnover of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis and affects multiple signalling cascades within the cell, ultimately resulting in cancer cell death. By inhibiting a single molecular target, the proteasome, VELCADE affects multiple signalling pathways. Thus, the mechanisms by which VELCADE elicits its antitumour activity may vary among tumour types, according to the extent to which each affected pathway is critical to the inhibition of tumour growth. Specifically, VELCADE is thought to be efficacious in multiple myeloma via its inhibition of nuclear factor κB activation, its attenuation of interleukin-6-mediated cell growth, a direct apoptotic effect, and possibly through antiangiogenic and other effects.

VELCADE is a modified dipeptidyl boronic acid. The product is provided as a mannitol boronic ester, which in reconstituted form, consists of the mannitol ester in equilibrium with its hydrolysis product, the monomeric boronic acid.

From the point of view of the ATC code, Velcade is under the pharmacotherapeutic group "Other antineoplastic agents" with the ATC code: L01XX32.

On 26 April 2004 bortezomib was approved under exceptional circumstances in the EU for the treatment of MM (also known as plasma cell myeloma) patients who have received at least 2 prior therapies (third line) and, as such, the MAH was to provide additional data (Specific Obligations, SOs) as defined in Annex IIC of the Commission Decision.

The clinical development program for bortezomib included 3 Phase 1 dose-escalation studies of both bortezomib monotherapy (either on solid tumours and in haematological malignancies patients), and bortezomib in combination with other chemotherapeutics in solid tumours (e.g., gemcitabine, irinotecan, and docetaxel).

On 20 April 2005 (type II/05 variation), VELCADE was approved as monotherapy for the treatment of progressive MM in patients who have received at least 1 prior therapy and who have already undergone or are unsuitable for bone marrow transplantation.

Approval for the second line indication was based on results from Phase 3 Study M34101-039 (APEX) that compared VELCADE with high-dose dexamethasone in 669 multiple myeloma subjects who had received 1 to 3 prior lines of therapy.

In July 2008, the type II/28 variation was granted to extend the indication from the setting of monotherapy for relapsed patients to an earlier stage of the MM disease (front-line therapy) in combination with melphalan and prednisone. The clinical study that formed the basis for this submission was the Phase 3 study MMY-3002 (VISTA): an open-label multicentric randomized placebo-controlled trial to investigate the efficacy of bortezomib (Velcade) in untreated patients with a diagnosis of MM who cannot be treated with high-dose chemotherapy/stem cell transplantation (HDC/SCT) because of age (> 65 y) or other conditions.

The final 5-year survival data from study VISTA were considered in December 2011 (type II/53 variation); the median overall survival was 56.4 months in the Vc-MP treatment group and 43.1 months in the MP treatment group. The median OS of 43.1 months in the MP group is longer than historically reported (30 to 36 months), most likely because of the use of VELCADE and other newer agents administered on relapse.

On January 2009 the first 5-year renewal was approved with general condition for an additional 5-year renewal on the basis of pharmacovigilance grounds. Although the pharmacovigilance strategy has proven ability to identify safety concerns, the number and kind of unlisted serious adverse events support the concern that additional safety risks connected with Velcade treatment may become evident in the future. Thus a careful monitoring of any newly emerging safety signal trough PSUR cycles on a six month basis was recommended.

In December 2011, in the context of the 7th annual re-assessment, all SOBs/FUMs were considered fulfilled and the positive overall benefit-risk profile for the use of VELCADE in all lines of multiple myeloma, either as single agent or in combination with melphalan and prednisone, confirmed; thus, the CHMP granted the switch from under exceptional circumstances to normal approval licence. However, based on the recent emergence of new treated-related AE, as a precautionary measure the CHMP decided to keep the PSUR cycle on 6-month basis.

The registered formulation of bortezomib is intravenous injection 1 mg (1 mg/ml) and 3.5 mg (1 mg/ml) powder for solution for injection IV.

The recommended starting dose of bortezomib is 1.3 mg/m2 body surface area twice weekly for two weeks (days 1, 4, 8, and 11) followed by a 10-day rest period (days 12-21). This 3-week period is considered a treatment cycle.

2.3. The development programme/Compliance with CHMP guidance/Scientific advice

On 18 November 2005 J&JPRD received EMA scientific advice on the design of Study LYM-3001 (REF: EMEA/386156/005). Overall, the CHMP scientific advice that mostly regarded the study design was followed.

In a number of meetings with the Rapporteur, J&JPRD presented the status of Study LYM-3001 within the context of the overall VELCADE development plan.

In particular, during the meeting held on 14.04.2010, the MAH presented the IDMC recommendation for stopping the study and the aggregated blinded data summary for Phase III study LYM-3011 at data cut-off on November 2009.

In the meeting held on 05.10.2010 an overview of LYM-3001 study results was discussed.

In October 2011, EMA was informed by the MAH that Millennium Pharmaceuticals, Inc (MPI), co-sponsor of J&JPRD for Velcade development program announced the intention to withdraw the supplemental new drug application (sNDA) for use of Velcade in combination with rituximab in patients with relapsed follicular lymphoma. According to MPI the withdrawal was based upon discussions with external advisors and the U.S. Food and Drug Administration (FDA).

2.4. General comments on compliance with GMP, GLP, GCP

Study LYM 3001

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices (GCP) and applicable regulatory requirements. Known instances of non conformance were documented and are not considered to have had an impact on the overall conclusions of this study.

It was partly carried out outside the EU.

EU country clinical sites: Belgium, Czech Republic, Finland, France, Germany, Greece, Great Britain, Hungary, Italy, Netherlands, Poland, Portugal, Slovakia, Spain, Sweden

Non EU country clinical sites : Israel, South Africa, Argentina, Brasil, Canada, China India, Korea, Mexico, Russia, Thailand, USA, Australia, Romania, Ukraine

Study M34103-061

This study was performed in accordance with Good Clinical Practice (GCP), according to the International Conference on Harmonisation (ICH) final guideline (01 May 1996) and including the archiving of essential documents.

It was carried out in 15 sites in the United States.

GCP inspections carried out by other regulatory authorities on LYM-3001 and M34103-061 study sites are described in the table below:

Inspections conducted on trial sites participating in Study LYM-3001

Year	Protocol	Health Authority	Start Date	End Date	Clinical Investigator Name	Clinical Investigator Site Location - Country	Clinical Investigator Site Location - Full Address
2011	26866138LYM3002	People's Republic of China: Province & State Drug and Food Administrations United States: Food & Drug Administration	01/03/2011	03/03/2011	Hui-qiang, Huang, MD	China	22F, Ward 4, Internal Medicine, Sun Yat-Sen University Cancer Center, 651# East Dongfeng Road, Guangzhou, China 510060

Inspections conducted on trial sites participating in Study M34103-061

Year	Protocol	Health Authority	Start Date	End Date	Clinical Investigator Name	Clinical Investigator Site Location - Country	Clinical Investigator Site Location - Full Address
2007	C05005	United Stated: Food & Drug Administration	26/09/2007	27/09/2007	Robert Belt, MD	USA	Oncology/Hematology Associates of Kansas City 4320 Wornall, Suite 212 Kansas City, MO 64111
2006	M34103-053	United Stated: Food & Drug Administration	11/10/2006	03/11/2006	Andre Goy, MD	USA	Hackensack Medical Center 30 Prospect Ave, Suite 400 Hackensack, NJ 07601

2.5. Type of application and other comments on the submitted dossier

- Legal basis

This is a type II variation (C.I.6) to add a new therapeutic indication to the marketing authorisation of Velcade

- Significance of paediatric studies

A class waiver Decision (EMA/820860/2010 P/345/2010), was given for treatment of follicular lymphoma. since it does not normally occur in the paediatric population.

3. SCIENTIFIC OVERVIEW AND DISCUSSION

3.1. Introduction

The rationale for the use of Velcade in combination with rituximab is based on the following non-clinical and clinical evidence.

Non-clinical evidence suggest that VELCADE- and rituximab-mediated apoptosis both involve inhibition of the NF-κB pathway in NHL, supporting a mechanistic rationale for combining rituximab and VELCADE. Rituximab (Mabthera, approved in 1998) is a chimeric anti-CD20 monoclonal antibody. It binds to CD20-positive B-cells and causes antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and apoptosis.

A number of non-clinical studies, mostly performed in vitro on NHL/B-cell lymphoma cell lines, demonstrated the ability of bortezomib alone to correlate with the down-regulation of NF-κB activity and the associated decrease in Bcl-2 expression (see non-clinical section).

A limited number of non-clinical studies aimed to assess the in vivo efficacy of bortezomib in combination with rituximab. One of these studies was performed in a tumor xenograft mouse model and showed a less than additive in vivo effect (De Vos al, 2004).

Another study assessed Velcade in combination with rituximab in 6-8-week old SCID mice inoculated via tail vein injection with (1 x 106) Raji cells. However, the results from this study have been presented only as a poster (Hernandez-Ilizaliturri et al., 2003); thus, it is not possible to soundly comment on the conclusion of the authors "Proteasome inhibition by PS341 induces apoptosis, cell growth arrest and renders various NHL cell lines more susceptible to rituximab-associated CMC. In vivo, administration of PS341 with rituximab was more effective in controlling lymphoma growth and in prolonging survival than rituximab or PS341 monotherapy alone."

Several VELCADE doses and schedules have been evaluated in patients with lymphoma.

Many studies reported the activity of the twice weekly schedule of VELCADE (administered on Days 1, 4, 8, and 11) in patients with lymphomas. The dose-limiting toxicity and maximum-tolerated dose (MTD) of weekly VELCADE were determined in a Phase 1 dose-escalation study. Fifty-three patients (48 with androgen-independent prostate cancer) received 128 cycles of VELCADE in doses ranging from 0.13 to 2.0 mg/m2 IV administered weekly on Days 1, 8, 15, and 22 of a 35-day cycle. The dose-escalation scheme was controlled via continuous reassessment. The results of this study demonstrated the MTD and the recommended Phase 2 dose of VELCADE to be 1.6 mg/m2 when administered according to a once-weekly schedule. The adverse events observed at this dose were moderate and most patients received 1.6 mg/m2 once weekly for 4 weeks out of the 5-week cycle for 2 or more cycles without experiencing significantly increased toxicity during the second cycle of treatment. At this dose, diarrhea was the most common toxicity; however, most cases were Grade 1 or 2 and were self-limiting. At higher doses, the incidence and intensity of diarrhea increased as well as neurological and cardiovascular events. This study demonstrated that inhibition of NF-κB-related markers and anti-tumor activity was observed in patients with androgen-independent prostate cancer at 1.6 mg/m2 (Papandreou et al., 2004).

Clinical data from 2 Phase 2 studies of VELCADE monotherapy for the treatment of indolent and aggressive NHL in subjects previously treated for this disease provide further indications of antitumor activity.

In one study, 7 of 9 assessable subjects with NHL achieved objective response including 1 CR and 1 CRu. Of 10 assessable subjects with MCL, 1 achieved CRu, and both subjects with marginal zone lymphoma (MZL) achieved PR lasting more than 8 months (O'Connor et al., 2005).

In a separate study of previously treated subjects with NHL, 12 of 29 assessable subjects with MCL achieved CR or PR, and 4 of 21 assessable subjects with other types of B-cell NHL achieved CR/CRu or PR (Goy et al., 2005).

The safety and efficacy of VELCADE in combination with rituximab was examined in a prospective, randomized, multicenter, 2-arm, non-comparative, open-label, 2-stage clinical study in subjects with relapsed or refractory indolent B-cell lymphoma, including NHL and MZL (Study M34103-061). VELCADE at the higher dose of 1.6 mg/m2 administered weekly was generally better tolerated than the lower dose of 1.3 mg/m2 administered twice weekly and had a similar efficacy. Therefore, the weekly VELCADE schedule in combination with rituximab was chosen for this Phase 3 study Study LUM-3001 (also supported by the Phase 1 dose-escalation study conducted by Papandreou (2004).

3.2. Non clinical aspects

Pharmacology

No new non-clinical study was presented by the MAH in this application. A review from the available published non-clinical studies was provided.

Bcl-2 and NF-kB in FL

The t(14;18) translocation occurs in 85-90% of follicular lymphoma tumours leading to over expression of the antiapoptotic protein Bcl-2 and to the constitutively active NF-κB signalling. These effects can contribute to tumorigenicity and resistance to therapy. NF-kB has been shown to play an important role in a variety of cellular processes, including cell cycle regulation and apoptosis. Targeting the NF-kB pathway may represent a rational approach in follicular lymphoma malignancy.

The t(14;18) lymphoma cell line DHL-4 displayed elevated levels of several NF-kB subunits and increased Bcl-2 expression; a decrease in endogenous Bcl-2 levels was observed in DHL-4 cells transfected with an IkBa super-repressor (IkBa-SR) expression vector. Molecular suppression of the constitutively active NF-κB by the expression of the I-κBα-super-repressor reduced the expression of Bcl-2 (Heckman et al., 2002).

Single agent bortezomib and down-regulation of Bcl-2 and NF-kB

Non-clinical studies have demonstrated that bortezomib targets these downstream effectors of the t(14;18) genetic lesion leading to antitumor effects and sensitization to other targeted therapies.

In two non-Hodgkin's lymphoma cell lines derived from mantle cell lymphoma (MCL) samples and in patient MCL biopsy specimens, bortezomib led to cell cycle arrest in G1 and rapid induction of apoptosis that was associated with the down-regulation of bcl-2 family members bcl-xL and bfl/A1, and the activation of caspase 3, that mediates bcl-2 cleavage, resulting in the release of cytochrome c from the mitochondria. (Pham et al., 2003).

Regulation of BCL-2 gene transcription was examined in seven different human cancer cell lines including two pancreatic (MIA-PaCa-2, PANC-1), two prostate (LNCaP, PC-3), two lung (Calu-1, A549) and one breast (MCF-7) cancer cell line. The apoptotic activity of bortezomib was shown to correlate with the down-regulation of NF-κB activity and the associated decrease in Bcl-2 expression (Fahy et al., 2005).

In a panel of five B-cell lymphoma cell lines, all derived from patients with transformed follicular lymphoma (DHL-4, DHL-7, DoHH2, CRL, SUD4), bortezomib treatment had similar effects on apoptotic and NF-KB signalling pathways in these cell lines, different cell cycle effects were observed and induction of a further mechanism of cell death, mitotic catastrophe, was observed in the more sensitive cell line, which may provide some pointers to the difference in sensitivity between cell lines (Strauss et al., 2007).

Bortezomib combined with agents other than rituximab

In t(14;18)-positive, EBV-negative NHL cell lines NHL cell lines DoHH2 and WSU-FSCCL the effect of activating the TRAIL pathway with agonistic monoclonal antibodies to TRAIL receptors TRAIL-R1 (mapatumumab) and TRAIL-R2 (lexatumumab) was investigated. While bortezomib alone had no effect in this assay, combination of bortezomib and either TRAIL-R agonist antibody, showed a trend to prolonged time until recurrence of lymphoma cells, indicating greater cell kill with the combination therapy. This was statistically significant for lexatumumab, but not for mapatumumab (Smith and Joshi, 2007).

In Hodgkin lymphoma (L428) and non-Hodgkin lymphoma Ramos (Burkitt lymphoma), HF1 (follicular lymphoma), and SUDHL4 (large B-cell lymphoma) cell lines, bortezomib produced a marked induction of apoptosis at concentrations ranging from 2.5 to 20 nM when combined with the histone deacetylase inhibitor, PCI 24781 (Bhalla et al, 2009).

Bortezomib combined with rituximab

The combination of bortezomib and rituximab has been suggested because follicular lymphoma cells express CD20, the B-cell antigen targeted by rituximab, and rituximab is approved for the treatment of follicular lymphoma (Buske et al., 2006).

In the SUDHL-16 diffuse large B-cell lymphoma (DLBCL) cell line, the combination of bortezomib and rituximab produced additive effects on inhibition of cell proliferation and induction of apoptosis. The combination was also effective in the SUDHL-16 DLBCL tumor xenograft model in mice. However, the *in vivo* effects appeared less than additive because of the high 77% delay in tumor growth produced by rituximab alone at the single dose selected for study (De Vos et al., 2004).

The *in vitro* cytotoxic effects of bortezomib in combination with anti-CD20 (rituximab) or anti-CD52 (campath) monoclonal antibodies was studied on peripheral blood mononuclear cells (PBMC) obtained from 73 randomly selected, untreated B-CLL patients; PBMC from 12 healthy volunteers were obtained and examined, as well. The combination of bortezomib and rituximab demonstrated additive effects on apoptosis, which were accompanied by an additive down-regulation of Bcl-2 expression (Smolewski et al., 2006).

The effects of combined treatment with bortezomib and rituximab on patient-derived MCL cell lines (Jeko, Mino, SP53) and tumor samples from patients with MCL (primary cells) was studied. Bortezomib in combination with rituximab demonstrated additive or greater than additive cytotoxic effects and enhanced the down-regulation of NF-κB (Alinari et al., 2009).

Ecotoxicity/environmental risk assessment

The applicant provided an ERA and refined the PEC surfacewater in phase I by estimating consumption data of 1 845 181 mg/year in 2018. The applicant concluded that the PEC surfacewater is orders of magnitude below the threshold value of 0.01 µg/L. Therefore, studies on environmental fate and effects were not conducted and the ERA ended in phase I.

The refinement in phase I is not in line with the guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00, June 2006) because the refinement is not based on reasonably justified market penetration data, e. g. published epidemiological data (see Question 4, Q & A document EMA/CHMP/SWP/44609/2010, adopted 2011).

However, the conclusion of the applicant can be endorsed as data on the prevalence of both diseases are publicly available (e.g. www.orpha.net). Including the prevalence values found by the CHMP and the current treatment regime described in the SmPC in a PEC surfacewater calculation the result is clearly below the action limit. Hence, no further assessment in phase II is deemed to be necessary.

In response to the CHMP Request for Supplementary Information, the MAH presented missing data regarding the Kow for bortezomib carrying out a different method of analysis from what suggested by the "guideline on the ERA". Even if the choice of the different method used is not soundly justified and not GLP compliant, it is considered overall acceptable. The log Kow of bortezomib calculated (2.0 at pH=7) is below the threshold of 4.5 thus no persistence, bioaccumulation and toxicity screening is needed.

Discussion on non-clinical aspects

No new in vitro and in vivo non-clinical study was presented in this application. The following conclusions come from published data.

The majority of follicular lymphoma tumours present with the t(14;18) translocation that leads to over-expression of the antiapoptotic protein Bcl-2 and constitutively activation of NF-κB signalling which can contribute to tumorigenicity and resistance to therapy.

Single-agent bortezomib showed an efficacy in down-regulating both Bcl-2 and NF-kB in different NHL cell lines, B cell lymphoma cell lines and other cancer cell lines.

Bortezomib showed a trend to prolong time to recurrence of lymphoma cells when associated with the agonistic monoclonal antibody to TRAIL receptors lexatumumab, and produced an induction of apoptosis in Hodgkin lymphoma, NHL, and large B-cell lymphoma cell lines when associated with the histone deacetylase inhibitor, PCI 24781

Evidence from the scientific literature also shows that FLs express CD20, the B-cell antigen targeted by rituximab: in diffuse large B-cell lymphoma cell line, the combination of bortezomib and rituximab produced additive effects on inhibition of cell proliferation and induction of apoptosis.

The combination of bortezomib and rituximab demonstrated additive effects on apoptosis, which were accompanied by an additive down-regulation of Bcl-2 expression in peripheral blood mononuclear cells obtained from untreated B-CLL patients. Bortezomib in combination with rituximab demonstrated additive cytotoxic effects and enhanced the down-regulation of NF-κB both in patient-derived MCL cell lines and tumour samples from patients with MCL (primary cells).

Evidence from the available literature did not highlight any new safety and toxicological concern of bortezomib in the proposed new indication "treatment of follicular non-Hodgkin lymphoma" respect to the current indication in multiple myeloma. The two haematological conditions share a similar pathology pathway.

The waiving of original studies by literature data is considered acceptable and in line with guideline ICH S 9 section 3.5 "Combination of Pharmaceuticals", that considers toxicology studies investigating the safety of combinations of pharmaceuticals intended to treat patients with advanced cancer, not warranted.

Conclusion on non-clinical aspects

In the present application the MAH did not provide any new in vitro and in vivo non-clinical study neither on single-agent bortezomib nor on the combination of bortezomib and rituximab.

A review of published and not published non-clinical studies was performed. The waiving of original studies by literature data is considered acceptable.

No changes in the SmPC section 5.3 are considered necessary.

3.3. Clinical aspects

Tabular overview of clinical studies

Study Number[a] Principal Investigator (Country) Start/End Date (day Month year)	Study Description/Design, Objectives, Type of Control	Subjects Evaluated Sex M/F Age (yr): Mean (Range) Race (W/B/Ot)	Treatment Regimen/ Duration Route of Administration Batch Number (Formula Number)	Study Status Type of Study Report CTD Location of Report or Publication
Intrinsic Factor Pharmacokinetic Studies				
NCI CTEP 6432 Millennium Pharmaceuticals, Inc. Patricia LoRusso (US) Start:28 September 2004 End: 05 February 2010 (last subject completed)	Phase 1 dose escalation, pharmacokinetic study (PK) study evaluating VELCADE in subjects with advanced malignancies and varying degrees of hepatic impairment. Subjects were assigned to 1 of 4 hepatic function cohorts according to their hepatic function (normal function, or mild, moderate, or severe impairment) Objectives: to evaluate the safety, tolerability, and the maximum tolerated dose (MTD) of VELCADE in patients with various degrees of liver dysfunction; and to identify the PK and pharmacodynamic (PD) profile of bortezomib in patients with advanced malignancy and mild, moderate, or severe liver insufficiency. To search for dietary influences on bortezomib disposition and effectiveness. To search for influences of proteasome inhibition on cytochrome P450 activity. Control: normal hepatic function group	61 subjects 31 M/30 F 60.1 years (30 to 85 years) 57/2/2 (Asian) *Normal hepatic function:* 14 subjects 8 M/6 F 63.9 years (47 to 79 years) 14/0/0 *Mild hepatic impairment:* 17 subjects 7 M/10 F 62.5 years (35 to 85 years) 15/0/2 (Asian) *Moderate hepatic impairment:* 12 subjects 6 M/6 F 57.8 years (30 to 75 years) 12/0/0 *Severe hepatic impairment:* 18 subjects 10 M/8 F 56.4 years (35 to 74 years) 16/2/0	VELCADE for Injection administered at doses of 0.5, 0.7, 1.0, or 1.3 mg/m^2 on Days 1, 4, 8, and 11 on a 21-day cycle within each hepatic impairment category. Doses were assigned using a standard 3 + 3 dose escalation paradigm. There was no dose escalation for the normal hepatic function group (1.3 mg/m^2 only). Treatment was to continue until 1 of the following occurred: disease progression, intercurrent illness that prevented further treatment, unacceptable adverse event, failure to recover from toxicity within 2 weeks, subject decided to withdraw from the study, or general or specific changes in the subject's condition that rendered the subject unacceptable for further treatment in the judgment of the investigator. No batch numbers were assigned or logged in.	Completed[b] Full report
Patient Pharmacodynamic and Pharmacokinetic/Pharmacodynamic Studies				
DM98-194 Millennium Pharmaceuticals, Inc. Christos Papandreou (US) Start: 07 October 1998 End: 20 December 2001 (last subject completed)	Phase 1, open-label, single-center, single-agent, dose escalation study of bortezomib in subjects with histologically confirmed malignancies. This was the first clinical study of bortezomib. Primary Objectives: to determine the dose-limiting toxicity and MTD of bortezomib when administered as an IV bolus weekly for 4 consecutive weeks (followed by 2-week recovery period). To evaluate the PK of bortezomib following a single IV dose. To evaluate the PD of bortezomib by measurement of 20S proteasome inhibition of peripheral blood lymphocytes of treated subjects. Secondary Objectives: to evaluate the relationship between toxicity and 20S proteasome inhibition in peripheral blood lymphocytes. To evaluate the response to treatment in patients with measureable or evaluable disease.	53 subjects treated 51 M/2 F 65.5 years (45 to 78 years) 49/1/3 (Hispanic) *0.13 to 0.60 mg/m^2:* 10 subjects total 9 M/1 F 63.9 years (52 to 73 years 9/1/0 *0.75 to 0.90 mg/m^2:* 9 subjects 8 M/1 F 65.3 years (51 to78 years) 9/0/0 *1.00 to 1.32 mg/m^2:* 8 subjects 8 M/0 F 64.0 years (45 to 77 years) 8/0/0 *1.45 mg/m^2:* 6 subjects 6 M/0 F 63.7 years (58 to71 years) 5/0/1 (Hispanic) *1.6 mg/m^2:* 13 subjects 13 M /0 F 63.6 years (52 to 73 years) 11/0/2 (Hispanic)	VELCADE for Injection, at doses of 0.13, 0.25, 0.40, 0.60, 0.75, 0.80, 0.85, 0.90, 1.00, 1.10, 1.21, 1.32, 1.45, 1.60, 1.80, or 2.00 mg/m^2, was administered on Days 1, 8, 15, and 22 followed by a 2-week rest period (14 days after the last dose; 1 treatment cycle comprised the 5-week period). Subjects were to receive at least 2 5-week treatment cycles for all dose levels. Thereafter, subjects who had stable disease or experienced a response to treatment may have continued treatment indefinitely, at the investigator's discretion. Batch Numbers: Initially, VELCADE for Injection was supplied by the Sponsor in a liquid formulation in vials containing 2 mL VELCADE. The batch numbers of VELCADE liquid formulation used in this study were 75411S and 75414S.	Completed[b] Full report EMEA/H/C/539

DM98-194 (continued)	Control: NA	*1.8 mg/m²:* 2 subjects 2 M/0 F 71.0 years (64 to 78 years) 2/0/0 *2.0 mg/m²:* 5 subjects 5 M/0 F 67.0 years (53 to 75 years) 5/0/0	In April 1999, the liquid formulation of VELCADE was replaced by a lyophilized powder formulation. The Sponsor subsequently provided VELCADE for Injection as a sterile lyophilized powder in vials containing 2.5 mg VELCADE and 25 mg mannitol USP. The batch numbers of VELCADE lyophilized powder used in this study were 98-217 and 258388.	
M34103-058 Millennium Pharmaceuticals, Inc. Study Director: Dixie-Lee Esseltine (US) Start: 16 February 2004 End: 21 June 2005 (last evaluable patient completed Cycle 4, Day 1)	Phase 1, randomized, open-label, multicenter, single- and multiple-dose PK/PD prospective study of VELCADE administered IV at 2 dose levels in subjects 18 years of age or older with relapsed multiple myeloma following 1 or more previous therapies and a life expectancy of 3 months or more. Primary Objectives: to characterize the PK of bortezomib at 2 dose levels (1.0 mg/m² and 1.3 mg/m²) after single and multiple dose administration. To describe the PD of bortezomib using the same doses and to evaluate the bortezomib PK/PD relationship. Exploratory Objective: to evaluate the bortezomib PK/pharmacogenomic relationship Control: NA	42 subjects 23 M/19 F 29/7/6 (1 Asian or Pacific Islander, 3 Hispanic, 2 Other) *Group A:* 21 subjects 12 M/9 F 60.9 years (41 to 83 years) 15/2/4 (1 Other, 1Asian or Pacific Islander, 2 Hispanic) *Group B:* 21 subjects 11 M/10 F 59.6 years (36 to79 years) 14/5/2 (1 Hispanic, 1 Other)	*Group A:* VELCADE for Injection 1.0 mg/m² on Days 1, 4, 8, and 11 of a 21-day cycle (3 cycles). After Cycle 3, the VELCADE dose could be increased to 1.3 mg/m² at the discretion of the investigator. *Group B:* VELCADE for Injection 1.3 mg/m² on Days 1, 4, 8, and 11 of a 21-day cycle (3 cycles). Upon completion of the PK/PD assessment portion of the study (Cycle 1 through Cycle 3), patients who required additional therapy were allowed to continue treatment with VELCADE at the discretion of the investigator during Cycle 4 through Cycle 8 (maximum 8 cycles). Batch Numbers: *VELCADE investigational product:* YB010A3, YB012A2, YB040A2, and D7-1-1	Completed[b] Full report EMEA/H/C/539 (Specific Obligation 009)
26866138-CAN-1006 Prof. Andrzej Hellmann (Poland) Start: 20 August 2007 End: 08 March 2010 Last subject completed: 17 May 2010	Phase 1, open-label, multicenter, 2-stage, PK drug-drug interaction study of VELCADE in subjects 18 years of age or older with documented relapsed or refractory multiple myeloma or non-Hodgkin lymphoma (NHL) following prior antineoplastic therapy and who had not been previously treated with VELCADE. Primary Objective: to evaluate the effect of coadministration of cytochrome P450 3A4 (*CYP3A4)* inducers on the PK profile of bortezomib. Rifampicin was used to assess the effect of a potent *CYP3A4* inducer and dexamethasone to assess the effect of a relatively weak inducer. Secondary Objective: to evaluate the impact of *CYP3A4* inducers on the PD and safety profiles of VELCADE. Control: Group A	61 subjects 30 M/31 F 59/0/2 **Stage 1:** *Group A:* 30 subjects 15 M/15 F 64.7 years (34 to 80 years) 29/0/1 *Group B:* 13 subjects 6 M/7 F 60.2 years (41 to75 years) 13/0/0 **Stage 2:** *Group C:* 18 subjects 9 M/9 F 62.3 years (33 to79 years) 17/0/1	**Stage 1:** *Group A:* VELCADE for Injection 1.3 mg/m² administered weekly on Days 1, 4, 8, and 11 of a 21-day cycle (3 cycles). At discretion of investigator subjects could continue beyond 4 cycles. *Group B:* Same as Group A for Cycles 1 and 2. During Cycle 3 add rifampicin PO 600 mg daily on Days 4 through 10 of a 21-day cycle. **Stage 2:** *Group C:* VELCADE for Injection 1.3 mg/m² administered weekly on Days 1, 4, 8, and 11 of a 21-day cycle for 2 cycles. During Cycle 3, add dexamethasone 40 mg PO once daily on Days 1 through 4 and 9 through 12. Batch Numbers: *VELCADE investigational product:* 6GZSN-1, 7AZTC00, 7HZSZ00, 7KZTA01 *Rifampicin tablets:* 605930 *Dexamethasone tablets:* 7483401	Completed[b] Full Report
Efficacy and Safety Controlled Clinical Studies				
26866138-LYM-3001 Synopsis B. Coiffier (France) Start: 22 March 2006 End: 15 June 2010 (clinical data cutoff; study completion)	Phase 3, randomized, open-label, active-controlled, multicenter, multinational, prospective study of the combination of VELCADE and rituximab (Vc-R) with single-agent rituximab, in subjects with relapsed or refractory, rituximab-naïve or -sensitive follicular B-cell NHL. Primary Objective: To determine whether Vc-R provides benefit to subjects with relapsed or refractory, rituximab-naive or -sensitive, follicular B-cell NHL relative to treatment with rituximab alone, as assessed by prolongation of progression-free survival (PFS). Secondary Objectives: objective response rate (complete remission [CR] + complete remission unconfirmed [CRu] + partial remission [PR]); overall CR rate (CR+CRu); duration of response; time to progression (TTP); overall survival rate; 1-year survival rate; safety and tolerability. Control: rituximab	676 subjects 309 M/367 F 57 years (21 to 84 years) 508/6/162 (140 Asian, 21 Other, 1 Native Hawaiian/ Other Pacific Islander) *Vc-R group:* 336 subjects 172 M/164 F 56.8 years (24 to 83 years) 250/4/82 (71 Asian, 11 Other) *Rituximab group:* 340 subjects 137 M/203 F 57.3 years (21 to 84 years) 258/2/80 (69 Asian, 10 Other, 1 Native Hawaiian/Other Pacific Islander)	*Vc-R group:* VELCADE for Injection 1.6 mg/m² administered weekly on Days 1, 8, 15, and 22 of a 35-day cycle (for up to 5 cycles) in combination with 4 doses of 375 mg/m² rituximab once weekly on Days 1, 8, 15, and 22 of Cycle 1 and in combination with a single dose of 375 mg/m² rituximab on Day 1 of Cycles 2 to 5 (total of 8 doses of rituximab) *Rituximab group:* Rituximab IV 375 mg/m² once weekly on Days 1, 8, 15, and 22 of Cycle 1, and as a single dose of 375 mg/m² on Day 1 of Cycles 2 to 5 (total of 8 doses) Batch Numbers: *VELCADE investigational product:* 4IBSJ00, 5EBS101, 5FBS300, 5FBS500, 5FBS501, 5JBS000, 5KBS700, 6DBS101 *Rituximab:* B2021, B2028, B2036, B2071, B2095, B2122, B4002, B4003, B5003, B5015, M63045, M70267, M72389	Completed Full Report Mod5.3.5.1\LYM-3001

M34103-061 Millennium Pharmaceuticals, Inc. Synopsis A. Goy (US) Start: 10 May 2004 End: 20 April 2006 (last subject completed)	Phase 2, randomized, open-label, non-comparative, multicenter, 2-stage prospective study of Vc-R in subjects with relapsed or refractory indolent B-cell NHL Primary Objective: to determine the response rate (CR/CRu/PR) of Vc-R Secondary Objectives: to determine the response rate (CR/CRu/PR) of Vc-R through the time of the first disease response evaluation; overall CR rate (CR/CRu); TTP; duration of response; time to first response; safety and tolerability Additional endpoints: survival; PFS; change from baseline lesion measurement; Karnofsky Performance Status Control: NA	81 subjects 41 M/40 F 74/5/2 (1 Asian or Pacific Islander; 1 Hispanic) *Twice-weekly Vc-R group:* 41 subjects 20 M/21 F 61.7 years (33 to 86 years) 39/2/0 *Weekly Vc-R group:* 40 subjects 21 M/19 F 63.3 years (40 to 85 years) 35/3/2 (1 Asian or Pacific Islander; 1 Hispanic)	*Twice-weekly Vc-R:* VELCADE for Injection 1.3 mg/m^2 twice-weekly on Days 1, 4, 8, and 11 of a 21-day cycle in combination with 4 doses of rituximab 375 mg/m^2 IV administered weekly on Days 1, 8, and 15 of Cycle 1, and on Day 1 of Cycle 2. VELCADE dosing was to continue for 5 cycles (approximately 15 weeks) *Weekly Vc-R* VELCADE for Injection 1.6 mg/m^2 administered weekly on Days 1, 8, 15, and 22 of a 35-day cycle in combination with 4 doses of rituximab 375 mg/m^2 IV administered weekly on Days 1, 8, 15, and 22 of Cycle 1. VELCADE dosing was to continue for 3 cycles (approximately 15 weeks) Batch Numbers: *VELCADE investigational product:* YB010A, YB012A, YB005A, D7-1-1, and D9-1-1 *VELCADE commercial product:* WB009A1 and COM-MAINL *Rituximab*: Commercially available product used	Completed Full Report Mod5.3.5.1\M34103-061

[a] The sponsor is Johnson & Johnson Pharmaceutical Research & Development (J&JPRD) unless otherwise stated and listed after the study number.
[b] Available upon request.
KEY: B=Black; CR=complete remission; CRu=complete remission unconfirmed; CTD=common technical document; EMA=European Medicines Agency; F=female; IV=intravenous; M=male; MTD=maximal tolerated dose; NA=not applicable; NDA=New Drug Application; NHL=non-Hodgkin lymphoma; Ot=other; PD=pharmacodynamic(s); PFS=progression-free survival; PK=pharmacokinetic(s); PO=per os, orally; PR=partial remission; TTP=time to progression; US=United States; USP=United States Pharmacopeia; Vc-R=VELCADE + rituximab; W=White.

Clinical efficacy

Dose-response studies and main clinical studies

Efficacy data of Velcade in combination with rituximab were based on the pivotal Phase III study LYM-3001 and supportive Phase II study M34103-061.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of efficacy for trial LYM-3001

Title: A Randomized, Open-Label, Multicenter Study of VELCADE With Rituximab or Rituximab Alone in Subjects With Relapsed or Refractory, Rituximab-Naïve or –Sensitive Follicular B-Cell Non-Hodgkin Lymphoma		
Study identifier	26866138-LYM-3001	
Design	Phase III efficacy and safety	
	Duration of enrollment: Duration of screening phase: Duration of post-treatment phase:	20 months approximately 28 days 20 months
Hypothesis	Superiority: there would be an improvement in the median PFS by 33% (i.e., from 10 months to 13.33 months) by the addition of Velcade to rituximab (page 3 synopsis)	

Treatments groups	Arm A		Velcade plus rituximab, 1.6 mg/m2 Velcade for IV on Days 1, 8, 15, and 22 of a 35-day cycle in combination with rituximab IV 375 mg/m2 on Days 1, 8, 15, and 22 of Cycle 1 and on Day 1 of Cycles 2 through 5(for a total of 8 doses).
	Arm B		rituximab IV 375 mg/m2 on Days 1, 8, 15, and 22 of Cycle 1, and on Day 1 of Cycles 2 through 5 (for a total of 8 doses)
Endpoints and definitions	Primary endpoint	progression -free survival (PFS)	interval (days) between the date of randomization and the date of Progression Disease (PD) or death, whichever occurred first, using the ITT population.
	Secondary endpoint	overall response rate	ORR proportion of subjects who achieve CR, CRu, or PR, using the response-evaluable population.
		overall CR rate	CR+CRu
		duration of response;	Duration of response (complete CR, CRu, or PR) was calculated from the date of initial documentation of a response to the date of first documented evidence of PD (or death due to PD).
		time to progression	TTP from the date of randomization until the date of first documented evidence of PD.
		overall survival	OS calculated for the ITT population, from the date of randomization to the date of death
		1-year survival rate;	1-year survival calculated for the ITT population
		rate of durable response	proportion of subjects who achieve durable response (CR, CRu, PR) with a duration of at least 6 months relative to the response-evaluable population.
	Key exploratory endpoints	patient-reported outcomes (PROs);	PRO for both treatment groups using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) the EuroQoL-5Dimension (EQ-5D)
		Medical Resource Utilization (MRU)	MRU related to the disease and the therapy in both treatment groups. Both MRU and utilities were to be collected for entry into a possible future economic evaluation model.
Database lock	27 July 2010		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	**Primary analysis set:** - Intent to treat (ITT) population, all randomized subjects, consisted of 676 subjects Unless specified otherwise, all efficacy analyses will be based on the ITT population.		
	Secondary and sensitivity analyses sets: - per protocol (PP) population, all subjects who are randomized to treatment with no major violation of inclusion/exclusion criteria and who undergo at least 1 post-baseline disease assessment (post-baseline tumor assessment by independent radiology reviewers/IRC), consisted of 641 subjects - response-evaluable population, all subjects in ITT population, who receive at least 1 dose of VELCADE or rituximab, have at least 1 measurable tumor mass (greater than 1.5 cm in the longest dimension and greater than 1.0 cm in the short axis) at baseline and have at least 1 post-baseline tumor assessment before any subsequent anti-lymphoma treatment by independent radiology reviewers/IRC, consisted of 639 subjects		
Descriptive statistics and estimate variability	Treatment group	Arm A Velcade plus rituximab	Arm B rituximab
	Number of subject	336 (ITT) 316 (PP)	340 (ITT) 325 (PP)
	ITT PFS number of events (PD or death), (%) Median days	212 (63.1) 389 (12.8 months)	228 (67.1) 334 (11.0 months)
	PP PFS number of events (PD or death), (%) Median days	204 (64.6) 414 (13.6 months)	223 (68.6) 338 (11.1 months)
	Overall response (CR+CRu+PR) n. patients (%) on response-evaluable population	199 (63) CR=56 (18) CRu= 23 (7) PR= 38 (12)	160 (49) CR= 44 (14) CRu= 15 (5) PR= 44 (14)
	Overall complete response (CR+CRu) n. patients (%)	79 (25)	59 (18)
	Duration of overall response Number of events (%) Median days ITT TTP Number of events (%) Median days	 117 (58.8) 488 (16.3 months) 204 (60.7) 406 (13.5 months)	 94 (58.8) 421 (14 months) 223 (65.6) 345 (11.5 months)
	ITT OS Number of events (%) Median days	79 (23.5) NE	80 (23.5) NE
	1-year survival rate % (95% CI)	90.5(87.4; 93.7)	90.1(86.9; 93.4)

	Time to Subsequent treatment (%)(95% CI	192 (57.1) 700 (23.4 months)	212 (62.4) 537 (17.9 months)
	durable response (CR, CRu, PR) n. patients (%)	159 (50)	124 (38)
Effect estimate per comparison	Primary endpoint PFS on ITT	Comparison groups	R vs Vc-R (<1 indicates an advantage for Vc-R)
		log-rank test	Hazard ratio 0.822
		(95% CI)	(0.681;0.991)
		P-value	p=0.039
	Secondary endpoint PFS on PP	Comparison groups	R vs Vc-R (<1 indicates an advantage for Vc-R)
		log-rank test	Hazard ratio 0.807
		(95% CI)	(0.667;0.976)
		P-value	0.026
	Secondary endpoint Overall response (CR+CRu+PR) rate	Comparison groups	Rituximab versus Vc-R(<1 indicates an advantage for Vc-R)
		Generalized Cochran-Mantel-Haenszel test for general association.	Odds Ratio 0.569
		(95% CL)	(0.415, 0.780)
		P-value	<0.001
	Secondary endpoint Overall complete response (CR+CRu) rate	Comparison groups	Rituximab versus Vc-R(<1 indicates an advantage for Vc-R)
		Generalized Cochran-Mantel-Haenszel test for general association.	Odds Ratio 0.665
		(95% CL)	(0.455, 0.973)
		P-value	0.035
	Secondary endpoint TTP	Comparison groups	R vs Vc-R (<1 indicates an advantage for Vc-R)
		log-rank test	Hazard ratio 0.808
		(95% CL)	(0.668;0.977)
		P-value	0.027
	Secondary endpoint OS	Comparison groups	Rituximab versus Vc-R(<1 indicates an advantage for Vc-R)
		Log rank test	Hazard ratio 0.971
		(95% CL)	(0.712;1.325)
		P-value	0.854
	Secondary endpoint durable response	Comparison groups	Rituximab versus Vc-R(<1 indicates an advantage for Vc-R)

	(CR, CRu, PR)	Generalized Cochran-Mantel-Haenszel test for general association.	Odds Ratio 0.608
		(95% CL)	(0.444, 0.833)
		P-value	0.002
Notes	Results showed are per the Independent Review Committee		

The pivotal trial **LYM-3001** presented in this application is a randomized, open-label, multicenter study of VELCADE with rituximab or single agent rituximab in relapsed or refractory follicular B-Cell Non-Hodgkin Lymphoma rituximab-naïve or –sensitive patients.

The trial regimen (VELCADE weekly in combination with rituximab) was mainly based on the Phase 2 M34103-061 trial, which is considered supportive for this application as detailed in the supportive study section.

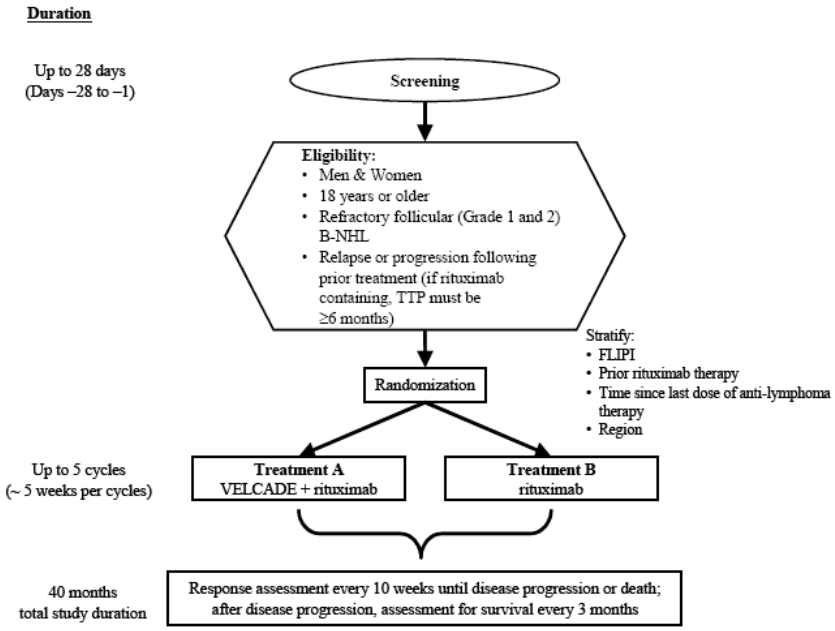
Besides primary and secondary endpoints already described, the following exploratory ad additional objectives have been included:

- patient-reported outcomes (PROs) for both treatment groups utilizing the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) instrument and a preference-based instrument EuroQoL-5Dimension (EQ-5D) to calculate utilities (Attachments 1 and 2 of the study protocol, Appendix 1.1 of this report).
- Medical Resource Utilization (MRU) related to the disease and the therapy in both treatment groups. Both MRU and utilities were to be collected for entry into a possible future economic evaluation model.
- Biomarker study for identification of patient populations that are more or less likely to respond to VELCADE and rituximab or rituximab alone through the evaluation of a defined set of biomarkers.
- time to next anti-lymphoma treatment, duration of treatment-free interval, and time to response.

Patients were randomised in ratio 1:1 to receive Velcade in combination with rituximab or rituximab alone. Regarding of the method of infusion used in the trial (Velcade followed by rituximab), as already highlighted in the scientific advice, the rational supporting this sequence should be clarified.

The original study protocol was issued on 11 November 2005 and the study design is reported below:

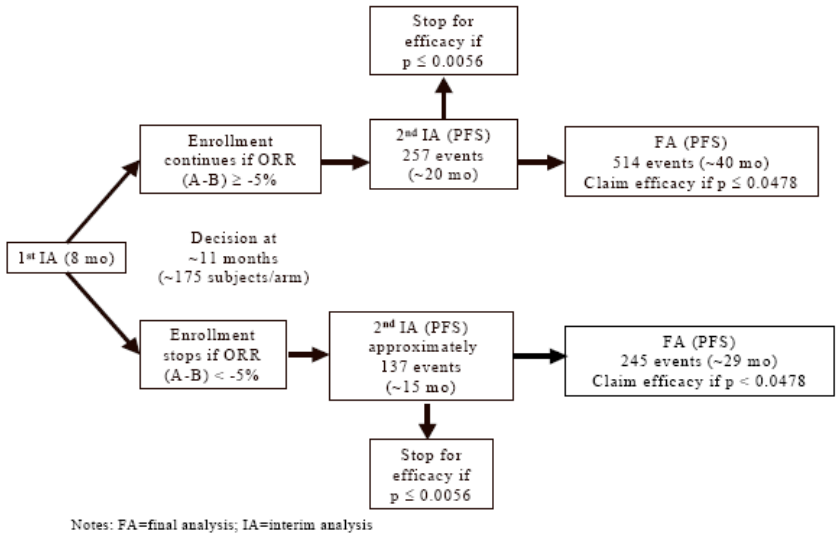
Figure 1: Study LYM-3001 Study Design



According to the statistical analysis plan the sample size calculation was based on the assumption that the median PFS of rituximab alone arm is 10 months. Assuming an additional improvement of median PFS by 33% in Velcade-Rituximab arm i.e., from 10 months to 13.33 months, a total number of 514

events was calculated to provide 90% power (alpha=0.05, 2-sided). Assuming 20 months for accrual, 20 months for follow-up, and about 5% dropout rate, a total of 670 subjects has been calculated to be enrolled in the study (335 subjects/group). The actual number of patients enrolled was 676 (340 in the rituximab arm and 336 in the Vc-R arm).

The planned analyses of efficacy results are summarised in the following scheme:



Notes: FA=final analysis; IA=interim analysis

The stopping boundary noted above was calculated using the O'Brien-Fleming method.

The clinical cut-off date for the first interim analysis was 11 April 2007 at which time the first 100 enrolled subjects had completed a minimum of 2 disease assessments. All safety data and tumor response data generated by the independent radiology review committee were submitted to the An Independent Data Monitoring Committee (IDMC) that recommended the study continuation until the achievement of 670 subjects.

The cut-off date for the second interim analysis was 17 November 2008 with 338 PFS events reported.

The IDMC recommended unmodified trial continuation with a follow-up meeting within 1 year to review the aggregate number (%) of PFS events and the number (%) of permanently censored patients and reasoning. A subsequent analysis with data cut-off on 2 November 2009 on 428 actual PFS events was performed reviewing the aggregate blinded data.

Following this analysis the IDMC concluded that the protocol-specified 514 PFS events would be difficult to achieve based on the number of patients lost to follow-up or permanently censored and recommended to stop the study.

The final analysis was performed based on a clinical cut-off date of 15 June 2010. The number of patients to be enrolled in the study (n=670) as well as the planned follow-up period (20 months) were reached.

Thus, early termination of study LYM-3001 was not due to a marked observed beneficial effect on a lower number of subjects, nor to a shorter follow-up duration, but to the awareness that the number of events initially planned (514) would not have been achieved within the set timeframe.

Given the initial hypothesised statistical assumptions (alpha = 0.05, median PFS in control arm = 10 months, median PFS in treatment group at least =13.33 months) with a number of 440 events, the calculated power was equal to 0.84935 (nearly 85%) which is still considered an acceptable value.

The Efficacy analysis sets have been already defined in the summary of LYM-3001 efficacy table.

The randomization was balanced by using randomly permuted blocks.

Study Population

676 subjects were enrolled in the study (the ITT population) by 164 investigators in 29 countries the majority of which outside US. The majority of enrolled patients were White (75%) and only a minority were Asians (21%) or Black/African-American (1%). This discrepancy could be justified by a lower frequency of NHL in Asians and a very low number of participating site centres from US.

Most demographic and baseline characteristics were balanced between the treatment groups and are summarized in the following table.

A slight higher proportion of female subjects in the rituximab group (60%) compared to Vc-R group (49%) was reported but no significant implications would be expected since sex does have a recognized prognostic value in FL.

Table 10: Demographic and Baseline Characteristics
(Study 26866138-LYM-3001: Intent-to-Treat Analysis Set)

	Rituximab (N=340)	Vc-R (N=336)	Total (N=676)
Age (years)[a]			
N	340	336	676
Category, n (%)			
≤65	253 (74)	255 (76)	508 (75)
>65	87 (26)	81 (24)	168 (25)
Mean	57.3	56.8	57.0
SD	12.00	11.12	11.56
Median	57.0	57.0	57.0
Minimum	21	24	21
Maximum	84	83	84
Sex, n (%)			
N	340	336	676
Male	137 (40)	172 (51)	309 (46)
Female	203 (60)	164 (49)	367 (54)
Race, n (%)			
N	340	336	676
Asian	69 (20)	71 (21)	140 (21)
Black/African-American	2 (1)	4 (1)	6 (1)
Native Hawaiian/other Pacific Islander	1 (<1)	0	1 (<1)
White	258 (76)	250 (74)	508 (75)
Other	10 (3)	11 (3)	21 (3)
Baseline body surface area (m^2)			
N	340	336	676
Category, n (%)			
<1.5	12 (4)	16 (5)	28 (4)
1.5 – 2	259 (76)	251 (75)	510 (75)
>2	69 (20)	69 (21)	138 (20)
Mean	1.82	1.84	1.83
SD	0.215	0.237	0.226
Median	1.82	1.82	1.82
Minimum	1.3	1.3	1.3
Maximum	2.7	2.6	2.7
Baseline ECOG performance status, n (%)			
N	340	336	676
0: asymptomatic	177 (52)	162 (48)	339 (50)
1: symptomatic, fully ambulatory	141 (41)	153 (46)	294 (43)
2: symptomatic, in bed <50% of the day	22 (6)	21 (6)	43 (6)
Creatinine clearance (mL/min), n (%)			
N	340	336	676
≤30	0	1 (<1)	1 (<1)
>30-60	50 (15)	43 (13)	93 (14)
>60	290 (85)	292 (87)	582 (86)
Hemoglobin (g/dL), n (%)			
N	340	336	676
<12	75 (22)	85 (25)	160 (24)
≥12	265 (78)	251 (75)	516 (76)

ECOG=Eastern Cooperative Oncology Group
[a] Age at randomization
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Grade 1 LF was diagnosed in 51% and Grade 2 in 48% of all subjects. The use of bortezomib in combination with rituximab in this population subset with documented Grade 1 or 2 LF should be reflected in SmPC section 4.1.

Most of the subjects (83%) were classified as Ann Arbor stage III or IV.

The median time since diagnosis was 3.4 years with a mean value of 4 years.

The study population was stratified by the factors reported in the following table to allow subgroup analyses.

Table 9: Distribution of Stratification Factors at Baseline Based on the CRF (Study 26866138-LYM-3001: Intent-to-Treat Analysis Set)

	Rituximab (N=340)	Vc-R (N=336)	Total (N=676)
FLIPI score, n (%)			
N	340	336	676
High	140 (41)	139 (41)	279 (41)
Intermediate	119 (35)	120 (36)	239 (35)
Low	81 (24)	77 (23)	158 (23)
Prior rituximab therapy, n (%)			
N	340	336	676
Yes	150 (44)	145 (43)	295 (44)
No	190 (56)	191 (57)	381 (56)
Time since last anti-lymphoma therapy, n (%)			
N	340	336	676
>1 year	185 (54)	200 (60)	385 (57)
≤1 year	155 (46)	136 (40)	291 (43)
Region, n (%)			
N	340	336	676
United States/Canada	26 (8)	23 (7)	49 (7)
European Union	132 (39)	130 (39)	262 (39)
Rest of World	182 (54)	183 (54)	365 (54)

CRF=case report form; FLIPI=Follicular Lymphoma International Prognostic Index
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FLIPI score, prior rituximab therapy, time since last dose of anti-lymphoma therapy were prognostic factors of clinical importance.

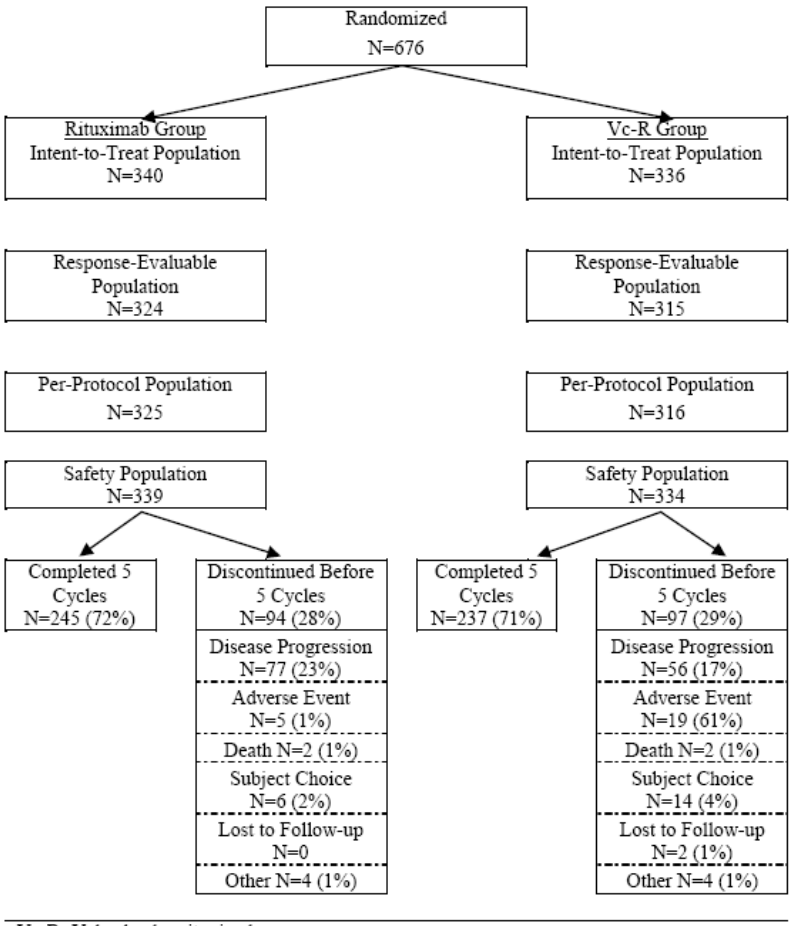
A high percentage of enrolled patients (54%) was rituximab naïve and a percentage of 44% received prior rituximab therapy. Of these patients 73% received the last rituximab treatment at least 12 months prior to study entry.

Thus the study population, although could partially reflect the target population for the sought indication at the time of the study initiation, is not representative of the current relapsing follicular lymphoma patient population that mainly consists of non-rituximab naïve patients.

All subjects received at least 1 prior line of systemic anti-lymphoma therapy before entering the study (range: from 1 to ≥6 regimens), with most of them receiving 1 (41%) or 2 (26%) prior lines of therapy. Regimens and numbers of the prior lines of anti-lymphoma therapy were similar between the treatment groups.

The subjects disposition and information on study completion/withdrawal are summarized in the following table.

Figure 2: Subject Disposition
(Study 26866138-LYM-3001)



Vc-R=Velcade plus rituximab
Note: Treatment group was based on the treatment actually received.

Note: Fig.2 should read: VcR group Adverse Event N=19 (6.1%)

The most frequently reported reason for discontinuation prior to completing 5 cycles of treatment in both treatment groups was disease progression (23% rituximab; 17% Vc-R). At the time of study completion (15 June 2010), the majority (64% in each treatment group) of subjects in the ITT population were discontinued due to the study closure, and 24% of subjects in each group died.

The median treatment duration was 20.3 weeks (range: 0 to 30 weeks) for the rituximab group and 23.3 weeks (range: 0 to 38 weeks) for the Vc-R group. Subjects in the rituximab group received a median total dose of 2,947.3 mg/m2 of rituximab. Similarly, in the Vc-R group, the median total dose of rituximab was 2,944.9 mg/m2 and the median total dose of VELCADE was 29.9 mg/m2.

Efficacy results

Primary Efficacy Analyses

According to the IRC assessments, 440 PFS events (PD or death) were observed (228 events in the rituximab group and 212 events in the Vc-R group) by the end of the study. A statistically significant improvement in PFS favouring the Vc-R group was observed (HR: 0.822; 95% CI: 0.681, 0.991; p=0.039) (as shown in the table below).

The median PFS as determined by the IRC was 334 days (11.0 months) in the rituximab group and 389 days (12.8 months) in the Vc-R group. The HR corresponds to a 22% improvement in PFS versus rituximab alone.

A clinical significant gain in PFS was originally set as a 33% increase in the Velcade-rituximab arm compared to single agent rituximab arm. However, the observed PFS improvement in the Velcade-rituximab arm is 16.4 % considering the median PFS, and 22% if calculated in terms of HR, resulting in a median statistically significant net increase of 1.8 months. The Applicant should discuss the clinical relevance of a gain of 1.8 months in a patient population with an indolent disease highly heterogeneous in terms of relapse onset and frequency, and with remission phases of increasingly shorter duration.

Table 19: Summary of Progression-Free Survival per the Independent Review Committee (Study 26866138-LYM-3001: Intent-to-Treat Analysis Set)

Descriptive[a]	Rituximab (N=340)	Vc-R (N=336)	Total (N=676)
Progression-free survival (days)			
Number of assessed	340	336	676
Number of censored (%)	112 (32.9)	124 (36.9)	236 (34.9)
Number of events (%)	228 (67.1)	212 (63.1)	440 (65.1)
25% quantile (95% CI)	142.0(137.0; 208.0)	204.0(142.0; 269.0)	199.0(140.0; 210.0)
Median (95% CI)	334.0(278.0; 365.0)	389.0(351.0; 456.0)	351.0(345.0; 389.0)
75% quantile (95% CI)	636.0(554.0; 942.0)	861.0(716.0; NE)	771.0(647.0; 1000.0)
P-value[b]	0.039		
Hazard ratio (95% CI)[c]		0.822 (0.681;0.991)	

CI=confidence interval; NE=not estimable
[a] Based on Kaplan-Meier product limit estimates.
[b] Based on log-rank test.
[c] Rituximab vs. Vc-R. A hazard ratio <1 indicates an advantage for Vc-R.
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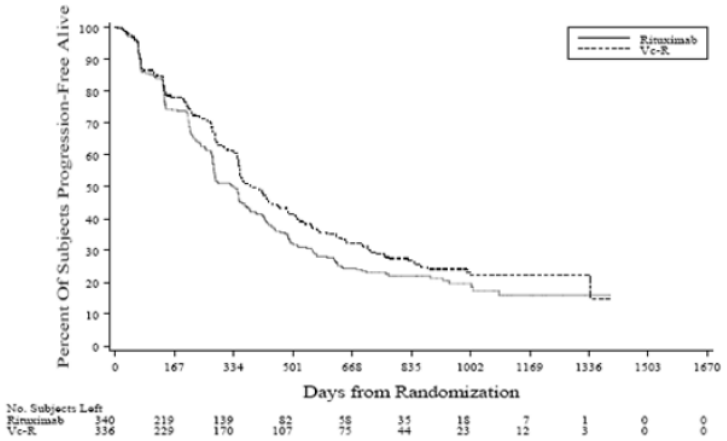
Figure 3: Kaplan-Meier Plot of Progression-Free Survival per the Independent Review Committee (Study 26866138-LYM-3001: Intent-to-Treat Analysis Set)



The median PFS as determined by the IRC for the PP population was 338 days (11.1 months) in the rituximab group and 414 days (13.6 months) in the Vc-R group. Thirty-three percent of all subjects were censored. The difference between treatment groups reached statistical significance (HR: 0.807; 95% CI: 0.667, 0.976; p=0.026).

Study 26866138-LYM-3001

Output DEFF02A: Summary of Progression Free Survival: per Independent Review Committee

Analysis Set: Per-Protocol

Descriptive (a)	Rituximab (N=325)	Vc-R (N=316)	Total (N=641)
Progression-Free Survival (Days)			
Number of Assessed	325	316	641
Number of Censored (%)	102 (31.4)	112 (35.4)	214 (33.4)
Number of Events (%)	223 (68.6)	204 (64.6)	427 (66.6)
25% Quantile (95% CI)	143.0(137.0; 208.0)	213.0(155.0; 271.0)	203.0(142.0; 212.0)
Median (95% CI)	338.0(278.0; 369.0)	414.0(352.0; 483.0)	353.0(345.0; 414.0)
75% Quantile (95% CI)	642.0(556.0; 1004.0)	881.0(717.0; NE)	827.0(653.0; 1004.0)
P-value(b)	0.026		
Hazard Ratio (95% CI)(c)		0.807 (0.667;0.976)	

There was a consistent treatment effect (HR ≤0.850) in favour of the Vc-R group in all sensitivity analyses with the exception of PFS based on the investigator assessment.

Improvements in PFS in all sensitivity analyses reached statistical significance with the exception of PFS for the ITT population as determined by the investigator.

Table 20: Progression-Free Survival: Primary and Sensitivity Analyses (Study 26866138-LYM-3001: All Subjects Analysis Set)

	Total Number of Events	------ Median (months) ----- Rituximab	Vc-R	Difference	Hazard Ratio (95% CI)	P-value
IRC: Intent-to-Treat Population						
Primary analysis (unstratified)	440	11.0	12.8	1.8	0.822(0.681, 0.991)	0.039
Stratified analysis	440	11.0	12.8	1.8	0.817(0.672, 0.993)	0.042
Censoring for missing visits but not for subsequent treatment	452	10.7	12.5	1.8	0.821(0.683, 0.988)	0.037
Censoring for subsequent treatment but not for missing visits	455	11.0	12.5	1.5	0.821(0.683, 0.987)	0.036
No censoring for either subsequent treatment or missing visits	484	11.1	13.0	1.9	0.817(0.683, 0.977)	0.026
IRC: Per-Protocol Population	427	11.1	13.6	2.5	0.807(0.667, 0.976)	0.026
Investigator: Intent-to-Treat Population	458	13.0	15.2	2.2	0.895(0.745, 1.075)	0.236
Composite PFS by IRC and Investigator: ITT population	514	9.2	11.5	2.3	0.850(0.715, 1.011)	0.065

IRC=Independent Review Committee; ITT=Intent-to-Treat; PFS=progression-free survival

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The PFS results as determined by the investigator as for PP population, while not statistically significant, are generally consistent with those determined by the IRC and indicate an improvement of 2.2 months in the median PFS. The median PFS per the investigator was 396 days (13.0 months) in the rituximab group and 464 days (15.2 months) in the Vc-R group (HR: 0.895; 95% CI: 0.745, 1.075; p=0.236) (as reported in the table below).

Study 26866138-LYM-3001

Output DEFF02B: Summary of Progression Free Survival: per Investigator

Analysis Set: Per-Protocol

Descriptive (a)	Rituximab (N=325)	Vc-R (N=316)	Total (N=641)
Progression-Free Survival (Days)			
Number of Assessed	325	316	641
Number of Censored (%)	101 (31.1)	99 (31.3)	200 (31.2)
Number of Events (%)	224 (68.9)	217 (68.7)	441 (68.8)
25% Quantile (95% CI)	178.0(138.0; 211.0)	247.0(198.0; 281.0)	206.0(169.0; 240.0)
Median (95% CI)	398.0(349.0; 443.0)	484.0(419.0; 554.0)	422.0(395.0; 487.0)
75% Quantile (95% CI)	974.0(713.0; 1215.0)	981.0(807.0; NE)	975.0(807.0; 1074.0)
P-value(b)	0.191		
Hazard Ratio (95% CI)(c)		0.883 (0.732;1.064)	

The MAH should discuss the conflicting PFS results between investigator and IRC in the intent to treat population.

Secondary Efficacy Analyses

Results of the key secondary endpoints (ORR, CR rate, durable response rate) have been evaluated in the **response-evaluable population** and showed a statistically significance in favour of Vc-R group (details are reported in the table below).

Table 21: Summary of Best Overall Response per Independent Radiology Review (Study 26866138-LYM-3001: Response-Evaluable Analysis Set)

Overall Best Response	Rituximab (N=324)	Vc-R (N=315)	Total (N=639)	P-value[a]	Odds Ratio[b] (95% CL)
Complete response (CR)	44 (14)	56 (18)	100 (16)		
Complete response/unconfirmed (CRu)	15 (5)	23 (7)	38 (6)		
Overall complete response (CR+CRu)[c]	59 (18)	79 (25)	138 (22)	0.035	0.665(0.455, 0.973)
Radiological only CR/CRu[d]	35 (11)	33 (10)	68 (11)		
Partial response	66 (20)	87 (28)	153 (24)		
Overall response (CR+CRu+PR)	160 (49)	199 (63)	359 (56)	<0.001	0.569(0.415, 0.780)
Stable disease	120 (37)	78 (25)	198 (31)		
Progressive disease	44 (14)	38 (12)	82 (13)		

[a] Generalized Cochran-Mantel-Haenszel test for general association.
[b] Rituximab versus Vc-R. An odds ratio <1 indicates an advantage for Vc-R.
[c] Radiological complete response (CR/CRu) verified by bone marrow and LDH.
[d] Radiological complete response (CR/CRu) not supported by bone marrow and LDH.
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-The overall durable (i.e., responses lasting for 6 months or more) response rate was higher in the Vc-R, suggesting that the addition of VELCADE to rituximab improves response duration (odds ratio: 0.608; 95% CL: 0.444, 0.833; p=0.002), the median duration of overall response was 13.8 months in the rituximab group and 16.0 months in the Vc-R group.

A significant improvement in TTP was demonstrated in Vc-R group (median TTP 13.3 months) over the rituximab group (median TTP 11.3 months) by the IRC (HR: 0.808; 95% CI: 0.668, 0.977; p=0.027). (table below)

Table 27: Summary of Time to Disease Progression per the Independent Review Committee (Study 26866138-LYM-3001: Intent-to-Treat Analysis Set)

Descriptive[a]	Rituximab (N=340)	Vc-R (N=336)	Total (N=676)
Time to disease progression (days)			
Number of assessed	340	336	676
Number of censored (%)	117 (34.4)	132 (39.3)	249 (36.8)
Number of events (%)	223 (65.6)	204 (60.7)	427 (63.2)
25% quantile (95% CI)	143.0(137.0; 208.0)	213.0(155.0; 274.0)	204.0(142.0; 213.0)
Median (95% CI)	345.0(279.0; 375.0)	406.0(351.0; 483.0)	353.0(346.0; 414.0)
75% quantile (95% CI)	642.0(556.0; 1004.0)	992.0(724.0; NE)	842.0(693.0; 1009.0)
P-value[b]	0.027		
Hazard ratio (95% CI)[c]		0.808 (0.668;0.977)	

CI=confidence interval; NE=not estimable
[a] Based on Kaplan-Meier product limit estimates.
[b] Based on log-rank test.
[c] Rituximab versus Vc-R. A hazard ratio <1 indicates an advantage for Vc-R.
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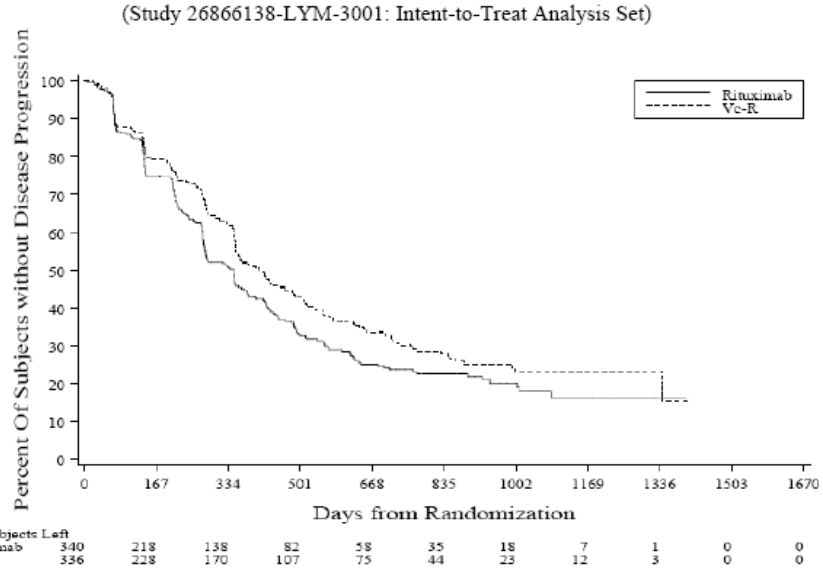
Figure 5: Kaplan-Meier Plot of Time to Disease Progression-per the IRC (Study 26866138-LYM-3001: Intent-to-Treat Analysis Set)



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At study completion, 159 subjects died (80 subjects [24%] in the rituximab group; 79 subjects [24%] in the Vc-R group) and 517 subjects were censored.

After a median duration of follow-up of 33.9 months, the median **OS** was not reached. However, no difference or trend was seen.

Table 29: Summary of Overall Survival
(Study 26866138-LYM-3001: Intent-to-Treat Analysis Set)

Descriptive[a]	Rituximab (N=340)	Vc-R (N=336)	Total (N=676)
Overall survival time (days)			
Number of assessed	340	336	676
Number of censored (%)	260 (76.5)	257 (76.5)	517 (76.5)
Number of events (%)	80 (23.5)	79 (23.5)	159 (23.5)
25% quantile (95% CI)	1070.0(848.0; 1263.0)	1001.0(861.0; NE)	1023.0(898.0; 1205.0)
Median (95% CI)	NE (NE ; NE)	NE (NE ; NE)	NE (NE ; NE)
75% quantile (95% CI)	NE (NE ; NE)	NE (NE ; NE)	NE (NE ; NE)
1-year survival rate % (95% CI)	90.5(87.4; 93.7)	90.1(86.9; 93.4)	90.3(88.0; 92.6)
P-value[b]	0.854		
Hazard ratio (95% CI)[c]		0.971 (0.712;1.325)	

CI=confidence interval; NE=not estimable
[a] Based on Kaplan-Meier product limit estimates.
[b] Based on Log rank test.
[c] Rituximab vs. Vc-R. A hazard ratio <1 indicates an advantage for Vc-R.
Note: Confidence intervals for 1-year survival rates are based on the Greenwood formula.

Additional efficacy Endpoints

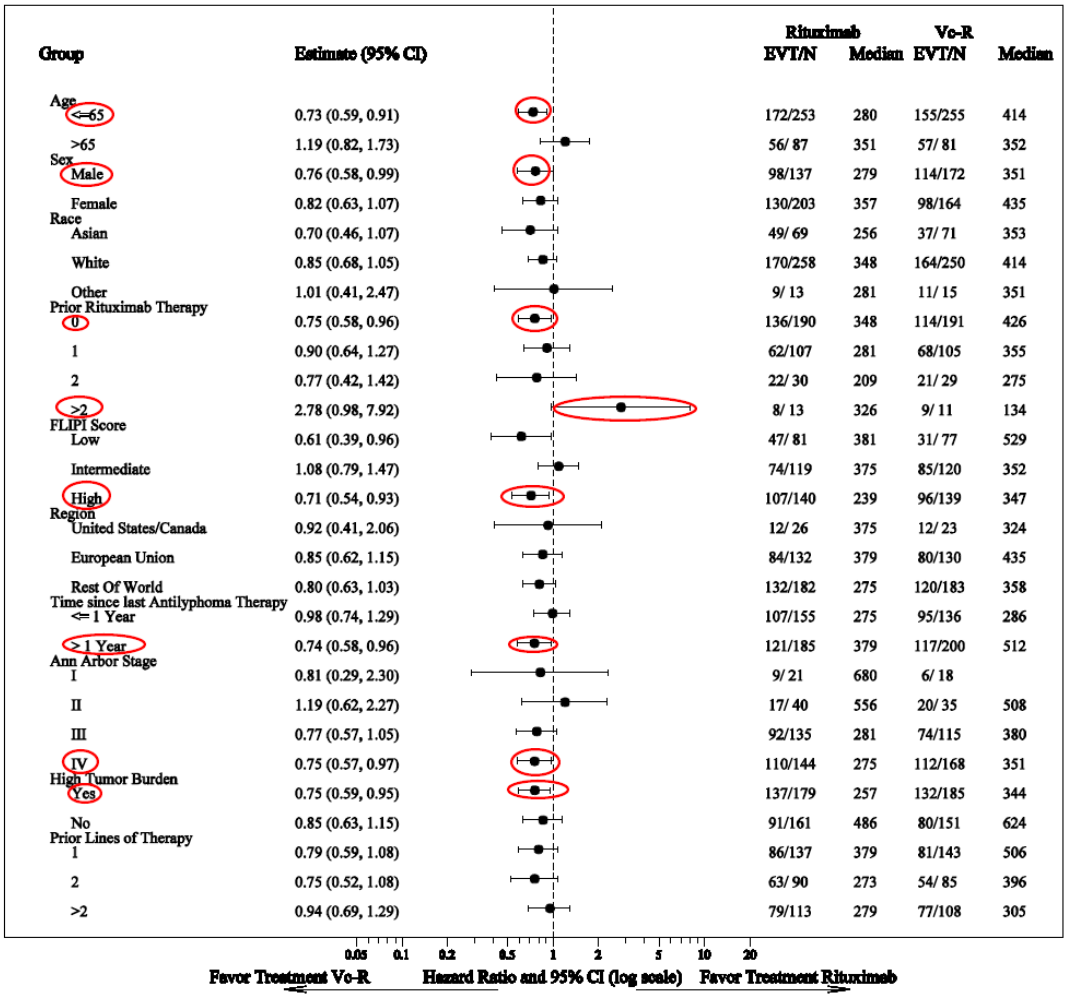
- Patients reported Outcomes: improvements in global health status were observed and maintained through week 120 for both arms. The improvement has been reported earlier in the rituximab group (starting from week 5) than in Vc-R group (starting from week 30).

- The median time to subsequent anti-lymphoma therapy was **significantly** longer (median time 23.0 months) for subjects in the Vc-R group compared with the rituximab group (median time 17.6 months).

Subgroup analyses

Subgroup analyses were performed on the primary efficacy endpoint, PFS, to estimate the effect size of VELCADE on PFS after accounting for various stratification factors. As stated in the Statistical Analysis Plan, these were exploratory analyses without pre-defined hypotheses specifications.

Figure 8: Subgroup Analysis of Progression-Free Survival
(Study 26866138-LYM-3001: Intent-to-Treat Analysis Set)



For subjects who had not received prior rituximab therapy, the median PFS was 348 days (11.4 months) for the rituximab group and 426 days (14.0 months) for the Vc-R group (HR: 0.749; 95% CI: 0.584, 0.961). The improved effect of Velcade in subjects who did not receive rituximab prior the study is statistically significant (p=0.023).

For subjects who had received prior rituximab treatment, PFS is 9.2 months in the rituximab group and 11.4 months in the Vc-Rituximab group with a HR of 0.92 (CI: 0.698, 1.235). The wide CI interval, probably due to the limited number of patients for whom events were reported (190 out of 295 patients), prevents a sound evaluation of the potential benefit of Velcade in the patient population representative of the actual clinical target for the claimed indication (see table below).

Study 26866138-LYM-3001

Output DEFF07A: Summary of Progression Free Survival by Prior Rituximab Therapy: per Independent Review Committee

Analysis Set: Intent-to-Treat

Descriptive (a)	Rituximab (N=340)	Vc-R (N=336)	Total (N=676)
Progression-Free Survival (Days)			
Prior Rituximab Therapy: YES			
Number of Assessed	150	145	295
Number of Censored (%)	58 (38.7)	47 (32.4)	105 (35.6)
Number of Events (%)	92 (61.3)	98 (67.6)	190 (64.4)
25% Quantile (95% CI)	138.0(106.0; 207.0)	142.0(134.0; 213.0)	140.0(134.0; 204.0)
Median (95% CI)	279.0(252.0; 348.0)	347.0(274.0; 422.0)	305.0(274.0; 351.0)
75% Quantile (95% CI)	554.0(430.0; NE)	698.0(506.0; 1000.0)	624.0(493.0; 849.0)
P-value(b)	0.609		
Hazard Ratio (95% CI)(c)		0.928 (0.698;1.235)	
Prior Rituximab Therapy: NO			
Number of Assessed	190	191	381
Number of Censored (%)	54 (28.4)	77 (40.3)	131 (34.4)
Number of Events (%)	136 (71.6)	114 (59.7)	250 (65.6)
25% Quantile (95% CI)	175.0(138.0; 217.0)	275.0(199.0; 331.0)	211.0(142.0; 270.0)
Median (95% CI)	348.0(280.0; 422.0)	426.0(366.0; 558.0)	389.0(351.0; 443.0)
75% Quantile (95% CI)	695.0(567.0; 1004.0)	1340.0(771.0; 1340.0)	924.0(716.0; NE)
P-value(b)	0.023		
Hazard Ratio (95% CI)(c)		0.749 (0.584;0.961)	

Stratification factors (prior Rituximab therapy, FLIPI score, time since last antilymphoma therapy, region) are based on CRF data.
(a) Based on Kaplan-Meier product limit estimates.
(b) Based on Log rank test.
(c) Rituximab vs. Vc-R. A hazard ratio < 1 indicates an advantage for Vc-R.
NE: Not estimable.

-Gender: the median PFS for male subjects was 279 days (9.2 months) for the rituximab group and 351 days (11.5 months) for the Vc-R group (HR: 0.757; 95% CI: 0.577, 0.993). The improved effect of Velcade in male is statistically significant (p=0.043). Considering as endpoint only the effect of rituximab, female show a better response than male.

-Age: the median PFS in for subjects ☐65 years of age was 372 days (12.2 months) for the rituximab group and 464 days (15.2 months) for the Vc-R group (HR: 0.810; 95% CI: 0.656, 1.000). The improved effect of Velcade in subjects > 65 is statistically significant (p=0.05).

The median PFS for subjects >65 years of age was 484 days (15.9 months) for both groups. Older patients instead, showed a better response to rituximab alone respect to younger subjects. (see table below).No differences per age stratum were noted in the number of prior lines of therapy.

Study 26866138-LYM-3001

Output DEFF10A: Summary of Progression Free Survival by Age: per Independent Review Committee

Analysis Set: Intent-to-Treat

Descriptive (a)	Rituximab (N=340)	Vc-R (N=336)	Total (N=676)
Progression-Free Survival (Days)			
Age: <=65			
Number of Assessed	253	255	508
Number of Censored (%)	81 (32.0)	100 (39.2)	181 (35.6)
Number of Events (%)	172 (68.0)	155 (60.8)	327 (64.4)
25% Quantile (95% CI)	138.0(135.0; 205.0)	202.0(138.0; 271.0)	143.0(137.0; 205.0)
Median (95% CI)	280.0(271.0; 349.0)	414.0(351.0; 487.0)	351.0(331.0; 396.0)
75% Quantile (95% CI)	597.0(491.0; 889.0)	1340.0(717.0; NE)	771.0(624.0; NE)
P-value(b)	0.005		
Hazard Ratio (95% CI)(c)		0.733 (0.589;0.911)	
Age: >65			
Number of Assessed	87	81	168
Number of Censored (%)	31 (35.6)	24 (29.6)	55 (32.7)
Number of Events (%)	56 (64.4)	57 (70.4)	113 (67.3)
25% Quantile (95% CI)	231.0(204.0; 281.0)	255.0(136.0; 280.0)	231.0(204.0; 275.0)
Median (95% CI)	351.0(283.0; 492.0)	352.0(281.0; 463.0)	352.0(344.0; 427.0)
75% Quantile (95% CI)	1004.0(513.0; NE)	733.0(508.0; 881.0)	763.0(623.0; 1004.0)
P-value(b)	0.353		
Hazard Ratio (95% CI)(c)		1.191 (0.823;1.725)	

(a) Based on Kaplan-Meier product limit estimates.
(b) Based on Log rank test.
(c) Rituximab vs. Vc-R. A hazard ratio < 1 indicates an advantage for Vc-R.
NE: Not estimable.

-FLIPI score: for subjects with a low FLIPI score at baseline, the median PFS was 12.5 months for the rituximab group and 17.4 months for the Vc-R group. The improved effect of Velcade in subjects with

good prognosis is statistically significant (p=0.031). The difference between treatments is still statistically significant (p=0.013) for subjects with a high FLIPI score at baseline, for whom the median PFS was 7.9 months for the rituximab group and 11.4 months for the Vc-R group (HR: 0.707; 95% CI: 0.536, 0.932). These subjects show a worse response to rituximab alone than subjects with low or intermediate FLIPI score. Whereas, for subjects with an intermediate FLIPI score at baseline, the median PFS was 12.3 months for the rituximab group and 11.6 months for the Vc-R group (HR: 1.075; 95% CI: 0.787, 1.469).

-Last anti-lymphoma therapy prior study: for subjects who received their last anti-lymphoma therapy >1 year prior to the study, the median PFS was 12.5 months for the rituximab group and 16.8 months for the Vc-R group. The improved effect of Velcade in subjects who received their last anti-lymphoma therapy >1 year is statistically significant (p=0.022).

-The improved effect of Velcade in subjects with poor prognostic factors such as Ann Arbor Stage IV is statistically significant (p=0.030). Thus, patients with more severe condition, benefitted most from the combination Velcade plus rituximab

-A positive treatment effect (HRs <1) was observed in both subgroups of high and no-high tumor burden subjects receiving Vc-R, but the effect reached a statistically significance (p=0.019) only in subjects with a high tumor burden. In terms of absolute better response, subjects with no high tumor burden show a better response.

Exploratory endpoints

The EORTC QLQ-C30 questionnaire on quality of life was administered at Screening, on Day 1 of each cycle, at the End-of-Treatment Visit and each Follow-up Visit to evaluate Patient-Reported Outcomes Analyses (PROs) on 5 functional scales, 1 global health and QoL scale, 3 symptom scales, and 6 single items over the past week. As expected, the number of subjects providing responses decreased over time from 668 at baseline, to 582 at end of treatment, to 44 at end of data collection. PRO data were collected until disease progression.

Results from the Global Health Status (EORTC QLQ-C30) questionnaire showed that both treatment groups showed improvements in compared to baseline. The rituximab group showed statistically significant improvements from baseline beginning at Week 5 continuing through Week 120. The Vc-R group showed statistically significant improvements from baseline beginning at the end of treatment (Week 30) continuing through Week 120. Statistically significant differences between the groups were observed only at 3 timepoints during treatment. These small transient differences favoured rituximab

Clinical studies in special populations

The Phase III study LYM-3001 did not aim to assess efficacy in special population.

As regard renal or hepatic impaired patients, normal and mild impaired patients were enrolled in the study as per inclusion criteria:

The number of patients with moderate to severe renal and hepatic impairments was low.

In the rituximab arm, no patient had ≤30 mL/min baseline creatinine clearance (i.e. severe renal impairment); in the Vc-R arm, 1 patient had a baseline creatinine clearance ≤30 mL/min.

In the rituximab arm 16 patients had at baseline ALT or AST ≥1.5 × ULN; in the Vc-R arm 20 patients had ALT or AST ≥1.5 × ULN.

As regard the elderly population, patients > 65 years enrolled in the study were 25% of the overall population.

Since a class waiver for the treatment of paediatric patients in the follicular lymphoma exists, no subjects under 19 years entered the study.

Analysis performed across trials (pooled analyses AND meta-analysis)

NA

Supportive study(ies)

The supportive Phase II study **M34103-061** was a randomized, multicenter, 2-arm, non-comparative, open label, 2-stage clinical study of combination therapy of VELCADE and rituximab in subjects who have relapsed or refractory indolent B-cell lymphoma (CD20+), including follicular lymphoma (FL) or marginal zone lymphoma (MZL). The broad goal of this study was to determine a dosing regimen for subsequent phase 3 development.

Adult patients with NHL (grade 1,2, and 3) or MZL (extranodal, nodal, and splenic) who had experienced progressive disease (PD) following prior therapy were eligible to participate in the study. There was no limit to the number of prior therapies a patient had received prior to enrolling in the study, but if a prior regimen included rituximab, patients were to have responded and the TTP from the first dose of rituximab was to have been at least 4 months. Patients previously treated with VELCADE were excluded.

Patients were randomly assigned in a 1:1 ratio to one of the following treatment arms:

Arm A: VELCADE 1.3 mg/m2 twice weekly (BIW) on Days 1, 4, 8, and 11 of a 21-day cycle in combination with 4 doses of rituximab 375 mg/m2 administered on Days 1, 8, and 15 of Cycle 1, and on Day 1 of Cycle 2. The VELCADE dosing regimen was to continue for 5 cycles (approximately 15 weeks = 20 doses i.e. 26 mg/m2 in 15 weeks).

Arm B: VELCADE 1.6 mg/m2 weekly (QW) on Days 1, 8, 15, and 22 of a 35-day cycle in combination with 4 doses of rituximab 375 mg/m2 on Days 1, 8, 15, and 22 of Cycle 1. The VELCADE dosing regimen was to continue for 3 cycles (approximately 15 weeks = 12 doses i.e. 19.2 mg/m2 in 15 weeks).

Figure 9-1 Timing of Dosing and Disease Evaluations

		Screening	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	30-Day Follow-up
Arm A	Dosing		V V V V R R R	V V V V R	V V V V	V V V V	V V V V	
	Disease Eval	√			√			√
Arm B		Screening	Cycle 1		Cycle 2		Cycle 3	30-Day Follow-up
	Dosing		V V V V R R R R		V V V V		V V V V	
	Disease Eval	√			√			√

Disease Eval = disease evaluation, R = rituximab infusion, V = VELCADE administration

The primary objective of this study was to determine the response rate (CR/CRu/PR) to VELCADE in combination with rituximab, according to the International Workshop Response Criteria (IWRC) for Non-Hodgkin's Lymphoma.

The secondary objectives of this study were the response rate (CR/CRu/PR) to VELCADE in combination with rituximab through the time of the first disease response evaluation, the overall CR

rate (CR/CRu), TTP, Duration of response (DR), time to first response, safety and tolerability. Additional endpoints included OS, PFS, and change from baseline in lesion measurement and KPS.

This study was not designed or powered to demonstrate differences between the 2 treatment groups, but rather focuses on the estimation of response rates within treatment groups in order to determine if the BIW arm, the QW arm, or both have sufficient effectiveness to warrant further clinical study.

Each treatment arm was to be evaluated independently. The sample size for each treatment arm was derived using Simon's minimax 2-stage design. The hypotheses were H0: $p \leq p0$ versus H1: $p \geq p1$, where p0 and p1 were response rates such that the test regimen does not or does merit further testing at given levels of statistical significance (α) and power (1-β). Rejection of H1 was possible at stage 1, but acceptance could only occur at stage 2. Rejection of H0 (or H1) meant that further (or no further) study should be carried out. In this clinical study, p0 and p1 were chosen to be 35% and 55%, respectively, for each treatment arm. The significance level, $\alpha = 0.10$, and type II error, $\beta = 0.20$, were used. Under the 2-stage design and hypotheses as described above, the concept of the 2-stage design yielded a sample size of 29 subjects, which satisfied the error constraints:

Stage 1: 6/17 and Stage 2: 13/29.

Therefore, the total number of evaluable subjects required was 58, 29 in each treatment arm.

It was estimated that a total of 66 patients would need to be enrolled to reach the aforementioned numbers of evaluable patients.

Safety evaluations were to be based on the incidence, intensity and type of AEs, clinically significant changes in the subject's vital signs, and clinical laboratory results. Safety variables were to be tabulated and presented for all subjects who receive any amount of study drug (VELCADE or rituximab), ie, the safety population.

The original protocol was finalized on 26 November 2003 and there were 2 protocol amendments (24 May 2004 and 30 November 2005). Among the purposes of the Amendments, are:

- To increase the target response rates at the first stage and final analyses. The response rate indicating that the regimen does not merit further study was increased from 30% to 35%, and the response rate indicating that the regimen does merit further study was increased from 50% to 55%.

- To broaden the eligibility criteria to include patients who had previously received rituximab, if they responded and their TTP from the first dose of rituximab was 4 months or longer.

A total of 81 patients were actually enrolled in the study and received at least 1 dose of study drug in 14 clinical sites in US.

Of the 81 patients dosed, 41 were enrolled in the BIW arm and were to receive up to 5 cycles of VELCADE at a dose of 1.3 mg/m2 BIW over 15 weeks and 40 were enrolled in the QW arm and were to receive up to 3 cycles of VELCADE at a dose of 1.6 mg/m2 QW over 15 weeks.

Patients were stratified according to Karnofsky performance status (<70 vs $\geq$70), LDH level ($\leq$ ULN vs > ULN), age ($\leq$60 vs >60), lymphoma subtype (follicular vs marginal zone) and prior rituximab therapy (no prior rituximab, TTP from first dose of rituximab < 6 months vs TTP from first dose of rituximab $\geq$ 6 months).

Baseline demographics and disease characteristics were similar in both arms. The median age opf the patients was above 60 years in both arms. About 80% of patients in both arms had ECOG PS=0.

Table below presents the baseline disease characteristics for each treatment arm. A majority (82%) of patients had Stage III or Stage IV disease at screening, with over 50% of patients having 4 or more

involved lymph node sites. A majority of patients did not have NHL symptoms. The majority of patients had follicular lymphoma with a higher rate in arm B (93%) than in arm A (80%).

The median time since initial diagnosis of disease to entry in this study was approximately 4 years (95% confidence intervals = 3.45, 5.62), with a range of ~4 months to ~26 years. In approximately one-third of patients, FLIPI scores were 3 or higher.

Table 10-7 Baseline Disease Characteristics (Treated Population)

	VELCADE 1.3 mg/m² biw N = 41	VELCADE 1.6 mg/m² qw N = 40
NHL Stage n (%)		
Stage I	2 (5)	1 (3)
Stage II	5 (12)	7 (18)
Stage III	16 (39)	12 (30)
Stage IV	18 (44)	20 (50)
Number of Involved Lymph Node Sites n (%)		
0	1 (2)	2 (5)
1	5 (12)	7 (18)
2	7 (17)	5 (13)
3	5 (12)	6 (15)
4	9 (22)	9 (23)
≥5	14 (34)	11 (28)
Number of Involved Extralymphatic Sites n (%)		
0	24 (59)	22 (55)
1	13 (32)	13 (33)
2	4 (10)	3 (8)
3	0	1 (3)
4	0	0
≥5	0	1 (3)
NHL Disease Symptoms n (%)		
No	31 (76)	32 (80)
Yes	10 (24)	8 (20)
Unexplained fever >38 °C in previous month	0	2 (5)
Recurring, drenching night sweats in previous month	2 (5)	5 (13)
Unexplained weight loss >10% body weight in previous 6 months	0	0
Others	8 (20)	3 (8)
Time Since Initial Diagnosis to First Dose (yrs)		
Mean (Std Dev)	5.50 (5.040)	7.04 (6.159)
Median	3.66	5.34
95% CI for Median	3.11, 5.14	3.33, 6.79
Minimum, Maximum	1.0, 26.1	0.3, 25.9
<6 months	0	1 (3)
≥6 months	41 (100)	39 (98)
FLIPI n (%)		
0-1	11 (29)	13 (33)
2	11 (29)	13 (33)
3	10 (26)	11 (28)
4-5	6 (16)	3 (8)
Missing	3	

Source: Section 14.1, Table 14.1.3.1T
biw = twice weekly dosing, CI = confidence interval, FLIPI = Follicular Lymphoma International Prognostic Index, NHL = non-Hodgkin's Lymphoma, qw = weekly dosing

Prior therapy

41 patients (100%) in the BIW arm and 39 patients (98%) in the QW arm received 1 or more prior lines of therapy. Thirty-two patients (78%) in the BIW arm and 35 patients (90%) in the QW arm received at least one prior line of therapy with rituximab as either a single agent or a component of

combination therapy, and 31 patients (76%) in the BIW arm and 24 patients (62%) received prior therapy with a rituximab-chemotherapy combination.

CHOP or CVP, with or without rituximab was a prior line of therapy in 33 patients (80%) in the BIW arm and 32 patients (82%) in the QW arm. Only 7 patients (2 in the BIW arm and 5 in the QW arm) received prior radioimmunotherapy.

Efficacy results

37/41 and 40/40 patients were evaluable for response in the BIW and QW arm, respectively.

Disease response was evaluated according to IWRC both by the investigator using local radiology interpretations, and by the sponsor using the results of the review by independent radiologists and a sponsor-derived algorithmic application of the IRWC. The sponsor assessment was considered to be the primary analysis.

Based on the sponsor assessment, disease response (CR/CRu/PR) occurred in 17 patients (46%) in the BIW arm and 15 patients (38%) in the QW arm. based on the. Overall, a slightly higher proportion of patients in the BIW arm had a disease response than those in the QW arm according to the sponsor assessment, but the 90% confidence intervals overlap broadly, indicating that these rates are similar.

Results from the investigator assessment followed a similar trend as the sponsor assessment, however, the investigator assessment tended to yield higher response rates overall than those from the sponsor assessment. Notably, based on the investigator assessment, 7 patients (19%) in the BIW arm and 6 patients (15%) in the QW arm achieved CR or CRu.

Table 11-2 Best Response to Treatment (Evaluable Population)

	Sponsor Assessment				Investigator Assessment			
	VELCADE 1.3 mg/m² biw N = 37		VELCADE 1.6 mg/m² qw N = 40		VELCADE 1.3 mg/m² biw N = 37		VELCADE 1.6 mg/m² qw N = 40	
Subjects with Best Response	n (%)	90% CI	n (%)	90% CI	n (%)	90% CI	n (%)	90% CI
CR/CRu/PR	17 (46)	(32, 61)	15 (38)	(25, 52)	21 (57)	(42, 71)	21 (53)	(38, 66)
CR + CRu	4 (11)	(4, 23)	1 (3)	(0, 11)	7 (19)	(9, 33)	6 (15)	(7, 27)
CR	3 (8)	(2, 20)	1 (3)	(0, 11)	4 (11)	(4, 23)	4 (10)	(3, 21)
CRu	1 (3)	(0, 12)	0		3 (8)	(2, 20)	2 (5)	(1, 15)
PR	13 (35)	(22, 50)	14 (35)	(23, 49)	14 (38)	(25, 53)	15 (38)	(25, 52)
SD	8 (22)	(11, 36)	17 (43)	(29, 57)	9 (24)	(13, 39)	13 (33)	(20, 47)
PD[a]	11 (30)	(18, 44)	7 (18)	(9, 30)	7 (19)	(9, 33)	5 (13)	(5, 25)
No Post-Baseline Assessment	1 (3)	(0, 12)	1 (3)	(0, 11)	0		1 (3)	(0, 11)

Source: Section 14.2, Table 14.2.1.1AE

biw = twice weekly dosing, CI = confidence interval, CR = complete response, CRu = complete response unconfirmed, PD = progressive disease, PR = partial response, qw = weekly dosing, SD = stable disease

a Subjects whose first post-baseline response assessment is PD.

According to the sponsor assessment, of the 29 patients in the BIW arm who had prior rituximab treatment, 13 (45%) had a response (ie, CR/CRu/PR) and of the 35 patients in the QW arm who had prior rituximab treatment, 11 (31%) had a response. Of the 8 patients in the BIW arm who did not receive prior rituximab treatment, 4 (50%) had a response, and of the 5 patients in the QW arm who did not receive prior rituximab treatment, 4 (80%) had a response. Per the investigator assessment, of the 29 patients in the BIW arm who had prior rituximab treatment, 15 (52%) had a response, and of the 35 patients in the QW arm who had prior rituximab, 18 (51%) had a response. Of the 8 patients in the BIW who did not receive prior rituximab, 6 (75%) had a response, and of the 5 patients in the QW arm who did not receive prior rituximab treatment, 3 had a response (60%).

Table 11-9 Best Response by Prior Rituximab Use (Evaluable Population)

	Sponsor Assessment				Investigator assessment			
	VELCADE 1.3 mg/m² biw		VELCADE 1.6 mg/m² qw		VELCADE 1.3 mg/m² biw		VELCADE 1.6 mg/m² qw	
	N (%)	90% CI	N (%)	90% CI	N (%)	90% CI	N (%)	90% CI
Patients who Received Prior Rituximab								
N	29	(29, 62)	35	(19, 47)	29		35	
CR/CRu/PR	13 (45)	(3, 25)	11 (31)		15 (52)	(35, 68)	18 (51)	(36, 66)
CR + CRu	3 (10)	(3, 25)	0		4 (14)	(5, 29)	5 (14)	(6, 28)
CR	3 (10)		0		3 (10)	(3, 25)	3 (9)	(2, 21)
CRu	0	(20, 51)	0	(19, 47)	1 (3)	(0, 15)	2 (6)	(1, 17)
PR	10 (34)	(12, 41)	11 (31)	(34, 64)	11 (38)	(23, 55)	13 (37)	(24, 52)
SD	7 (24)	(15, 44)	17 (49)	(8, 31)	7 (24)	(12, 41)	12 (34)	(21, 50)
PD[a]	8 (28)	(0, 15)	6 (17)	(0, 13)	7 (24)	(12, 41)	4 (11)	(4, 24)
No Post-Baseline Assessment	1 (3)	(29, 62)	1(3)	(19, 47)	0		1 (3)	(0, 13)
Patients who did not Receive Prior Rituximab								
N	8		5		8		5	
CR/CRu/PR	4 (50)	(19, 81)	4 (80)	(34, 99)	6 (75)	(40, 95)	3 (60)	(19, 92)
CR + CRu	1 (13)	(1, 47)	1 (20)	(1, 66)	3 (38)	(11, 71)	1 (20)	(1, 66)
CR	0		1 (20)	(1, 66)	1 (13)	(1, 47)	1 (20)	(1, 66)
CRu	1 (13)	(1, 47)	0		2 (25)	(5, 60)	0	
PR	3 (38)	(11, 71)	3 (60)	(19, 92)	3 (38)	(11, 71)	2 (40)	(8, 81)
SD	1 (13)	(1, 47)	0		2 (25)	(5, 60)	1 (20)	(1, 66)
PD[a]	3 (38)	(11, 71)	1 (20)	(1, 66)	0		1 (20)	(1, 66)
No Post-Baseline Assessment	0		0		0		0	

Source: Section 14.2, Table 14.2.1.1DE

biw = twice weekly dosing, CR = complete response, CRu = complete response unconfirmed, PD = progressive disease, PR = partial response, qw = weekly dosing, SD = stable disease

Response assessments made after the first PD are not included in the analysis.

Prior rituximab use determined from collection of prior therapy information on CRF.

a Subjects whose first post-baseline response assessment is PD.

Based on the sponsor assessment, the mean time to first response was approximately 76 days (2.5 months) for patients in the BIW arm and approximately 79 days (2.6 months) for patients in the QW arm. Based on the investigator assessment, the mean time to first response was approximately 72 days (2.4 months) for patients in the BIW arm and 92 days (3.0 months) for patients in the QW arm. By both assessments, the time to response was similar.

Table 11-4 Time to Response (Evaluable Population)

	Sponsor Assessment		Investigator Assessment	
Time to First Response[a]	VELCADE 1.3 mg/m² biw N = 37	VELCADE 1.6 mg/m² qw N = 40	VELCADE 1.3 mg/m² biw N = 37	VELCADE 1.6 mg/m² qw N = 40
N	17	15	21	21
Mean (Std Dev)	75.8 (43.31)	78.9 (39.52)	71.9 (31.16)	92.0 (57.49)
Median	59.0	63.0	62.0	67.0
Minimum, Maximum	32, 206	52, 196	42, 169	45, 278

Source: Section 14.2, Table 14.2.4E

biw = twice weekly dosing, qw = weekly dosing, Std Dev = standard deviation

a Duration in days from the date of first dose of study drug until date of first evidence of response (CR/CRu/PR). Only responders are included.

Duration of response based on the investigator assessment was similar to that seen with the sponsor assessment, with a median duration of response for all responding patients (CR/CRu/PR) of 255 days (8.4 months) in the BIW arm and 244 days (8.0 months) in the QW arm.

According to the sponsor assessment, the median TTP was 157 days (5.2 months) for patients in the BIW arm and 296 days (9.7 months) for patients in the QW arm. According to the investigator assessment the median TTP was 301 days (9.9 months) for patients in the BIW arm and 275 days (9.0 months) for patient in the QW arm. While the median TTP, as assessed by the sponsor, was longer in the QW arm than in the BIW arm, the confidence intervals around the medians overlap. In contrast the investigator assessment of TTP was essentially identical between the treatment arms. Therefore, the differences observed between the treatment arms in the median TTP based on the sponsor assessment do not reflect meaningful differences in overall TTP.

Table 11-7 Time to Progression (Treated Population)

	Sponsor Assessment		Investigator Assessment	
	VELCADE 1.3 mg/m² biw N = 41	VELCADE 1.6 mg/m² qw N = 40	VELCADE 1.3 mg/m² biw N = 41	VELCADE 1.6 mg/m² qw N = 40
Time to Progression/Relapse (days)				
Number of Events n (%)	17 (41)	18 (45)	17 (41)	23 (58)
Number of Censored Events n (%)	24 (59)	22 (55)	24 (59)	17 (43)
25th Percentile (95% CI)	59 (57, 119)	203 (66, 274)	98 (57, 279)	119 (108, 205)
Median (95% CI)	157 (70, NE)	296 (224, 483)	301 (126, NE)	275 (140, 468)
75th Percentile (95% CI)	NE (212, NE)	483 (303, NE)	NE (301, NE)	483 (303, NE)
Minimum, Maximum	0*, 518*	0*, 553*	0*, 518*	0*, 532*
Kaplan-Meier Estimates[a]				
6 Months	48.3% (n=11)	75.3% (n=20)	63.6% (n=15)	62.2% (n=21)
12 Months	38.7% (n=3)	35.2% (n=5)	29.7% (n=2)	36.7% (n=7)
Reason for Censor:				
Alternate Therapy	4 (17)	2 (9)	4 (17)	2 (12)
Death	1 (4)	1 (5)	1 (4)	1 (6)
Toxicity	1 (4)	0	2 (8)	0
Subject Decision	5 (21)	1 (5)	7 (29)	1 (6)
No PD Before Study Closure by Sponsor	6 (25)	9 (41)	8 (33)	11 (65)
No Post-Baseline Evaluation	2 (8)	0	2 (8)	0
PD by Investigator (no more scans performed)	5 (21)	8 (36)	0	0
Lost to Follow-up	0	1 (5)	0	2 (12)

Source: Section 14.2, Table 14.2.3.1T

biw = twice weekly dosing, CI = confidence interval, NE = not estimable, PD = progressive disease, qw = weekly dosing

Censored observations indicated as N*.

Subjects who do not have any post-baseline response assessment are censored at the first dose date for TTP analyses.

a Percent of event-free subjects (number of subjects at risk).

A review of the number of patients censored and the number of patients with events in the TTP analysis based on the sponsor assessment and investigator assessment was conducted.

A total of 13 patients were reported by the investigators to have PD and were censored in the sponsor assessment. In the majority of these cases (7 of 13), the sponsor assessment censored the patients on the same date as PD was reported by the investigators, and in all cases the reason for censoring was that no more tumour assessments were performed. In 4 of the 13 patients, the sponsor assessment censored the patients prior to the date of PD reported by the investigator, and in all cases the reason for censoring was that no more tumour assessments were performed. In 2 of the 13 patients, the sponsor assessment censored the patients after the date of PD reported by the investigator.

A total of 8 patients were censored in the analysis by the investigators and were reported by the sponsor assessment to have PD. In 3 of these 8 patients, the sponsor reported PD on the same date as the investigators censored these patients; reasons for censoring were that the sponsor ended the study before the patients had PD (2 patients) and that the patient decided to discontinue the study (1 patient). In 4 of these 8 patients, the sponsor reported PD prior to the date that the investigators censored the patients; reason for censoring were that the sponsor ended the study before the patients had PD (2 patients) and that the patient decided to discontinue the study (1 patient). Also, 1 patient had an additional tumour assessment by the investigator that was not included in the sponsor assessment. In 1 patient, the sponsor reported PD after the date that the investigator censored the patient; the reason for censoring was that the patient was lost to follow-up.

In the analysis of TTP using the sponsor assessment, patients without objective evidence of PD were censored. While this approach resulted in a different number of PD events compared to that using the investigator assessment, it ensured that PD was assessed uniformly among the investigative sites. This may have contributed to the difference in TTP in the BIW arm (5.2 months vs. 9.9 months) between the analyses; however, other factors may have also contributed to this difference.

The results of the PFS analyses, as per the sponsor assessment, were similar to those of the TTP analyses; 5.1 months for BIW and 9.9 months for QW .

Upon review of the study results, it is apparent that there are discrepancies between these two methods of determining response and progression. Response rate and complete response rate were higher in both treatment arms, when assessed by the investigators than by the sponsor.

Additional analyses have been performed in order to determine if these differences are primarily a result of differences in radiology interpretation between the independent reviewers and the investigative sites or differences in application of the IWRC between the sponsor, using a strict algorithm, and the investigators, or some combination of the two.

Table 11-8 Response Rates by Different Methods of Evaluation (Evaluable Population)

	VELCADE 1.3 mg/m² biw N = 37			VELCADE 1.6 mg/m² qw N = 40		
	Independent Review + Algorithm n (%)	Investigator Review + Algorithm n (%)	Investigator Assessment n (%)	Independent Review + Algorithm n (%)	Investigator Review + Algorithm n (%)	Investigator Assessment n (%)
CR/CRu/PR	17 (46)	21 (57)	21 (57)	15 (38)	17 (43)	21 (53)
SD	8 (22)	8 (22)	9 (24)	17 (43)	16 (40)	13 (33)
PD	11 (30)	8 (22)	7 (19)	7 (18)	5 (13)	5 (13)
No Post-Baseline Assessment	1 (3)	0	0	1 (3)	2 (5)	1 (3)

Source: Section 14.2, Table 14.2.1.1AE

biw = twice weekly dosing, CR = complete response, CRu = complete response unconfirmed, PD = progressive disease, PR = partial response, qw = weekly dosing, SD = stable disease

Note: Differences between shaded numbers within a treatment arm, in each row, are primarily due to differences between independent and local radiology interpretations. Differences between underlined numbers within a treatment arm, in each row, are primarily due to differences in application of the IWRC between the sponsor algorithm and the investigators.

In the BIW arm the differences observed between the sponsor and investigator assessment for both response rate and TTP were primarily a result of differences in selection and measurement of sites of disease by the independent radiologists and the investigators (or local radiologists). In the QW arm,

the differences observed between the sponsor and investigator assessment in response rate were a result both of differences in radiology interpretation and application of the IWRC.

Only 16 patients (39%) in the BIW arm completed VELCADE study treatment, whereas 32 patients (80%) in the QW arm completed VELCADE study treatment. Forty patients (98%) in the BIW arm and 38 patients (95%) in the QW arm completed rituximab study treatment.

Table 10-2 Patient Disposition: Treatment Completion Information

	VELCADE 1.3 mg/m² biw N = 41	VELCADE 1.6 mg/m² qw N = 40
Primary Reason for Termination of VELCADE Treatment		
Completion of Study Treatment	16 (39)	32 (80)
Progressive Disease	10 (24)	4 (10)
Unacceptable AE	5 (12)[a]	1 (3)
Initiation of Alternate Antineoplastic Therapy	1 (2)	0
Decision by the Patient or Investigator to Discontinue Treatment	9 (22)	2 (5)
Death	0	1 (3)
Primary Reason for Termination of Rituximab Treatment		
Completion of Study Treatment	40 (98)	38 (95)
Progressive Disease	1 (2)	1 (3)
Death	0	1 (3)

Source: Section 14.1, Table 14.1.1

AE = adverse events, biw = twice weekly dosing, qw = weekly dosing

a Patient 003-003 lists unacceptable AE as the reason for termination of VELCADE dosing. The database contains no link to an associated AE, however this subject is included in this table.

Both VELCADE regimens had predictable and manageable safety profiles; however the weekly regimen had a less severe adverse event profile and a lower rate of Grade 3-4 AEs (38% vs 64%). The most commonly reported Grade 3 or higher adverse events in the VELCADE 1.3 mg/m2 twice weekly and 1.6 mg/m2 once-weekly treatment groups, respectively, were in the system organ classes of Gastrointestinal Disorders (15% versus 18%), Blood and Lymphatic Disorders (17% versus 3%), and Nervous System Disorders (12% versus 8%).

In addition, the weekly treatment was more convenient to administer and delivered VELCADE at a higher relative dose intensity than the twice weekly treatment (a mean relative dose intensity of 89% and 71%, respectively). This indicates that VELCADE at the higher dose of 1.6 mg/m2 administered weekly was generally better tolerated than the lower dose of 1.3 mg/m2 administered twice weekly and had a similar efficacy. Therefore, the weekly VELCADE schedule in combination with rituximab was chosen for this Phase 3 study.

Biomarker Study from pivotal LYM-3001 study

Tumour samples for DNA and protein analysis, and a blood sample for DNA analysis were collected from all patients who consented and had samples available. These analyses were mandatory and patients were required to provide consent for this testing to participate in Study LYM-3001.

The objective of the study was to examine whether subjects with polymorphisms were responsive to treatment with Vc-R as this may be an alternative therapy for patients with limited treatment options in order to identify patients who would be predicted to be sensitive to the Vc-R combination drug treatment.

Exploratory Objectives:

The exploratory objective was to identify patient populations that were more or less likely to respond to bortezomib and rituximab (Vc-R) or rituximab alone through the evaluation of a defined set of biomarkers including:

- Performing association analyses of FCGR2A and FCGR3A polymorphisms (SNPs) with selected clinical study endpoints

- Performing association analyses of CD68, NF-κB (RELA/p65), PSMA5, and p27 protein expression levels with selected clinical study endpoints

- Performing association analyses of Notch-1 and Bcl-2 somatic mutations (single and in combination) with selected clinical study endpoints

- PSMB1, PSMB2, PSMB5, PSMB6, PSMB8, and PSMB9 polymorphisms (SNPs) with selected clinical study endpoints

- Performing combinations of biomarkers with selected clinical study endpoints.

Introduction

Prior studies of prognostic molecular markers for lymphoma and of specific response markers for bortezomib or rituximab allowed a specific series of candidate proteins and target gene polymorphisms and mutations to be specified in the protocol and investigated across the patient samples.

The biomarkers association that deemed to be most clinically appropriate was the **PSMB P11A heterozygote** in combination with **CD68 Low (0-50)** expression. Sub-populations of clinical interest are subjects with high tumour burden, prior rituximab and one or two prior lines of therapy

CD68 glycoprotein is expressed by macrophages and has been reported to be a prognostic marker for poor outcome in lymphoma (i.e. poor outcome of patients with low CD68) and is also associated with response to rituximab alone.

The chemical structure of bortezomib interacts with PSMB subunits 1, 2, and 5 and there is documented evidence of polymorphisms in these subunits as well as in PSMB6, 7, and 8. Polymorphisms within the subunits may affect the ability of the drug to bind effectively or may prevent autocatalytic processing of pro-sequences that could lead to variability in levels of proteasomes and/or response to bortezomib in individual patients. Correlation of these low-affinity polymorphisms has been associated with worse clinical response and progression-free survival (PFS) after rituximab therapy in studies of NHL.

Methods

Samples were collected from all subjects when available.

Biomarker evaluations were done on this population when biomarker data was generated for the clinical study endpoints.

The primary biomarker analysis was aimed at identification of differentially expressed proteins in the ITT population, mutations, or genotypes that were associated with clinical study endpoints.

Protein marker expression levels (CD68, NF-κB (P65), PSMA5, P27) were determined by immunohistochemistry (IHC).

For single-marker association analyses and pair-wise comparisons, a log rank test and Cox proportional hazard model was utilized for assessments of PFS, TTP, and OS between the treatment groups. Kaplan-Meier curves were utilized to estimate the distribution differences between groups in the time-to-event analyses. Comparison of the response rates between the treatment groups was conducted using the Fishers exact test. Single-marker association analyses were stratified by the covariates. including: FLIPI score (low [0 or 1 factor], intermediate [2 factors], high [≥3 factors]); prior rituximab therapy (yes, no); time since last dose of anti-lymphoma therapy (≤1 year, >1 year); region (United

States/Canada, European Union, Rest of World), age, sex, race, Ann Arbor stage (I, II, III, IV), Number of prior lines of therapy (1, 2 and more), and high tumor burden (yes, no).

For pair-wise comparison analysis, a simple exhaustive search method was used to ensure the optimal biomarker pair(s) was found. Specifically, biomarker pairs were formed by exhaustive combinations of two markers.

Subjects positive to both biomarkers were **356** (175 in Vc-R and 181 in R arms).

The demographics and baseline characteristics of subjects that have the biomarker pair (PSMB1 P11A and CD68 Low (0-50) were well balanced between treatment groups and between study groups as shown in Table below. As regard the race, white population in Vc-R positive biomarker pair was 88.6% vs 74.4% in the ITT population.

Table 5: Comparison of the Baseline Demographic Characteristics of the ITT Population With Biomarker Positive Cohort With the CD68/PSMB1 Pair

	ITT Population			Biomarker positive Population			P-values for ITT vs. Subset		
	Rituximab	Vc-R	Total	Rituximab	Vc-R	Total	Rituximab	Vc-R	Total
Age (years)									
N	339	336	675	181	175	356	0.7859	0.8933	0.7673
Mean (SD)	57.3 (12.01)	56.8 (11.12)	57.0 (11.57)	57.6 (11.55)	56.9 (10.64)	57.3 (11.10)			
Median	57	57	57	57	57	57			
Min, Max	21.0-84.0	24.0-83.0	21.0-84.0	22.0-82.0	31.0-79.0	22.0-82.0			
Age Group (years)									
≤65	252 (74.3)	255 (75.9)	507 (75.1)	133 (73.5)	133 (76.0)	266 (74.7)	0.8321	0.9786	0.8901
>65	87 (25.7)	81 (24.1)	168 (24.9)	48 (26.5)	42 (24.0)	90 (25.3)			
Sex									
Female	202 (59.6)	164 (48.8)	366 (54.2)	114 (63.0)	83 (47.4)	197 (55.3)	0.4499	0.7669	0.7325
Male	137 (40.4)	172 (51.2)	309 (45.8)	67 (37.0)	92 (52.6)	159 (44.7)			
Race									
Other	82 (24.2)	86 (25.6)	168 (24.9)	25 (13.8)	20 (11.4)	45 (12.6)	0.0053	0.0002	<0.0001
White	257 (75.8)	250 (74.4)	507 (75.1)	156 (86.2)	155 (88.6)	311 (87.4)			
Region									
Rest of World	182 (53.7)	183 (54.5)	365 (54.1)	81 (44.8)	78 (44.6)	159 (44.7)	0.0522	0.0338	0.0041
USA/Canada/Europe	157 (46.3)	153 (45.5)	310 (45.9)	100 (55.2)	97 (55.4)	197 (55.3)			
FLIPI									
High	140 (41.3)	139 (41.4)	279 (41.3)	77 (42.5)	70 (40.0)	147 (41.3)	0.9412	0.7801	0.9565
Intermediate	118 (34.8)	120 (35.7)	238 (35.3)	63 (34.8)	60 (34.3)	123 (34.6)			
Low	81 (23.9)	77 (22.9)	158 (23.4)	41 (22.7)	45 (25.7)	86 (24.2)			
Ann Arbor Stage									
I	21 (6.2)	18 (5.4)	39 (5.8)	12 (6.6)	10 (5.7)	22 (6.2)	0.9895	0.2116	0.6484
II	40 (11.8)	35 (10.4)	75 (11.1)	20 (11.0)	22 (12.6)	42 (11.8)			
III	134 (39.5)	115 (34.2)	249 (36.9)	73 (40.3)	44 (25.1)	117 (32.9)			
IV	144 (42.5)	168 (50.0)	312 (46.2)	76 (42.0)	99 (56.6)	175 (49.2)			
High Tumor Burden									
No	160 (47.2)	151 (44.9)	311 (46.1)	86 (47.5)	78 (44.6)	164 (46.1)	0.9452	0.9366	0.9984
Yes	179 (52.8)	185 (55.1)	364 (53.9)	95 (52.5)	97 (55.4)	192 (53.9)			
Follicular Lymphoma Grade									
Grade 1	168 (49.7)	179 (53.3)	347 (51.5)	79 (43.9)	89 (50.9)	168 (47.3)	0.207	0.6037	0.2046
Grade 2	170 (50.3)	157 (46.7)	327 (48.5)	101 (56.1)	86 (49.1)	187 (52.7)			
Prior Rituximab Therapy									
No	192 (56.6)	189 (56.3)	381 (56.4)	97 (53.6)	96 (54.9)	193 (54.2)	0.5055	0.7635	0.493
Yes	147 (43.4)	147 (43.8)	294 (43.6)	84 (46.4)	79 (45.1)	163 (45.8)			
Prior Lines of Therapy									
1	137 (40.4)	143 (42.6)	280 (41.5)	79 (43.6)	79 (45.1)	158 (44.4)	0.931	0.8052	0.6907
2	90 (26.5)	85 (25.3)	175 (25.9)	48 (26.5)	44 (25.1)	92 (25.8)			
3	53 (15.6)	55 (16.4)	108 (16.0)	28 (15.5)	28 (16.0)	56 (15.7)			
4	32 (9.4)	26 (7.7)	58 (8.6)	15 (8.3)	10 (5.7)	25 (7.0)			
5	12 (3.5)	12 (3.6)	24 (3.6)	6 (3.3)	9 (5.1)	15 (4.2)			
6+	15 (4.4)	15 (4.5)	30 (4.4)	5 (2.8)	5 (2.9)	10 (2.8)			
Time Since Last Lymphoma Treatment (year)									
GT1-EU	100 (29.5)	100 (29.8)	200 (29.6)	65 (35.9)	66 (37.7)	131 (36.8)	0.6203	0.2308	0.158
GT1-RW	68 (20.1)	69 (20.5)	137 (20.3)	31 (17.1)	26 (14.9)	57 (16.0)			
GT1-US	20 (5.9)	17 (5.1)	37 (5.5)	11 (6.1)	9 (5.1)	20 (5.6)			
LE1-EU	41 (12.1)	42 (12.5)	83 (12.3)	22 (12.2)	27 (15.4)	49 (13.8)			
LE1-RW	104 (30.7)	102 (30.4)	206 (30.5)	47 (26.0)	46 (26.3)	93 (26.1)			
LE1-US	6 (1.8)	6 (1.8)	12 (1.8)	5 (2.8)	1 (0.6)	6 (1.7)			

One hundred eighteen subjects (118, 33% of 356) were those in which the presence of the biomarker pair was associated to a PFS improvement of 7.5 months (82%) in Vc-R vs R arms. A trend for better OS (p=0.055, HR: 0.426 [0.174, 1.046] was also showed.

This means that 33% of patients who had a high PFS response expressed the biomarker-pair.

This pair was considered as the biomarker positive subgroup. The biomarker negative subgroup did not have this biomarker pair and has a different PSMB1 genotype and CD68 expression level (see table below).

Table 6: Comparison of Biomarker Positive Population With Biomarker Negative Population for PFS and OS

		Biomarker Positive (N=118)		Biomarker Negative (N=238)		Total (N=356)	
		Vc-R	Rituximab	Vc-R	Rituximab	Vc-R	Rituximab
PFS	N	57	61	118	120	175	181
	Median (months)	16.6	9.1	12.5	12.5	13.6	11.3
	95% CI	(0.26-0.639)		(0.759-1.425)		(0.621-1.032)	
	p-value	0.0001		0.8097		0.0855	
	HR	0.407		1.04		0.801	
		Vc-R	Rituximab	Vc-R	Rituximab	Vc-R	Rituximab
OS	N	57	61	118	120	175	181
	Median (months)	NA	NA	NA	NA	NA	NA
	95% CI	(0.174-1.046)		(0.617-1.658)		(0.527-1.239)	
	p-value	0.0550		0.9645		0.3270	
	HR	0.426		1.011		0.808	

Biomarker positive=PSMB P11A heterozygote and CD68 "Low" biomarker pair, Biomarker negative= all subjects without this pair, Vc-R=bortezomib+rituximab, PFS=progression free survival, OS=overall survival, CI=confidence interval, HR=hazard ratio

This group also had a significantly better overall response rate 73.7% for those treated with Vc-R compared to 48.3% with R alone (p=0.0077) Table 7, and a longer time to next treatment (p=0.0013) and duration of treatment free interval (p=0.0017).

Table 7: Comparison of Biomarker Positive Population With Biomarker Negative Population for ORR and CR

		Biomarker Positive (N=117)		Biomarker Negative (N=224)		Total (N=341)	
		Vc-R	Rituximab	Vc-R	Rituximab	Vc-R	Rituximab
ORR	N	57	60	111	113	168	173
	Total (%)	73.7	48.3	62.2	55.8	66.1	53.2
	p-value	0.0077		0.3448		0.0203	
		Vc-R	Rituximab	Vc-R	Rituximab	Vc-R	Rituximab
CR	N	57	60	111	113	168	173
	Total (%)	33.3	23.3	36.9	35.4	35.7	31.2
	p-value	0.3044		0.8895		0.4220	

Note: Not all patients had response data available.
Biomarker positive=PSMB P11A heterozygote and CD68 "Low" biomarker pair, Biomarker negative= all subjects without this pair, Vc-R=bortezomib+Rituximab, ORR=overall response rate, CR=complete response

Generally, subjects expressing the biomarker pair showed a comparable incidence of AEs, regardless the association with a PFS improvement of 7.5 months. Similar treatment exposure (in terms of mg of bortezomib or rituximab) was observed in the biomarker pair positive and biomarker pair "negative" populations.

5.4. Safety

Similar AE profiles were observed in the biomarker positive and biomarker negative populations as shown in Table 9.

Table 9: Treatment Emergent Adverse Events for ITT Population, Biomarker Positive Population and Biomarker Negative Population

	ITT Population			Biomarker Negative Population			Biomarker Positve Population		
	Rituximab N=339 N (%)	Vc-R N=334 N (%)	Total N=673 N (%)	Rituximab N=61 N (%)	Vc-R N=57 N (%)	Total N=118 N (%)	Rituximab N=120 N (%)	Vc-R N=118 N (%)	Total N=238 N (%)
Any adverse event	265 (78.2)	316 (94.6)	581 (86.3)	96 (80.0)	115 (97.5)	211 (88.7)	52 (85.2)	53 (93.0)	105 (89.0)
Related adverse events	156 (46.0)	290 (86.8)	446 (66.3)	44 (36.7)	103 (87.3)	147 (61.8)	37 (60.7)	48 (84.2)	85 (72.0)
Related adverse events – Rituximab	156 (46.0)	206 (61.7)	362 (53.8)	44 (36.7)	74 (62.7)	118 (49.6)	37 (60.7)	31 (54.4)	68 (57.6)
Related adverse events – bortezomib	-	276 (82.6)	276 (41.0)		98 (83.1)	98 (41.2)		46 (80.7)	46 (39.0)
Any serious adverse event	37 (10.9)	59 (17.7)	96 (14.3)	12 (10.0)	21 (17.8)	33 (13.9)	11 (18.0)	6 (10.5)	17 (14.4)
Any related serious adverse event	12 (3.5)	35 (10.5)	47 (7.0)	5 (4.2)	9 (7.6)	14 (5.9)	4 (6.6)	5 (8.8)	9 (7.6)
Related serious adverse events - Rituximab	12 (3.5)	24 (7.2)	36 (5.3)	5 (4.2)	6 (5.1)	11 (4.6)	4 (6.6)	2 (3.5)	6 (5.1)
Related serious adverse events - bortezomib	-	28 (8.4)	28 (4.2)	-	7 (5.9)	7 (2.9)	-	5 (8.8)	5 (4.2)
Grade 3 or 4 or 5 toxicity adverse events	70 (20.6)	152 (45.5)	222 (33.0)	19 (15.8)	47 (39.8)	66 (27.7)	17 (27.9)	20 (35.1)	37 (31.4)
Grade 3	52 (15.3)	115 (34.4)	167 (24.8)	14 (11.7)	38 (32.2)	52 (21.8)	11 (18.0)	15 (26.3)	26 (22.0)
Grade 4	15 (4.4)	29 (8.7)	44 (6.5)	4 (3.3)	6 (5.1)	10 (4.2)	4 (6.6)	5 (8.8)	9 (7.6)
Grade 5	3 (0.9)	8 (2.4)	11 (1.6)	1 (0.8)	3 (2.5)	4 (1.7)	2 (3.3)	-	2 (1.7)
Adverse events leading to withdrawal of treatment	5 (1.5)	19 (5.7)	24 (3.6)	2 (1.7)	6 (5.1)	8 (3.4)	1 (1.6)	2 (3.5)	3 (2.5)
Related adverse events leading to withdrawal of treatment	3 (0.9)	14 (4.2)	17 (2.5)	2 (1.7)	4 (3.4)	6 (2.5)	-	2 (3.5)	2 (1.7)
Bortezomib related adverse events leading to withdrawal of treatment	3 (0.9)	7 (2.1)	10 (1.5)	2 (1.7)	2 (1.7)	4 (1.7)	-	-	-
Rituximab related adverse events leading to withdrawal of treatment	-	10 (3.0)	10 (1.5)	-	4 (3.4)	4 (1.7)	-	2 (3.5)	2 (1.7)
Number of subjects who died due to adverse event	2 (0.6)	6 (1.8)	8 (1.2)	1 (0.8)	2 (1.7)	3 (1.3)	1 (1.6)	-	1 (0.8)

In Table 9 headings over column 4-6 and 7-9 are likely to be mixed up. In fact, 118 were subjects defined in the text as "positive" while 238 were the overall subjects defined as "negative".

PFS Stratified by Clinical Covariates

The 118 subjects treated with bortezomib + rituximab maintained longer PFS when biomarker positive and stratified by any FLIPI score, by tumor burden, by Ann Arbor score, by age, by region, by sex, and by race.

In patients with higher risk and poor prognosis, e.g. high tumor burden, medium or high FLIPI, older than 65, or with prior rituximab treatment, greater PFS improvement were observed in patients when biomarker positive comparing to when biomarker negative. Longer PFS was maintained regardless of time from last treatment or number of previous treatments by prior rituximab or by number of rituximab treatments less than or equal to 2.

Table 11. Progression Free Survival [Stratification by Clinical Covariates] for CD68 Low [0-50]/PSMB1 P11A Heterozygote

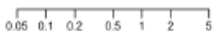
Biomarker	Subgroup	HR (95% CI)	HR (log scale)	R N	R Median	VC-R N	VC-R Median
Overall	FLIPILM: Overall	0.80 (0.62, 1.03)		181	345	175	414
	FLIPILM: High	0.69 (0.47, 1.01)		77	275	70	347
	FLIPILM: Low+Int	0.88 (0.62, 1.23)		104	414	105	487
Positive	FLIPILM: Overall	0.41 (0.26, 0.64)		61	277	57	506
	FLIPILM: High	0.51 (0.26, 1.01)		26	275	20	367
	FLIPILM: Low+Int	0.40 (0.22, 0.73)		35	288	37	569
Negative	FLIPILM: Overall	1.04 (0.76, 1.43)		120	381	118	380
	FLIPILM: High	0.82 (0.52, 1.30)		51	273	50	344
	FLIPILM: Low+Int	1.18 (0.77, 1.81)		69	492	68	456
Overall	HITUBD: Overall	0.80 (0.62, 1.03)		181	345	175	414
	HITUBD: NO	0.78 (0.51, 1.18)		86	492	78	624
	HITUBD: YES	0.77 (0.56, 1.06)		95	275	97	331
Positive	HITUBD: Overall	0.41 (0.26, 0.64)		61	277	57	506
	HITUBD: NO	0.28 (0.13, 0.58)		28	326	27	576
	HITUBD: YES	0.53 (0.29, 0.96)		33	253	30	366
Negative	HITUBD: Overall	1.04 (0.76, 1.43)		120	381	118	380
	HITUBD: NO	1.09 (0.63, 1.86)		58	763	51	624
	HITUBD: YES	0.88 (0.60, 1.30)		62	280	67	280
Overall	TLAST: Overall	0.80 (0.62, 1.03)		181	345	175	414
	TLAST: ≤ 1 year	0.82 (0.56, 1.20)		73	253	69	346
	TLAST: > 1 year	0.78 (0.55, 1.10)		108	381	106	519
Positive	TLAST: Overall	0.41 (0.26, 0.64)		61	277	57	506
	TLAST: ≤ 1 year	0.47 (0.25, 0.91)		28	239	23	351
	TLAST: > 1 year	0.38 (0.20, 0.70)		33	322	34	576
Negative	TLAST: Overall	1.04 (0.76, 1.43)		120	381	118	380
	TLAST: ≤ 1 year	1.06 (0.66, 1.70)		45	273	46	280
	TLAST: > 1 year	1.00 (0.65, 1.53)		75	427	72	485
Overall	REGION2: Overall	0.80 (0.62, 1.03)		181	345	175	414
	REGION2: REST OF WORLD	0.73 (0.51, 1.05)		81	277	78	396
	REGION2: USA/CAN/EU	0.89 (0.62, 1.28)		100	375	97	429
Positive	REGION2: Overall	0.41 (0.26, 0.64)		61	277	57	506
	REGION2: REST OF WORLD	0.39 (0.21, 0.71)		31	253	30	506
	REGION2: USA/CAN/EU	0.47 (0.24, 0.92)		30	326	27	431
Negative	REGION2: Overall	1.04 (0.76, 1.43)		120	381	118	380
	REGION2: REST OF WORLD	1.00 (0.63, 1.60)		50	281	48	351
	REGION2: USA/CAN/EU	1.09 (0.71, 1.68)		70	486	70	417
Overall	AGEGRP: Overall	0.80 (0.62, 1.03)		181	345	175	414
	AGEGRP: ≤65	0.66 (0.49, 0.89)		133	287	133	431
	AGEGRP: >65	1.43 (0.87, 2.35)		48	427	42	350
Positive	AGEGRP: Overall	0.41 (0.26, 0.64)		61	277	57	506
	AGEGRP: ≤65	0.41 (0.25, 0.68)		47	277	47	506
	AGEGRP: >65	0.42 (0.15, 1.15)		14	349	10	489.5
Negative	AGEGRP: Overall	1.04 (0.76, 1.43)		120	381	118	380

Table 11. Progression Free Survival [Stratification by Clinical Covariates] for CD68 Low [0-50]/PSMB1 P11A Heterozygote

Biomarker	Subgroup	HR (95% CI)	HR (log scale)	R N	R Median	VC-R N	VC-R Median
	AGEGRP: ≤65	0.80 (0.55, 1.16)		86	346	86	429
	AGEGRP: >65	2.22 (1.21, 4.08)		34	501	32	280
Overall	SEX: Overall	0.80 (0.62, 1.03)		181	345	175	414
	SEX: FEMALE	0.85 (0.59, 1.21)		114	381	83	396
	SEX: MALE	0.63 (0.43, 0.92)		67	280	92	417
Positive	SEX: Overall	0.41 (0.26, 0.64)		61	277	57	506
	SEX: FEMALE	0.40 (0.22, 0.72)		40	288	36	506
	SEX: MALE	0.42 (0.21, 0.85)		21	220	21	431
Negative	SEX: Overall	1.04 (0.76, 1.43)		120	381	118	380
	SEX: FEMALE	1.23 (0.78, 1.95)		74	486	47	346
	SEX: MALE	0.76 (0.48, 1.20)		46	282	71	414
Overall	RACEGRP2: Overall	0.80 (0.62, 1.03)		181	345	175	414
	RACEGRP2: OTHER	0.91 (0.45, 1.82)		25	220	20	346
	RACEGRP2: WHITE	0.80 (0.61, 1.06)		156	348	155	426
Positive	RACEGRP2: Overall	0.41 (0.26, 0.64)		61	277	57	506
	RACEGRP2: OTHER	0.39 (0.11, 1.38)		8	141	7	351
	RACEGRP2: WHITE	0.41 (0.26, 0.67)		53	279	50	519
Negative	RACEGRP2: Overall	1.04 (0.76, 1.43)		120	381	118	380
	RACEGRP2: OTHER	1.24 (0.53, 2.89)		17	281	13	155
	RACEGRP2: WHITE	1.04 (0.74, 1.47)		103	417	105	414
Overall	ANNARBOR: Overall	0.80 (0.62, 1.03)		181	345	175	414
	ANNARBOR: ≤II	0.94 (0.45, 1.95)		32	492	32	771
	ANNARBOR: ≥III	0.77 (0.58, 1.01)		149	283	143	366
Positive	ANNARBOR: Overall	0.41 (0.26, 0.64)		61	277	57	506
	ANNARBOR: ≤II	0.32 (0.09, 1.24)		10	326	11	-
	ANNARBOR: ≥III	0.42 (0.26, 0.68)		51	275	46	396
Negative	ANNARBOR: Overall	1.04 (0.76, 1.43)		120	381	118	380
	ANNARBOR: ≤II	1.40 (0.58, 3.39)		22	-	21	491
	ANNARBOR: ≥III	0.97 (0.69, 1.36)		98	348	97	351
Overall	PRIORTX: Overall	0.80 (0.62, 1.03)		181	345	175	414
	PRIORTX: >1	0.87 (0.63, 1.20)		102	338	96	351
	PRIORTX: 1	0.74 (0.49, 1.10)		79	351	79	529
Positive	PRIORTX: Overall	0.41 (0.26, 0.64)		61	277	57	506
	PRIORTX: >1	0.43 (0.23, 0.81)		34	279	26	475
	PRIORTX: 1	0.37 (0.19, 0.72)		27	277	31	506
Negative	PRIORTX: Overall	1.04 (0.76, 1.43)		120	381	118	380
	PRIORTX: >1	1.10 (0.74, 1.64)		68	348	70	346
	PRIORTX: 1	0.94 (0.56, 1.60)		52	424	48	529
Overall	PRITUX: Overall	0.80 (0.62, 1.03)		181	345	175	414
	PRITUX: NO	0.70 (0.49, 0.98)		97	348	95	485
	PRITUX: YES	0.95 (0.66, 1.39)		84	338	80	324
Positive	PRITUX: Overall	0.41 (0.26, 0.64)		61	277	57	506
	PRITUX: NO	0.34 (0.19, 0.61)		33	275	35	553
	PRITUX: YES	0.47 (0.22, 0.99)		28	326	22	431
Negative	PRITUX: Overall	1.04 (0.76, 1.43)		120	381	118	380
	PRITUX: NO	0.96 (0.62, 1.50)		64	424	60	483
	PRITUX: YES	1.15 (0.73, 1.80)		56	347	58	280
Overall	RPRLINES: Overall	0.80 (0.62, 1.03)		181	345	175	414

Table 11. Progression Free Survival [Stratification by Clinical Covariates] for CD68 Low [0-50]/PSMB1 P11A Heterozygote

Biomarker	Subgroup	HR (95% CI)	HR (log scale)	R N	R Median	VC-R N	VC-R Median
	RPRLINES: ≤2	0.81 (0.62, 1.05)		173	347	170	417
	RPRLINES: >2	0.82 (0.21, 3.13)		8	231.5	5	315.5
Positive	RPRLINES: Overall	0.41 (0.26, 0.64)		61	277	57	506
	RPRLINES: ≤2	0.40 (0.26, 0.64)		58	275	56	431
	RPRLINES: >2	0.00 (0.00, Inf)		3	326	1	519
Negative	RPRLINES: Overall	1.04 (0.76, 1.43)		120	381	118	380
	RPRLINES: ≤2	1.07 (0.77, 1.47)		115	414	114	414
	RPRLINES: >2	0.58 (0.12, 2.72)		5	134	4	280



PFS Benefit in Biomarker Positive Subjects, by Each Biomarker

The MAH determined the individual contributions of each biomarker to the PFS benefit found in subjects with both biomarkers (PSMB1 P11A heterozygote and CD68 Low).

Within the biomarker pair positive population, subjects with only **PSMB1 P11A (C/G)** had 16.6 months median PFS when treated with Vc-R compared to 9.5 months median PFS when treated with R alone, showing a 7.1 month PFS advantage when the combination Vc-R was used.

This benefit was not seen in biomarker "negative" (not associated to a PFS improvement of 7.5 months) subjects with Vc-R.

Subjects with **higher CD68** expression do better on rituximab alone (16.2 months median PFS) than those with lower CD68 expression (9.3 months median PFS).

However, subjects with **low CD68** expression (0-50) had significantly longer PFS (14 months median) when treated with the combination Vc-R than those with low CD68 treated with rituximab alone (9.3 months median); this is a 4.7 month PFS advantage (HR=0.64 (95% CI: 0.475-0.864).

Table 12. Progression Free Survival [CD68 Low [0-50] Compared to PSMB1 P11A Heterozygote]

Biomarker	PFS Vc-R Median Months	PFS R Median Months	PFS Vc-R vs. R Median Months	PFS Improvement	% PFS Improvement	Vc-R vs R	PFS Logrank P-value	PFS HR (95% CI)	Total	Total Vc-R	Total R
CD68 Positive Follicular 0-50 Vc-R vs R	14	9.3	14 vs 9.3	4.7	51.10%	123 vs 142	0.0032	0.64 (0.475-0.864)	265	123	142
CD68 Positive Follicular >50 Vc-R vs R	11.4	16.2	11.4 vs 16.2	-4.8	-29.70%	52 vs 39	0.1069	1.535 (0.908-2.596)	91	52	39
PSMB1/P11A C/G Vc-R vs R	16.6	9.5	16.6 vs 9.5	7.2	75.70%	74 vs 79	0.0164	0.623 (0.421-0.92)	153	74	79
PSMB1/P11A [C/C G/G] Vc-R vs R	12.5	12.3	12.5 vs 12.3	0.2	1.30%	101 vs 102	0.7212	0.941 (0.672-1.319)	203	101	102

Vc-R=bortezomib+rituximab, R=rituximab

Subjects treated with bortezomib + rituximab maintained longer PFS when positive for **CD68** low (0-50) and stratified by any FLIPI score, by tumor burden, by Ann Arbor score, by age, by region, by sex, and by race. When CD68 high, they did better on rituximab alone as expected.

Subjects treated with bortezomib + rituximab maintained longer PFS when positive for **PSMB P11A** heterozygote and stratified by any FLIPI score, by tumor burden, by Ann Arbor score, by age, by region, by sex, and by race.

When **CD68 high**, they did better on rituximab alone as expected.

Results

The glycoprotein CD68 expressed by macrophages associated with poor prognosis in follicular lymphoma (low CD68), and the drug (bortezomib and rituximab) target gene PSMB1 (C/G heterozygote highly expressed), were considered as candidates for prognostic factors for follicular lymphoma and for response to bortezomib or rituximab.

Analysis were performed on the single biomarkers or on the biomarker pair. Subjects positive to both biomarkers were 356 (175 in Vc-R and 181 in R arms). The endpoints evaluated were PFS, TTP and OS between the treatment groups.

As regard the race, white population in Vc-R positive biomarker pair was 88.6% vs 74.4% in the ITT population.

Among the biomarker pair positive population (53% of the overall randomised population=670), 118 (33%) subjects showed a very high PFS improvement of 7.5 months =82% in Vc-R vs R arms (the correspondent PFS median value resulted from the clinical analysis was of 1.8 months= 16.3%), while the remaining 238 (76%) showed a PFS of 12.5 months in both arms (no improvement was in Vc-R arm). The 118 subjects had also a trend for OS benefit, a significantly better overall response rate, and a significantly longer time to next treatment.

When the biomarker association analyses were stratified by the covariates, the longer PFS was conserved by any FLIPI score, by tumor burden, by Ann Arbor score, by age, by region, by sex, and by race. In patients with higher risk and poor prognosis, e.g. high tumor burden, medium or high FLIPI, older than 65, or with prior rituximab treatment, greater PFS improvement were observed in patients when biomarker positive comparing to when biomarker negative.

The MAH determined the individual contributions of each biomarker to the PFS benefit found in subjects with both biomarkers (PSMB1 P11A heterozygote and CD68 Low).

Within the biomarker pair positive population, subjects with only PSMB1 P11A had the same median PFS when treated with Vc-R of 16.6 months (significantly higher than R) that correspond to the median PFS level obtained when biomarkers are together.

Subjects with higher CD68 expression do better on rituximab alone (16.2 months median PFS) than those with lower CD68 expression (9.3 months median PFS).

However, subjects with low CD68 expression (0-50) had significantly longer PFS (14 months median) when treated with the combination Vc-R than those with low CD68 treated with rituximab alone (9.3 months median); this is a 4.7 month PFS advantage (HR=0.64 (95% CI: 0.475-0.864).

As regard the safety, subjects expressing the biomarker pair showed a comparable incidence of AEs, regardless the association with a PFS improvement of 7.5 months. Similar treatment exposure (in terms of mg of bortezomib or rituximab) was observed in the biomarker pair positive and biomarker pair "negative" populations.

Discussion on supportive studies

Phase II Study **M34103-061** evaluated 2 different schedules of Velcade in combination with rituximab, with the aim of selecting the most appropriate regimen to be tested in the phase 3 trial. The vast majority of the patients enrolled in the trial had a follicular B-cell Non-Hodgkin Lymphoma subtype.

The planned duration of treatment was 15 weeks in both arms, but the planned overall exposition to Velcade is different between the two arms being higher (26 vs 19.2 mg/m2) in the BIW arm.

The duration of rituximab in this trial was limited to four administrations and therefore different to what was subsequently done in the phase 3 trial.

Disease response was evaluated both by the investigators and by the sponsor. The sponsor assessment used a the review by independent radiologists and a "sponsor-derived algorithmic application of the IWRC". In the CSR, it is reported that the investigator assessment provides an evaluation more consistent with standard medical practice; nevertheless the sponsor assessment was considered to be the primary analysis. A definition of the "sponsor-derived algorithmic application of the IWRC" was not provided in the CSR.

The response rate was similar in both treatment arms; based on the sponsor assessment a response was observed in 46% of patients in the BIW arm and in 38% of patients in the QW arm had a best response of CR/CRu/PR. Of these, 11% in the BIW arm and 3% in the QW arm had CR/CRu.

The activity was higher in rituximab naïve patients.

Several inconsistencies were observed between the sponsor and investigator assessment and this limits the interpretation of efficacy data. TTP in the two arms was similar as per investigator assessment (9.0 vs 9.9 in BIW and QW, respectively), while a relevant difference was reported as per the sponsor assessment (5.2 vs 9.7 in BIW and QW, respectively): more than 50% of patients were censored and the relevance of this observation is limited.

The completion of VELCADE study treatment was higher in the QW arm than in the BIW arm (80% vs 39%) and even the tolerability was better in the QW arm, with a relevant lower rate of Grade 3-4 AEs (38% vs 64%). The mean relative dose intensity was higher for the weekly administration.

In conclusion, some activity was observed in this pretreated population and, although the inconsistencies between investigator and sponsor assessment are no fully clear, the choice of the QW schedule for the phase 3 trial is endorsed.

Preliminary results from **biomarker study** from pivotal LYM-3001 study confirm that a low expression of CD68 glycoprotein is a prognostic marker for poor outcome in lymphoma while a positive polymorphisms in PSMB1 P11A gene correlates with a better Velcade clinical response. Velcade showed a better clinical response in patients with low CD68 expression i.e. when lymphoma is more severe.

Results showed that the expression of both biomarkers is 50% of the follicular NHL population; only 33% (low but not negligible) of this showed a much better clinical response in Vc-R arm vs R arm (PFS improvement of 7.5 months =82% in Vc-R), but no correlation with the biomarkers expression and parameters such as sex, gender, race can be done.

The investigation into genomic biomarkers for diagnosis (predictive markers of safety, efficacy or metabolic response to treatment) or prognosis (outcome of the disease) although explorative, is acknowledged since it gives an insight in the mechanism of action of the medicinal product but also in patient selection and the treatment adverse events. This could play a role in the risk minimisation measures identifying patients susceptible to develop ADRs.

Discussion on clinical efficacy

The discussion focuses on the pivotal trial LYM-3001.

Design and conduct of clinical studies

The multicenter Phase 3 Study LYM-3001 (29 Countries involved) study was correctly designed to show superiority, in terms of PFS as primary endpoint, of Vc-R treatment vs single agent R for the initially claimed indication: Velcade in combination with rituximab for the treatment of patients with relapsed follicular non-Hodgkin lymphoma.

Assuming an expected median PFS improvement of 33%, with a 5% dropout, the calculated sample size was reached enrolling 676 patients (336 in Vc-R arm and 340 in single-agent rituximab arm). A total of 514 events would have provided 90% power (alpha=0.05, 2-sided) to detect the hypothesised effect.

At the time of the study design presentation, the EMA scientific advice (issued in 2005) requested by the MAH, agreed on the MAH proposals in terms of choice of rituximab as comparator, PFS as primary endpoint and statistic evaluation (e.g. two planned interim analyses).

However, changes applied by the MAH to the protocol following the analysis of events reached in the second interim analysis, significantly altered the initial robustness of the study.

Although the number of patients to be enrolled in the study was reached, due to the high percentage of censored patients or lost to follow-up at the second interim analysis cut-off, the IDCM concluded that the protocol-specified 514 PFS events would be unachievable in any reasonable timeframe and the study was prematurely closed. It appears that the same IDMC were aware of the accumulating unblinded study data through interim analyses. In particular it appears that the decision to terminate the study was made in light of knowledge of results from the second interim analysis. If the decision to stop the study was based on any interim information the Type I error of the study is not controlled.

The impossibility to reach the scheduled number of PFS events appears to be quite objective and not influenced by the unblinded results from the second interim analysis.

The enrolled patient population encompasses a high percentage of rituximab-naïve patients (54%) and minor percentages of patients with one or more prior rituximab therapies. In EU current clinical practice, the great majority of patients receive rituximab as first-line therapy. Additionally, many patients receive rituximab maintenance therapy for two years after induction therapy.

Thus the study population is not representative of the current relapsing follicular lymphoma patient population that mainly consists of non-rituximab naïve patients. This greatly impacts on the transferability of the study results to the target population of the sought indication.

The choice of PFS as primary endpoint is in principle endorsable considered the indolent nature of the disease. However, due to the fact that NHL is highly heterogeneous in terms of relapse onset and frequency, and is characterized by remission phases of increasingly shorter duration, the suitability of PFS to predict clinical benefit is largely dependent on the magnitude of the observed effect, as well as on the number of previous relapses and duration of treatment free intervals. Unfortunately, no pre-specified subgroup analyses addressing the effect on PFS according to the number of previous treatments have been planned. These limitations question PFS as a meaningful clinical outcome in the sought indication.

The choice of rituximab single agent as comparator is acceptable considering that there is no gold standard in the second-line treatment of relapsing FL. However, as already pointed out, all patients, at present, receive rituximab as first-line therapy, and the majority of relapsing patients receive a combination of two drugs, including rituximab. Intensive chemotherapy supported by autologus stem cell transplantation for patients with relapsed NHL is an additional option.

Thus, under this scenario, the choice of rituximab single agent as active comparator in relapsing NHL gives limited information on the benefit of Velcade in the treatment of relapsed NHL patients.

The choice of the sequence of administration of the combined medicinal products (Velcade followed by Rituximab) in the treatment schedule, was based on the fact that: Rituximab infusion takes more time (90 min) than Velcade (3-5 sec bolus); Rituximab infusion can be associated with hypersensitivity reactions that could affect the administration of the second treatment. Thus, the administration of Velcade first is preferable.

In order to select those subjects with greater Vc-R efficacy results, in response to the CHMP Request for Supplementary Information, the MAH changed the claimed indication into "Velcade in combination with rituximab for the treatment of adult patients with relapsed follicular non-Hodgkin lymphoma whose time since last antilymphoma therapy (TLAT) was greater than one year". This was based on a post-hoc sub-group analysis without any pre-specified statistical method used to test for an interaction.

As other post-hoc analysis was performed for the stratification factors (FLIPI score (low [0 or 1 factor], intermediate [2 factors], or high [≥3 factors]); prior rituximab therapy (yes, no); time since last dose of anti-lymphoma therapy (≤1 year, >1 year); and region (US/Canada, EU, Rest of the World), the exploratory nature of these analyses does not allow to draw any conclusion on the treatment effect.

Efficacy data and additional analyses

The median PFS as determined by the IRC on the **ITT** population was 11.0 months in the rituximab group and 12.8 months in the Vc-R group (HR: 0.822; p=0.039), corresponding to a 16.4% improvement based on median days (22% based on HR) that is almost half than expected (33%). The percentage of censored was 32.9 in R and 36.9 in Vc-R arms. The claim of an indication in follicular NHL

is thus supported by only one pivotal study the primary endpoint of which did not meet the pre-calculated value for clinical and statistical significance.

The clinical relevance of a gain of 1.8 months in relapsing NHL patients is highly questionable also considering the absence of any improvement on one-year survival rate and the inability to affect the result of the following therapeutic treatment in case of disease progression. Furthermore, the statistical significance remains borderline even considering the remaining alpha as threshold value.

Recent results from 2 phase II studies further question the rationale of any bortezomib containing combinations in patients with follicular lymphoma since the expected primary end points were not met (Fowler et al., J Clin Oncol 2011 Sep 1;29(25):3389-3399, Sehn et al. J Clin Oncol 2011 Sep 1;29(25):3396-3401).

Results from non pre-specified sub-group analysis show that a limited gain in PFS following Velcade treatment is observed primarily in the subgroup of patients who had no prior rituximab exposure and thus do not represent the large majority of relapsed NHL patients in EU.

In the non-rituximab naïve patient population, PFS is 9.2 months in the rituximab group and 11.4 months in the Vc-Rituximab group with a HR of 0.92 (CI: 0.698, 1.235). The wide CI interval, probably due to the limited number of patients for whom events were reported (190 out of 295 patients), prevents a sound evaluation of the potential benefit of Velcade in the patient population representative of the actual clinical target for the claimed indication. All available PFS data have been collected at the time of the final analysis and study closure, thus no additional data can support the therapeutic benefit of Vc-R in previously rituximab-treated relapsed-refractory NHL patients.

Uncertainties on the magnitude of treatment effect are further raised by the observed discrepancy in the evaluation of PFS data between the independent radiologic review committee and investigators.

Results of the secondary efficacy and additional endpoints are in line with the primary efficacy endpoint with the exclusion of one-year survival rate. The median OS was not estimable at the time of data cut-off.

In the subgroup analysis of PFS in the ITT population, patients with a low and high FLIPI score showed a better effect on PFS when treated with Velcade R (low FLIPI: 381 vs 529 days in Vc-R arm; high FLIPI: 239 vs 347 days in Vc-R arm), whereas patients with an intermediate FLIPI score showed a slightly higher better response to single-agent rituximab (375 vs 352 days in Vc-R arm. No clarification for these findings was provided.

Further observed discrepancies were as follow: PFS was 10.7 months for the R-group and 4.4 months Vc-R-group in 24 subjects who had received more than 2 prior lines of rituximab therapy; the median PFS in the Rest of the World region was 11.8 months for the Vc-R group, similar than the median PFS of rituximab in EU, 12.5 months.

No PK/efficacy analyses were performed in special populations. The starting dose modification (1.0 mg/m2) for Velcade in patients with various degrees of hepatic impairment currently present in the SmPC section 4.2 for myeloma multiple indication, is now proposed by the MAH on a purely theoretical basis.

As regard the elderly population, patients > 65 years old were 25% accounting for 168 patients out of 676 patients. No sound conclusion on the effect of Velcade in this population is thus possible. However, it is noted that, in patients > 65 years, PFS was practically the same in both groups (Vc-R vs. R).

Results from the Global Health Status (EORTC QLQ-C30) showed that patients in rituximab group had an improvement from baseline beginning at Week 5 (end of first treatment cycle) continuing through

Week 120 (28 months), while patients in Vc-R group had an improvement beginning at the Week 30 (end of treatment) continuing through Week 120 (28 months). These results reflect the greater toxicity of the combination as compared to rituximab monotherapy.

The post-hoc analysis performed and presented by the MAH in response to the CHMP Request for Supplementary Information, identified the subpopulation with time since last antilymphoma treatment (TLAT) > 1 year as the one with a greater treatment effect in terms of PFS (4.3 months, HR=0.744) notwithstanding the previous exposure to rituximab.

Comparing to the overall population, in the subgroup with TLAT > 1 year, pre-treatment with rituximab largely enhance the PFS.

The reliability of the gain in PFS in the subgroup of patients with TLAT >1 year, is considered questionable on the basis of the exploratory and post-hoc nature of the analysis. Besides several methodological weaknesses in the approach of the statistical analysis, there is no straightforward and statistically sound evidence provided that treatment effect (improvement in PFS) in the sub-population of subjects with TLAT > 1 year would be any different from the treatment effect demonstrated in the original study population or in the subpopulation of subjects whose TLAT is less than 1 year

Contrary to what was observed in the overall population, a consistent trend in favour of the Vc-R combination has been reported across all FLIPI scores in the TLAT>1 subpopulation.

Subjects who previously received 2 or more prior lines of rituximab therapy did not benefit from Vc-R treatment. This is of utmost importance since practically all patients today have received at least one treatment with rituximab, and substantial portion receive maintenance therapy (likely second line).

In the responses to the CHMP Request for Supplementary Information, the MAH has shown that subjects treated with Velcade and with TLAT >1 year, and who had had 0, 1 and 2 prior lines of rituximab had longer PFS than those treated with rituximab alone. However, this was a post-hoc analysis on a subpopulation; since statistical analyses based on a subpopulation are not considered confirmatory, also these findings are deemed only exploratory.

In patients with more than 2 prior lines of rituximab no PFS improvement was found.

Overall, the point that the benefit of Vc-R treatment in patients > 65 years and in patients who previously received 2 or more prior lines of rituximab therapy is questionable, remains. Further, it is of importance that many NHL-patients in the EU are, indeed, > 65 years old and/or have previously received 2 or more prior lines of rituximab therapy.

The Vc-R benefit is negligible in terms of overall response rate and no clinically significant gain is seen in terms of complete response, thus Vc-R seems to be of no use even in bridging high risk patients to bone marrow transplantation, which represents a therapeutic option in this set of patients. It has to be demonstrated whether in patients not eligible to bone marrow transplantation (i.e. in which no complete or acceptable partial response are not achieved) Vc-R would result in significant clinical benefit.

Further, the clinical relevance of the PFS 1.8 month gain in a patient population with an indolent disease highly heterogeneous in terms of relapse onset and frequency, is still considered as a major concern.

Conclusions on clinical efficacy

Results from study LYM-3001 do not provide sufficient robust evidence in favour of the efficacy of Vc-R in either the initially sought indication ”for the treatment of patients with relapsed follicular non-

Hodgkin lymphoma" or in the indication proposed by the MAH in response to the CHMP Request for Supplementary Information "for the treatment of adult patients with relapsed follicular non-Hodgkin lymphoma whose time since last antilymphoma therapy (TLAT) was greater than one year.".

The clinical relevance of the PFS 1.8 month gain in a patient population with an indolent disease highly heterogeneous in terms of relapse onset and frequency, is still considered as a major concern.

The reliability of the gain in PFS of 4.3 months in the subgroup of patients with TLAT >1 year, is considered questionable on the basis of the exploratory and post-hoc nature of the analysis.

Clinical safety

Patient exposure

Out of 676 patients enrolled in Study LYM-3001, 339 was the safety population in the rituximab arm and 334 in the Vc-R arm. Overall, the % of patients who did not complete the 5 treatment cycles was similar in both arms (28-29%). Among treasons, were progressive disease 23% in R group and 17% in Vc-R group; adverse events 1% in R group and 6.1% in Vc-R group.

Adverse events

Overall, treatment-emergent adverse events (TEAEs) were experienced by 78% of subjects in the rituximab group and 95% of subjects in the Vc-R group; among the related AEs, the majority (83%) were considered related to Velcade (vs 62% related to rituximab). Serious AEs were higher in Vc-R group (18% vs 11%) being related to Velcade in 8% of patients.

An higher % of toxicity grade 3 or higher AEs were reported in the Vc-R arm (46% vs 21%).

Table 45: Overview of Treatment-Emergent Adverse Events
(Study 26866138-LYM-3001: Safety Analysis Set)

	Rituximab (N=339) n (%)	Vc-R (N=334) n (%)	Total (N=673) n (%)
Any adverse event	265 (78)	316 (95)	581 (86)
Related adverse events	156 (46)	290 (87)	446 (66)
Related adverse events – rituximab	156 (46)	206 (62)	362 (54)
Related adverse events – VELCADE	0	276 (83)	276 (41)
Any serious adverse event	37 (11)	59 (18)	96 (14)
Any related serious adverse event	12 (4)	35 (10)	47 (7)
Related serious adverse events – rituximab	12 (4)	24 (7)	36 (5)
Related serious adverse events – VELCADE	0	28 (8)	28 (4)
Toxicity Grade 3 or higher adverse events	70 (21)	152 (46)	222 (33)
Grade 3	52 (15)	115 (34)	167 (25)
Grade 4	15 (4)	29 (9)	44 (7)
Grade 5	3 (1)	8 (2)	11 (2)
Adverse Events Leading to Withdrawal from Treatment	5 (1)	19 (6)	24 (4)
Related AEs leading to withdrawal from treatment	3 (1)	14 (4)	17 (3)
Rituximab-related AEs leading to withdrawal from treatment	3 (1)	7 (2)	10 (1)
VELCADE-related AEs leading to withdrawal from treatment	0	10 (3)	10 (1)
Number of subjects who died due to treatment-emergent adverse event(s)	2 (1)	6 (2)	8 (1)

AE=adverse events
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TEAEs reported by ≥5% of subjects in either treatment group are summarized in table below.

Table 47: Overall, Toxicity, Seriousness, Relatedness, and Discontinuation of Most Frequent (>=5%) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Study 26866138-LYM-3001: Safety Analysis Set)

MedDRA System Organ Class	Rituximab (N=339) Category, n (%)					Vc-R (N=334) Category, n (%)				
Preferred Term	TEAE	Rel	G≥3	Ser	Disc	TEAE	Rel	G≥3	Ser	Disc
General Disorders and Administration Site Conditions	117 (35)	62 (18)	11 (3)	6 (2)	1 (<1)	199 (60)	155 (46)	17 (5)	6 (2)	0
Pyrexia	35 (10)	17 (5)	1 (<1)	2 (1)	0	84 (25)	52 (16)	2 (1)	6 (2)	0
Fatigue	27 (8)	11 (3)	0	0	0	75 (22)	60 (18)	5 (1)	0	0
Asthenia	25 (7)	10 (3)	6 (2)	2 (1)	0	48 (14)	35 (10)	8 (2)	1 (<1)	0
Oedema Peripheral	20 (6)	1 (<1)	2 (1)	1 (<1)	1 (<1)	31 (9)	12 (4)	3 (1)	1 (<1)	0
Chills	17 (5)	16 (5)	0	0	0	28 (8)	25 (7)	0	0	0
Infections and Infestations	92 (27)	14 (4)	15 (4)	13 (4)	0	178 (53)	78 (23)	36 (11)	24 (7)	7 (2)
Upper Respiratory Tract Infection	20 (6)	2 (1)	1 (<1)	0	0	40 (12)	13 (4)	6 (2)	1 (<1)	0
Nasopharyngitis	8 (2)	0	0	0	0	22 (7)	3 (1)	0	0	0
Herpes Zoster	5 (1)	3 (1)	1 (<1)	0	0	43 (13)	29 (9)	12 (4)	4 (1)	1 (<1)
Gastrointestinal Disorders	86 (25)	34 (10)	7 (2)	7 (2)	0	227 (68)	198 (59)	42 (13)	11 (3)	2 (1)
Diarrhoea	28 (8)	7 (2)	0	2 (1)	0	174 (52)	155 (46)	25 (7)	5 (1)	1 (<1)
Nausea	25 (7)	12 (4)	0	0	0	98 (29)	87 (26)	7 (2)	1 (<1)	1 (<1)
Vomiting	25 (7)	11 (3)	2 (1)	1 (<1)	0	79 (24)	71 (21)	8 (2)	4 (1)	1 (<1)
Abdominal Pain	18 (5)	3 (1)	2 (1)	2 (1)	0	46 (14)	32 (10)	3 (1)	2 (1)	0
Constipation	14 (4)	1 (<1)	0	0	0	59 (18)	31 (9)	1 (<1)	1 (<1)	0
Abdominal Pain Upper	7 (2)	3 (1)	0	0	0	20 (6)	11 (3)	1 (<1)	0	0
Respiratory, Thoracic and Mediastinal Disorders	75 (22)	23 (7)	8 (2)	7 (2)	1 (<1)	102 (31)	35 (10)	8 (2)	4 (1)	1 (<1)
Cough	31 (9)	4 (1)	0	0	0	51 (15)	10 (3)	0	0	0
Dyspnoea	16 (5)	5 (1)	4 (1)	1 (<1)	0	25 (7)	8 (2)	2 (1)	1 (<1)	0
Musculoskeletal and Connective Tissue Disorders	74 (22)	14 (4)	4 (1)	1 (<1)	0	117 (35)	58 (17)	12 (4)	0	1 (<1)
Back Pain	25 (7)	4 (1)	3 (1)	0	0	37 (11)	10 (3)	5 (1)	0	0
Pain in extremity	15 (4)	5 (1)	0	0	0	46 (14)	24 (7)	5 (1)	0	0
Arthralgia	10 (3)	0	0	1 (<1)	0	21 (6)	10 (3)	2 (1)	0	1 (<1)
Muscle Spasms	8 (2)	1 (<1)	0	0	0	16 (5)	6 (2)	0	0	0
Myalgia	5 (1)	2 (1)	0	0	0	18 (5)	14 (4)	1 (<1)	0	0
Skin and Subcutaneous Tissue Disorders	59 (17)	29 (9)	2 (1)	2 (1)	0	82 (25)	52 (16)	3 (1)	1 (<1)	0
Pruritus	15 (4)	6 (2)	1 (<1)	0	0	25 (7)	20 (6)	0	0	0
Rash	10 (3)	4 (1)	0	0	0	24 (7)	15 (4)	1 (<1)	0	0

Note: Percentages of sub-groups calculated with the number of subjects in each group as the denominator.
TEAE=treatment-emergent adverse events; G≥3=toxicity Grade ≥3; Ser=serious AE; Rel=drug-related AE; Disc=AE leading to discontinuation (continued)

Table 47: Overall, Toxicity, Seriousness, Relatedness, and Discontinuation of Most Frequent (>=5%) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Continued)
(Study 26866138-LYM-3001: Safety Analysis Set)

MedDRA System Organ Class	Rituximab (N=339) Category, n (%)					Vc-R (N=334) Category, n (%)				
Preferred Term	TEAE	Rel	G≥3	Ser	Disc	TEAE	Rel	G≥3	Ser	Disc
Nervous System Disorders	54 (16)	20 (6)	1 (<1)	2 (1)	0	156 (47)	131 (39)	23 (7)	7 (2)	4 (1)
Headache	24 (7)	10 (3)	0	0	0	42 (13)	20 (6)	0	0	0
Paraesthesia	10 (3)	3 (1)	0	0	0	39 (12)	35 (10)	2 (1)	0	0
Dizziness	9 (3)	5 (1)	0	0	0	20 (6)	9 (3)	1 (<1)	0	1 (<1)
Peripheral Sensory Neuropathy	2 (1)	0	0	0	0	54 (16)	52 (16)	9 (3)	1 (<1)	1 (<1)
Neuralgia	1 (<1)	0	0	0	0	23 (7)	22 (7)	6 (2)	0	1 (<1)
Blood and Lymphatic System Disorders	50 (15)	27 (8)	22 (6)	6 (2)	1 (<1)	91 (27)	77 (23)	55 (16)	7 (2)	3 (1)
Neutropenia	24 (7)	15 (4)	15 (4)	2 (1)	0	58 (17)	54 (16)	37 (11)	2 (1)	2 (1)
Leukopenia	18 (5)	16 (5)	5 (1)	1 (<1)	0	27 (8)	25 (7)	6 (2)	0	0
Anaemia	15 (4)	6 (2)	6 (2)	0	0	24 (7)	18 (5)	7 (2)	1 (<1)	0
Thrombocytopenia	13 (4)	6 (2)	2 (1)	0	0	32 (10)	31 (9)	10 (3)	0	0
Metabolism and Nutrition Disorders	35 (10)	12 (4)	7 (2)	0	0	80 (24)	41 (12)	19 (6)	4 (1)	0
Decreased Appetite	9 (3)	5 (1)	0	0	0	40 (12)	30 (9)	1 (<1)	1 (<1)	0
Psychiatric Disorders	30 (9)	2 (1)	1 (<1)	1 (<1)	0	38 (11)	16 (5)	3 (1)	0	0
Insomnia	18 (5)	1 (<1)	0	0	0	30 (9)	13 (4)	2 (1)	0	0
Vascular Disorders	26 (8)	11 (3)	0	1 (<1)	0	55 (16)	29 (9)	6 (2)	6 (2)	2 (1)
Hypertension	9 (3)	4 (1)	0	0	0	21 (6)	4 (1)	3 (1)	0	0
Hypotension	7 (2)	5 (1)	0	0	0	24 (7)	17 (5)	0	4 (1)	0
Immune System Disorders	25 (7)	24 (7)	4 (1)	1 (<1)	3 (1)	31 (9)	27 (8)	5 (1)	6 (2)	1 (<1)
Hypersensitivity	21 (6)	20 (6)	3 (1)	1 (<1)	2 (1)	27 (8)	25 (7)	3 (1)	4 (1)	1 (<1)
Hepatobiliary Disorders	16 (5)	7 (2)	5 (1)	3 (1)	0	21 (6)	13 (4)	8 (2)	0	0
Hepatic Function Abnormal	11 (3)	6 (2)	3 (1)	0	0	16 (5)	10 (3)	7 (2)	0	0

Note: Percentages of sub-groups calculated with the number of subjects in each group as the denominator.
TEAE=treatment-emergent adverse events; G≥3=toxicity Grade ≥3; Ser=serious AE; Rel=drug-related AE; Disc=AE leading to discontinuation
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In the rituximab group, grade 3 or higher AEs occurred most frequently in the system organ class (SOC) of Blood and Lymphatic System Disorders (6%).

In the Vc-R group, grade 3 or higher AEs occurred most frequently in the SOC of Blood and Lymphatic System Disorders but with a higher incidence compared to rituximab arm (16%), Gastrointestinal Disorders (13%), Infections and Infestations (11%), Nervous System Disorders (7%), and Metabolism and Nutrition Disorders (6%).

Considering the SOC Blood an Lymphatic System Disorders, among Grade > 3 AEs occurred with a frequency higher o 10%, neutropenia and thrombocytopenia were found in 17% and 10% of Vc-R patients vs 7% and 4% of patients in rituximab arm. In 1 patients in Vc-R arm, neutropenia was one of the reasons for discontinuation.

Table TAE01PI: Most Frequently Reported Treatment-Emergent Adverse Events (≥ 10% in Vc-R arm) with Grades 3 and ≥ 4 Intensity (Study 26866138-LYM-3001: Safety Analysis Set)

	Vc-R (N=334)			Rituximab (N=339)		
MedDRA System Organ Class	Total	Toxicity Grade, n (%)		Total	Toxicity Grade, n (%)	
MedDRA Preferred Term	n (%)	3	≥ 4	n (%)	3	≥ 4
Any treatment-emergent event	316 (95)	115 (34)	37 (11)	265 (78)	52 (15)	18 (5)
Blood and lymphatic system disorders						
Neutropenia	58 (17)	19 (6)	18 (5)	24 (7)	7 (2)	8 (2)
Thrombocytopenia	32 (10)	5 (1)	5 (1)	13 (4)	1 (<1)	1 (<1)
Gastrointestinal disorders						
Abdominal pain	46 (14)	2 (1)	1 (<1)	18 (5)	2 (1)	0
Constipation	59 (18)	1 (<1)	0	14 (4)	0	0
Diarrhoea	174 (52)	25 (7)	0	28 (8)	0	0
Nausea	98 (29)	7 (2)	0	25 (7)	0	0
Vomiting	79 (24)	8 (2)	0	25 (7)	2 (1)	0
General disorders and administration site conditions						
Asthenia	48 (14)	8 (2)	0	25 (7)	6 (2)	0
Fatigue	75 (22)	5 (1)	0	27 (8)	0	0
Pyrexia	84 (25)	2 (1)	0	35 (10)	1 (<1)	0
Infections and infestations						
Herpes zoster	43 (13)	12 (4)	0	5 (1)	1 (<1)	0
Upper respiratory tract infection	40 (12)	6 (2)	0	20 (6)	1 (<1)	0

(a) represents MedDRA high level term peripheral neuropathies NEC.

Serious adverse events and deaths

Serious TEAEs were higher in Vc-R arm (8% vs 0% in rituximab arm). AEs under SOC Infections and infestations were the primarily serious AEs in Vc-R patients (7% vs 4% in rituximab arm).

Death incidence was similar among the treatments (24%); in R arm 17% of patients died to disease progression as compared to Vc-R arm (15%). In both arms, fatal cases occurred mostly after 60 days of treatment that means before completing cycle 2.

Table 51: Summary of Deaths and Causes of Death
(Study 26866138-LYM-3001: Safety Analysis Set)

	Rituximab (N=339) n (%)	Vc-R (N=334) n (%)	Total (N=673) n (%)
Cause of Death	80 (24)	78 (23)	158 (23)
Adverse events	4 (1)	7 (2)	11 (2)
Non Treatment-Emergent adverse event	2 (1)	1 (<1)	3 (<1)
Treatment-Emergent adverse event	2 (1)	6 (2)	8 (1)
Progressive disease	56 (17)	50 (15)	106 (16)
Other	20 (6)	21 (6)	41 (6)
Death from the First Dose of Study Medication	80 (24)	78 (23)	158 (23)
0 - 30 Days	2 (1)	2 (1)	4 (1)
31 - 60 Days	2 (1)	3 (1)	5 (1)
≥61 Days	76 (22)	73 (22)	149 (22)
Death Within 30 Days of Last Dose	4 (1)	9 (3)	13 (2)
Adverse events	2 (1)	6 (2)	8 (1)
Not related	2 (1)	3 (1)	5 (1)
Related	0	3 (1)	3 (<1)
Progressive disease	2 (1)	3 (1)	5 (1)

Note: "Other" cause of death refers to all documented causes of death other than adverse events or progressive disease.
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Peripheral Neuropathies

Peripheral sensory neuropathy confirmed to be a Velcade associated toxicity and it was the highest frequent AE in SOC Central Nervous System (55%).

Table 52: Overall, Toxicity, Seriousness, Relatedness, and Discontinuation for Treatment-Emergent Peripheral Neuropathies NEC
(Study 26866138-LYM-3001: Safety Analysis Set)

MedDRA Higher Level Term / Preferred Term	Category, n (%) TEAE	Related	Grade ≥3	Serious	Disc
			Rituximab (N=339)		
Peripheral Neuropathies NEC	3 (1)	0	0	0	0
Peripheral Motor Neuropathy	1 (<1)	0	0	0	0
Peripheral Sensorimotor Neuropathy	0	0	0	0	0
Peripheral Sensory Neuropathy	2 (1)	0	0	0	0
			Vc-R (N=334)		
Peripheral Neuropathies NEC	57 (17)	55 (16)	9 (3)	1 (<1)	1 (<1)
Peripheral Motor Neuropathy	5 (1)	5 (1)	2 (1)	0	0
Peripheral Sensorimotor Neuropathy	1 (<1)	1 (<1)	0	0	0
Peripheral Sensory Neuropathy	54 (16)	52 (16)	9 (3)	1 (<1)	1 (<1)

TEAE=treatment-emergent adverse event; Related=drug-related adverse event; Serious=serious adverse events; Disc=adverse event leading to discontinuation; NEC=not elsewhere classified
Note: Percentages of sub-groups calculated with the number of subjects in each group as the denominator.
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Thirty % of peripheral neuropathies occurred in Vc-R patients were not resolved.

Study 26866138-LYM-3001

Output DAE29: Summary of Time to Resolution/Improvement of Treatment-Emergent Peripheral Neuropathies NEC

Analysis Set: Safety

Parameter	Rituximab	Vc-R
Time to Event Resolution		
Number Assessed	3	68
Number Resolved	3(100)	48(71)
Number Censored	0(0)	20(29)
25th Quantile (95% CI)	8(8,115)	27(17,65)
Median (95% CI)	56(8,115)	109(75,206)
75th Quantile (95% CI)	115(8,115)	523(206,647)
Range	(8,115)	(1,1104)
Time to Event Resolution/Improvement		
Number Assessed	3	68
Number Resolved/Improved	3(100)	53(78)
Number Censored	0(0)	15(22)
25th Quantile (95% CI)	8(8,115)	19(13,29)
Median (95% CI)	56(8,115)	58(33,90)
75th Quantile (95% CI)	115(8,115)	174(99,573)
Range	(8,115)	(1,1104)

Herpes zoster

Herpes zoster events were experienced by 1% subjects in the rituximab group and 13% subjects in the Vc-R group. Four % of subjects in the Vc-R group experienced grade 3 adverse events, 1 of which led to discontinuation from the study. One % of events of herpes zoster were reported as serious (2 grade 2, 2 grade 3).

Laboratory findings

Most subjects entered the study with grade 0 or 1 haematology laboratory parameters which remained at grade 0 or 1 for the duration of the study.

With the exception of lymphocytes, there were no relevant increases in grade 3 or higher haematology test results due to the addition of Velcade to rituximab treatment.

Grade 3 and 4 haematology laboratory test results as the worst toxicity grade during treatment are summarized below:

-Hemoglobin (anemia): 3% rituximab; 4% Vc-R

-Lymphocytes (lymphocytopenia): 10% rituximab; 25% Vc-R

-Neutrophils (neutropenia): 10% rituximab; 17% Vc-R

-Platelet count (thrombocytopenia): 1% rituximab; 5% Vc-R

-WBC (leukopenia): 6% rituximab; 10% Vc-R

There were few significant changes in the safety laboratory parameters, more frequently found in the haematology group. Rituximab only treatment appears to have less important toxicities i.e. neutropenia and thrombocytopenia. No new safety concerns were observed in this study.

Safety in special populations

While in the rituximab arm the proportion of patients experiencing TEAEs was higher in patients with ALT or AST ≥1.5 × ULN (94% vs 78% with ALT or AST ≥1.5 × ULN), in the Vc-R arm there was no significant difference between the % of patients experiencing TEAEs (that was high about 100%) and the level of hepatic impairment.

Patients with creatinine clearance 31 to 60 ml/min experienced slightly higher rates of adverse events, a similar trend was observed in patients with creatinine clearance>60 ml/min. Within each treatment group, there were no notable differences in the rates and types of reported adverse events among the renal function categories (<30 mL/min,31 to 60 ml/min; >60 ml/min).

Immunological events

Acute hypersensitivity events were experienced by 7% of subjects in the rituximab group and 10% of subjects in the Vc-R group.

In the Vc-R group, grade 4 serious AEs of anaphylactic reaction were reported by 1% of subjects.

Safety related to drug-drug interactions and other interactions

NA

Discontinuation due to AES

In the safety population, 4% of subjects discontinued from treatment due to an AE, including 1% in the rituximab group and 6.1% in the Vc-R group.

Adverse events leading to withdrawal from treatment for more than 1 subject in either treatment group were hypersensitivity (2 subjects) in the rituximab group and pneumonia and neutropenia (2 subjects each) in the Vc-R group.

Both events of hypersensitivity in the rituximab group and both events of pneumonia in the Vc-R group were considered to be rituximab-related. The only Velcade-related AEs leading to withdrawal from treatment for more than 1 subject were 2 events of neutropenia.

The mean relative rituximab dose intensity was 0.97 for the rituximab group, and 0.96 for rituximab in the Vc-R group. The mean dose intensity of VELCADE in the Vc-R group was 1.16 mg/m2/week, indicating a mean relative dosing intensity of 0.88.

TAEAs leading to dose modifications were experienced by 5% of subjects in the rituximab group and 33% of subjects in the Vc-R group. The most frequent causes for dose modification in Vc-R arm were in SOC infections and infestations (11%) being herpes zoster (5%), nervous system disorders (12%) peripheral sensory neuropathy (6%). Dose modifications were also due to gastrointestinal disorders in 7% of Vc-R patients, and to blood and lymphatic systemic conditions in 6% of patients.

Table 50: Treatment-Emergent Adverse Events Leading to Dose Modifications
(Study 26866138-LYM-3001: Safety Analysis Set)

MedDRA System Organ Class Preferred Term	Rituximab (N=339) n (%)	Vc-R (N=334) n (%)	Total (N=673) n (%)
Total no. subjects with Treatment-Emergent Adverse Events Leading to Dose Modifications	18 (5)	111 (33)	129 (19)
Infections and infestations	8 (2)	36 (11)	44 (7)
Herpes zoster	2 (1)	16 (5)	18 (3)
Upper respiratory tract infection	1 (<1)	5 (1)	6 (1)
Pneumonia	1 (<1)	2 (1)	3 (<1)
Respiratory tract infection	2 (1)	1 (<1)	3 (<1)
Nasopharyngitis	0	2 (1)	2 (<1)
Viral infection	0	2 (1)	2 (<1)
Bronchitis	0	1 (<1)	1 (<1)
Bronchopneumonia	1 (<1)	0	1 (<1)
Fungal infection	1 (<1)	0	1 (<1)
Gastroenteritis	0	1 (<1)	1 (<1)
Hepatitis B	0	1 (<1)	1 (<1)
Infection	0	1 (<1)	1 (<1)
Influenza	0	1 (<1)	1 (<1)
Lower respiratory tract infection	1 (<1)	0	1 (<1)
Pharyngitis	0	1 (<1)	1 (<1)
Pyelonephritis	0	1 (<1)	1 (<1)
Respiratory tract infection viral	0	1 (<1)	1 (<1)
Sepsis	0	1 (<1)	1 (<1)
Nervous system disorders	0	39 (12)	39 (6)
Peripheral sensory neuropathy	0	19 (6)	19 (3)
Neuralgia	0	14 (4)	14 (2)
Paraesthesia	0	4 (1)	4 (1)
Polyneuropathy	0	2 (1)	2 (<1)
Dizziness	0	1 (<1)	1 (<1)
Headache	0	1 (<1)	1 (<1)
Hyporeflexia	0	1 (<1)	1 (<1)
Intercostal neuralgia	0	1 (<1)	1 (<1)
Loss of consciousness	0	1 (<1)	1 (<1)
Migraine	0	1 (<1)	1 (<1)
Peripheral motor neuropathy	0	1 (<1)	1 (<1)
Tremor	0	1 (<1)	1 (<1)
Gastrointestinal disorders	2 (1)	24 (7)	26 (4)
Diarrhoea	1 (<1)	11 (3)	12 (2)
Nausea	0	6 (2)	6 (1)
Abdominal pain	0	5 (1)	5 (1)
Vomiting	1 (<1)	4 (1)	5 (1)
Constipation	0	4 (1)	4 (1)
Gastritis	0	3 (1)	3 (<1)
Abdominal discomfort	0	1 (<1)	1 (<1)
Ascites	0	1 (<1)	1 (<1)
Gastrointestinal obstruction	1 (<1)	0	1 (<1)
Gastrointestinal pain	0	1 (<1)	1 (<1)
Blood and lymphatic system disorders	2 (1)	19 (6)	21 (3)
Neutropenia	1 (<1)	17 (5)	18 (3)

Note: Percentages calculated with the number of subjects in each group as denominator. (continued)

TEAEs causing cycle delays were experienced by 5% in the rituximab group and 15% of subjects in the Vc-R group; neutropenia was the reason in both arms at equal incidence (3%).

Post marketing experience

Discussion on clinical safety

Drug related AEs were reported by 87% of subjects in the Vc-R group and 46% in the rituximab group. In particular, infections (R 27%, Vc-R 53%) and nervous system disorders (R 16%, Vc-R 47%), occurred at higher rates in the Vc-R group. The safety of the Vc-R combination was consistent with the known safety profiles of Velcade and rituximab; anyway, not always toxicity related to Velcade was manageable (e.g. 30% of peripheral neuropathies occurred in Vc-R patients were not resolved vs 0% in R group).

The AEs experienced with the addition of weekly Velcade to rituximab led to dose modification (50% dose modification in the Vc-R group of which 42% related to AEs, 27% dose modification in the rituximab group of which 19% related to AEs) or to addition of supportive therapies.

AEs caused discontinuation before 5 cycles in 1% in R group and in 6.1% in the Vc-R group. This remarkably highlights the significant toxicity of Velcade when combined to rituximab.

More deaths from the treatment related AEs (6 vs. 2) were found in the Vc-R group. Despite of the small numbers, this finding further questions the rationale of bortezomib treatment in follicular NHL.

The safety profile of Velcade was not influenced by stratification factors.

Infectious complication, in particular viral reactivations (Herpes zoster), peripheral neuropathy and neutropenia were among the AEs with a higher incidence in the Vc-R arm.

Although no new safety signals were identified for Velcade and rituximab, safety concerns highlighted for the ITT population for the Vc-R combination are reflected in the subgroup (TLAT> 1 year) the MAH has selected for claiming a better efficacy. Besides the methodological issues, no advantage in terms of safety profile is shown when considering the sub-group population with TLAT > 1 year.

The percentage of herpes zoster infection in both arms is unmodified in the subgroup analysed and in the overall population (12% vs 1% and 13% vs 1%) being always much higher in the Vc-R arm. The same trend applies to the peripheral sensory neuropathy.

Due to the limited number of elderly patients included in the pivotal trial, no sound conclusion on the safety profile of Vc-R combination in this patient population is possible.

The rate of sensory neuropathy (16%) seems quite low compared to some recently published studies. For example in the recently published study with similar bortezomib dose and schedule (Fowler et al., J Clin Oncol 2011 Sep 1;29(25):3389-3399), thirty-two patients (44%) developed peripheral neuropathy.

The MAH states that the majority of cases with peripheral neuropathy were resolved at the time of study closure. The study was prematurely closed by MAH and therefore also some important safety data are missing. The potential long-term neurotoxicity of bortezomib which is not uncommon, remains an open question. The point is that not all neurotoxicity is reversible. Considering that the overall survival in follicular lymphoma may be almost 20 years, the relevance of this potentially long-term adverse reaction is of major importance in the treatment of NHL.

The cumulative toxicity of bortezomib based regimens has not been analysed. Information on cumulative toxicity are considered important since second line treatment is not likely to be curative and eventually almost all patients will need third line and following lines of treatment.

Conclusions on clinical safety

The safety profile of Velcade regimen 1.6 mg/m2 once weekly for 5 cycles, seen in the current study was generally similar to that seen in previously conducted studies of Velcade in patients with multiple myeloma; although being predictable, it was not always manageable considering the higher incidence of adverse events and adverse events leading to treatment discontinuation associated with Velcade administration. Overall a greater toxicity was observed for the combination Vc-R compared to rituximab monotherapy.

Risk management plan

In its responses to the CHMP request for Supplementary Information, the MAH submitted the updated RMP version 12.

Within the parallel procedure Velcade X/47, the MAH presented the RMP ver. 14 which took also into account the revised therapeutic indication of Velcade in combination with rituximab for the treatment of adult patients with relapsed follicular non-Hodgkin lymphoma whose time since last antilymphoma therapy was greater than one year.

The RMP aspects linked to the new sought indication will be assessed once the remaining issues are solved.

4. ORPHAN MEDICINAL PRODUCTS

Velcade is not an orphan medicinal product. See CHMP AR on similarity with Cladribine.

5. BENEFIT RISK ASSESSMENT

Benefits

Beneficial effects

Results from the single pivotal trial in support of the sought indication (Velcade in combination with rituximab for the treatment of patients with relapsed follicular non-Hodgkin lymphoma) showed that the combination of Vc-R induced a 16.4% statistically significant improvement in PFS (HR: 0.822; 95% CI: 0.681, 0.991; p=0.039) compared to rituximab single agent (from 11 months of single agent rituximab to 12.8 months Vc-R).

This effect was confirmed by a number of sensitivity analyses (HR ≤0.850) in favour of the Vc-R with the exception of PFS based on the investigator assessment.

In the non pre-specified sub-group analysis, poor prognosis and high risk patients (characterised by high FLIPI score and high tumour burden) seem to receive a greater benefit from the combination Vc-R.

Results of the secondary efficacy and additional endpoints are in line with the primary efficacy endpoint with the exclusion of one-year survival rate.

Velcade safety profile is sufficiently characterised and no new treatment-emergent toxicities were observed for the Vc-R combination.

In the responses to the CHMP Request for Supplementary Information, the MAH changed the initially proposed indication into the following: "Velcade in combination with rituximab is indicated for the treatment of adult patients with relapsed follicular non-Hodgkin lymphoma whose time since last antilymphoma therapy was greater than one year."

The post-hoc analysis performed, identified the subpopulation with time since last antilymphoma treatment (TLAT) > 1 year as the one with a greater treatment effect in terms of PFS (4.3 months, HR=0.744) notwithstanding the previous exposure to rituximab.

Comparing to the overall population, in the subgroup with TLAT > 1 year, pre-treatment with rituximab largely enhance the PFS.

Uncertainty in the knowledge about the beneficial effects

The evidence in favour of Vc-R benefit in the sought indication (Velcade in combination with rituximab for the treatment of patients with relapsed follicular non-Hodgkin lymphoma) derives from a single open-label phase 3 trial that was terminated early.

The gain in the primary endpoint, PFS, observed for the combination Vc-R compared to rituximab monotherapy is very limited (1.8 months, lower than expected), of questionable clinical relevance, and of borderline statistical significance, even considering the remaining alpha as threshold value.

Furthermore, the study was prematurely closed on the basis of feasibility when the IDMC concluded that the protocol-specified 514 PFS events would be unachievable in any reasonable timeframe. The impossibility to reach the scheduled number of PFS events appears to be quite objective and not influenced by the unblinded results from the second interim analysis.

Uncertainties on the magnitude of treatment effect are further raised by the observed discrepancy in the evaluation of PFS data between the independent radiologic review committee and investigators.

The patient population of the pivotal trial is not representative of the target population (pre-treated with rituximab) in the sought indication, thus the external validity of the efficacy results is questionable.

The premature censoring of a large fraction of subjects from the final analysis prevents a sound evaluation of the beneficial effects of the Vc-R combination in the sub-group population of rituximab-pre-treated relapsed FL patients that represents the EU target population.

Results of the secondary efficacy and additional endpoints are in line with the primary efficacy endpoint with the exclusion of one-year survival rate.

Although still of modest clinical relevance, the reliability of the gain in PFS in the subgroup of patients with TLAT >1 year (as presented in the MAH responses to the CHMP Request for Supplementary Information), is considered questionable on the basis of the exploratory and post-hoc nature of the analysis. Besides several methodological weaknesses in the approach of the statistical analysis, there is no straightforward and statistically sound evidence provided that treatment effect (improvement in PFS) in the sub-population of subjects with TLAT > 1 year would be any different from the treatment effect demonstrated in the original study population or in the subpopulation of subjects whose TLAT is less than 1 year.

In the subgroup analysis of PFS in the ITT population, patients with a low and high FLIPI score showed a better effect on PFS when treated with Velcade R (low FLIPI: 381 vs 529 days in Vc-R arm; high FLIPI: 239 vs 347 days in Vc-R arm), whereas patients with an intermediate FLIPI score showed a

slightly better response to single-agent rituximab (375 vs 352 days in Vc-R arm). No clarification for these findings was provided.

Contrary to what was observed in the overall population, a consistent trend in favour of the Vc-R combination has been reported across all FLIPI scores in the TLAT>1 subpopulation.

Although stratification factors were considered in the study design (FLIPI score (low [0 or 1 factor], intermediate [2 factors], or high [≥3 factors]); prior rituximab therapy (yes, no); time since last dose of anti-lymphoma therapy (≤1 year, >1 year); and region (US/Canada, EU, Rest of the World), the subgroup analysis was not pre-specified, thus the statistical method used to test for an interaction was not defined in the study protocol or in the Statistical Analysis Plan.

With regard to the elderly population, patients > 65 years represented the 25% of the enrolled population, accounting for 168 patients out of 676 patients. No sound conclusion on the effect of Velcade in this population is thus possible. However, it is noted that, in patients > 65 years, PFS was practically the same in both groups (Vc-R vs. R).

Subjects who previously received 2 or more prior lines of rituximab therapy did not benefit from Vc-R treatment. This is of utmost importance since practically all patients today have received at least one treatment with rituximab, and substantial portion receive maintenance therapy (second line?).

After adjusting for prognostic factors, there is still quite notable inconsistency in the treatment effect in the two age groups. Overall, the analyses show that there is no conclusive evidence that age is or is not a treatment effect-modifying factor in the Vc-R group. Results were similar in the subgroup of patients > 65 years old and whose TLAT was >1 year.

In response to the CHMP Request for Supplementary Information, the MAH has shown that subjects treated with Velcade and whose TLAT >1 year, and who had had 0, 1 and 2 prior lines of rituximab had longer PFS than those treated with rituximab alone. However, this was a post-hoc analysis on a subpopulation; since statistical analyses based on a subpopulation are not considered confirmatory, also these findings are deemed only exploratory.

In patients with more than 2 prior lines of rituximab no PFS improvement was found.

Overall, the point that the benefit of Vc-R treatment in patients > 65 years and in patients who previously received 2 or more prior lines of rituximab therapy is questionable, remains. Further, it is of importance that many NHL-patients in the EU are, indeed, > 65 years old and/or have previously received 2 or more prior lines of rituximab therapy.

Results from the Global Health Status (EORTC QLQ-C30) showed that patients in rituximab group had an improvement from baseline beginning at Week 5 (end of first treatment cycle) continuing through Week 120 (28 months), while patients in Vc-R group had an improvement beginning at the Week 30 (end of treatment) continuing through Week 120 (28 months). These results reflect the greater toxicity of the combination as compared to rituximab monotherapy.

The Vc-R benefit is negligible in terms of overall response rate and no clinically significant gain is seen in terms of complete response, thus Vc-R seems to be of no use even in bridging high risk patients to bone marrow transplantation, which represents a therapeutic option in this set of patients. It has to be demonstrated whether in patients not eligible to bone marrow transplantation (i.e. in which no complete or acceptable partial response are not achieved) Vc-R would result in significant clinical benefit.

Further, the clinical relevance of the PFS 1.8 month gain in a patient population with an indolent disease highly heterogeneous in terms of relapse onset and frequency, is still considered as a major concern.

Risks

Unfavourable effects

No difference in the 1-year survival and OS rates was observed between Vc-R combination and rituximab monotherapy.

The safety profile of Velcade in combination with rituximab, although being predictable, was not always manageable also considering the high discontinuation rate due to AEs observed in the clinical study population (6.1% of patients in Vc-R arm vs only 1% in R arm discontinued).

The Vc-R combination exerted an overall greater toxicity compared to single agent rituximab both in terms of frequency as well as severity of AEs (e.g. any AEs, related AEs, SAEs, toxicity of grade 3 and higher and AEs leading to withdrawal).

A two-fold increase in SAE and Grade 3 AEs, and a 6-fold increase in the rate of discontinuations due to adverse events was observed for the combination compared to rituximab monotherapy,

Of particular concern are a 3-fold greater incidence of severe neutropenia associated with an increased number of overall infections in the combination arm. Of note, Herpes zoster infections were reported in 13% (Vc-R) vs 1% (R).

Peripheral sensory neuropathy was developed in 16% of subjects receiving Vc-R compared to only 1% in the rituximab arm, confirming to be a Velcade associated event. Although the rate of this AE is lower than that observed in other studies with Velcade, about 30% of the peripheral neuropathy cases did not resolve.

More deaths from the treatment related AEs were found in the Vc-R group (6 vs. 2). Since the gain in PFS was only 1.8 months, the MAH is asked to evaluate whether the observed increase in deaths in the bortezomib group is acceptable in the second line treatment of follicular NHL.

Although no new safety signals were identified for Velcade and rituximab, safety concerns highlighted for the ITT population for the Vc-R combination are reflected in the subgroup (TLAT> 1 year) the MAH has selected for claiming a better efficacy. Besides the methodological issues, no advantage in terms of safety profile is shown when considering the sub-group population with TLAT > 1 year.

The serious AEs were also higher in the Vc-R arm respect to the R arm (18% vs 10%). Six % in the Vc-R arm and 2% in the R arm of related AEs led to withdrawal from treatment; this is even higher than results obtained in the overall population (4% Vc-R and 1% R).

The percentage of herpes zoster infection in both arms is unmodified in the subgroup analysed and in the overall population (12% vs 1% and 13% vs 1%) being always much higher in the Vc-R arm. The same trend applies to the peripheral sensory neuropathy.

Uncertainty in the knowledge about the unfavourable effects

Due to the limited number of elderly patients included in the pivotal trial, no sound conclusion on the safety profile of Vc-R combination in this patient population is possible.

The rate of sensory neuropathy (16%) seems quite low compared to some recently published studies. For example in the recently published study with similar bortezomib dose and schedule (Fowler et al., J Clin Oncol 2011 Sep 1;29(25):3389-3399), thirty-two patients (44%) developed peripheral neuropathy.

The MAH states that the majority of cases with peripheral neuropathy were resolved at the time of study closure. The study was prematurely closed by MAH and therefore also some important safety data are missing. The potential long-term neurotoxicity of bortezomib which is not uncommon, remains an open question. The point is that not all neurotoxicity is reversible. Considering that the overall survival in follicular lymphoma may be almost 20 years, the relevance of this potentially long-term adverse reaction is of major importance in the treatment of NHL.

The cumulative toxicity of bortezomib based regimens has not been analysed. Information on cumulative toxicity are considered important since second line treatment is not likely to be curative and eventually almost all patients will need third line and following lines of treatment.

Balance

Importance of favourable and unfavourable effects

Generally, the availability of new additional therapeutic options in the treatment of relapsed FL is considered of great clinical value. However, the 1.8 month difference in median PFS observed for Vc-R arm vs single agent rituximab, instead of 3.33 months initially set, is of questionable clinical relevance considering the borderline statistical significance, and the uncertainties in the external validity of the efficacy data due to the enrolment of patients that do not represent the EU relapsed population. The clinical relevance of Vc-R in the subgroup population with TLAT > 1 year is still considered of modest clinical relevance and greatly affected by methodological weaknesses in the approach of the statistical analysis.

The lack of difference in the one-year survival rate and in all-cause mortality after a median study follow-up of 34 months, further weaken the clinical relevance of PFS results; thus Vc-R seems to be of no use even in bridging high risk patients to bone marrow transplantation, which represents a therapeutic option in this set of patients. It has to be demonstrated whether in patients not eligible to bone marrow transplantation (i.e. in which no complete or acceptable partial response are not achieved) Vc-R would result in significant clinical benefit.

The greater toxicity observed with the Vc-R combination compared to rituximab monotherapy is of concern considered the marginal gain observed in the efficacy outcomes.

Benefit-risk balance

Results from the single pivotal trial in support of the sought indication (Velcade in combination with rituximab for the treatment of patients with relapsed follicular non-Hodgkin lymphoma) showed that the combination of Vc-R induced a statistically significant, although limited, improvement in PFS compared to single agent rituximab in the relapsed NHL population. The positive effect on PFS was confirmed for the majority of secondary endpoints and by sensitivity analyses.

In response to the CHMP Request for Supplementary Information, the MAH changed the initially proposed indication into the following:" Velcade in combination with rituximab is indicated for the treatment of adult patients with relapsed follicular non-Hodgkin lymphoma whose time since last antilymphoma therapy was greater than one year."

The post-hoc analysis performed, identified the subpopulation with time since last antilymphoma treatment (TLAT) > 1 year as the one with a greater treatment effect in terms of PFS (4.3 months, HR=0.744) notwithstanding the previous exposure to rituximab.

The following issues greatly limit the importance of the observed favourable effect:

-the clinical relevance of a gain of 1.8 months in PFS in the overall population, is considered marginal,

-the transferability of the observed efficacy results to the actual EU relapsed NHL population (pre-treated with rituximab), is questionable,

-no pre-specified analysis was planned to investigate the effect of Vc-R combination in the sub-group population; the exploratory nature of the analysis in the TLAT > 1 year does not allow to draw any conclusion on the treatment effect.

On the other hand, the safety profile of Velcade, although well characterized, seems to be not easily manageable when Velcade is combined with rituximab as demonstrated by the high incidence of treatment discontinuation due to AEs in the combination arm. The unfavourable effects mainly represented by the significant toxicity of the Vc-R combination largely exceed the limited and questionable clinical significant benefit observed in patients treated with the Vc-R combination.

A greater overall toxicity in terms of both frequency and severity of AEs, was observed for the Vc-R combination compared to rituximab monotherapy both in the overall population and in the sub-group considered.

Discussion on the benefit-risk assessment

The MAH initially applied for the following indication: Velcade in combination with rituximab is indicated for the treatment of patients with relapsed follicular non-Hodgkin lymphoma. In Study LYM-3001, the median PFS as determined by the IRC on the ITT population was 11.0 months in the rituximab group and 12.8 months (+1.8 months) in the Vc-R group (HR: 0.822; p=0.039), corresponding to a 16.4% improvement based on median days (22% based on HR) that is almost half than expected (33%).

The clinical relevance of a gain of 1.8 months in relapsing NHL patients is highly questionable and is not likely to have an effect on OS nor to affect the result of the therapeutic treatment in case of disease progression.

In current EU clinical practice almost all patients receive rituximab in first line therapy. Results from subgroup analyses show that a limited gain in PFS following Velcade treatment is observed primarily in the subgroup of patients who had no prior rituximab exposure and thus do not represent the large majority of relapsed NHL patients in EU.

The premature censoring of a large fraction of subjects from the final analysis prevents a sound evaluation of the beneficial effects of the Vc-R combination in the sub-group population of rituximab-pre-treated relapsed FL patients that represents the EU target population.

The discrepancy in the evaluation of PFS data noted between the independent radiologic review committee and investigator, resulting in different outcomes of the statistical analysis of PFS in the ITT population, raises uncertainties on the magnitude of treatment effect.

Results of the secondary efficacy and additional endpoints are in line with the primary efficacy endpoint with the exclusion of one-year survival rate. The median OS was not estimable at the time of data cut-off.

Limited information on the efficacy and safety of Vc-R combination is at present available in the elderly population.

In response to the CHMP Request for Supplementary Information, the MAH changed the initially proposed indication into the following: "Velcade in combination with rituximab is indicated for the treatment of adult patients with relapsed follicular non-Hodgkin lymphoma whose time since last antilymphoma therapy was greater than one year.".

The post-hoc analysis performed, identified the subpopulation with time since last antilymphoma treatment (TLAT) > 1 year as the one with a greater treatment effect in terms of PFS (4.3 months, HR=0.744) notwithstanding the previous exposure to rituximab. Comparing the overall population, in the subgroup with TLAT > 1 year, pre-treatment with rituximab largely enhance the PFS.

The clinical relevance of Vc-R in the subgroup population with TLAT > 1 year is still considered of modest clinical relevance and greatly affected by methodological weaknesses in the approach of the statistical analysis, since no pre-specified analysis was planned to investigate the treatment effect in the sub-group population. The exploratory nature of the analysis in the TLAT > 1 year does not allow to draw any conclusion on the treatment effect.

The safety profile of Velcade in combination with rituximab, although being predictable, was not always manageable considering the high discontinuation rate due to AEs observed in the clinical study population (6.1% of patients in Vc-R arm vs only 1% in R arm discontinued).

The Vc-R combination exerted an overall greater toxicity compared to rituximab single agent both in terms of frequency as well as severity of AEs: more deaths from the treatment related AEs (6 vs. 2), more AEs in all safety aspects and more SAEs (18 vs. 11%) were observed in the Vc-R group.

The potential long-term neurotoxicity of bortezomib which is not uncommon remains an open question since the study was prematurely closed by MAH and therefore some important safety data are missing.

Results from the Global Health Status (EORTC QLQ-C30) showed that patients in rituximab group had an improvement from baseline beginning at Week 5 (end of first treatment cycle) continuing through Week 120 (28 months), while patients in Vc-R group had an improvement beginning at the Week 30 (end of treatment) continuing through Week 120 (28 months). These results reflect the greater toxicity of the combination as compared to rituximab monotherapy.

The greater toxicity observed for the Vc-R combination as compared to rituximab monotherapy, both in the overall population and in the subgroup with TLAT > 1 year, largely overwhelms the limited and questionable benefit of Velcade when added to rituximab in the treatment of relapsed FL.

5.1. Conclusions

The overall B/R of Velcade in combination with rituximab in the treatment of patients with relapsed follicular non-Hodgkin lymphoma or, as modified by the MAH in response to the CHMP Request for Supplementary Information, in the treatment of adult patients with relapsed follicular non-Hodgkin lymphoma whose time since last antilymphoma therapy was greater than one year, is negative.