18 December 2014
EMA/74029/2015 adopted
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: VELCADE

International non-proprietary name: BORTEZOMIB

Procedure No. EMEA/H/C/000539/II/0072

Marketing authorisation holder (MAH): Janssen-Cilag International N.V.

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ABMT	autologous bone marrow transplantation
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
ATP	all-treated population
BFI	Brief Fatigue Inventory
BR	bendamustine-rituximab
BSA	body surface area
CHMP	committee for medicinal products for human use
CHOP	cyclophosphamide-doxorubicin-vincristine-prednisone
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CR	complete response
CRF	case report form
CRu	complete response, unconfirmed
CSR	clinical study report
CT	computed tomography
CTC	Common Toxicity Criteria
CVAD	cyclophosphamide-vincristine-doxorubicin-dexamethasone
DLBCL	Diffuse Large B-Cell Lymphoma
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC-QLQ	European Organisation for Research and Treatment of Cancer- Quality of Life Questionnaire
EQ-5D	European Quality of Life-5 Dimension Questionnaire
EU	European Union
FACT	Functional Assessment of Cancer Therapy
FDA	United States Food and Drug Administration
FFPE	formalin-fixed paraffin embedded
GCB	germinal center B-like
GCP	good clinical practice
G-CSF	granulocyte colony stimulating factor
GOG	Gynecologic Oncology Group
HBV	Hepatitis B virus

HIV	human immunodeficiency virus
HR	hazard ratio
ICF	Informed consent form
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IPI	International Prognostic Index
IRB	Institutional Review Board
IRC	Independent Review Committee
ITT	intent to treat
IV	intravenous(ly)
IVRS	interactive voice response system
IWRC	International Workshop to Standardize Response Criteria for Non-Hodgkin Lymphoma
KPS	Karnofsky Performance Status
LDH	lactate dehydrogenase
LVEF	left ventricular ejection fraction
MAH	marketing authorisation holder
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MIPI	mantle cell lymphoma international prognostic index
MIPIb	MIPI with biologic index
MM	multiple myeloma
MRU	medical resource utilization
MUGA	multiple uptake gated acquisition
NCI-CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
NEC	not elsewhere classified
NHL	Non-Hodgkin lymphoma
NTx	neurotoxicity
OR	odds ratio
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PO	orally
PP	per protocol
PR	partial response
PRO	patient-reported outcomes
PSMB	proteasome subunit B
QoL	quality of life
R-CHOP	rituximab-cyclophosphamide-doxorubicin-vincristine-prednisone
R-DHAP	rituximab-dexamethasone-cytarabine-cisplatin

R-FC	rituximab-fludarabine-cyclophosphamide
R-HyperCVAD	rituximab-fractionated cyclophosphamide-vincristine-doxorubicin-dexamethasone
ROW	rest of the world
SAP	Statistical Analysis Plan
SC	subcutaneous
SCT	stem cell transplantation
SD	standard deviation
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SPD	sum of the product of the diameters
TFI	treatment-free interval
TTNT	time to next treatment
TTP	time to progression
UK	United Kingdom
ULN	upper limit of normal
US	United States
VAS	visual analogue scale
Vc	VELCADE
VcR-CAP	VELCADE-rituximab-cyclophosphamide-doxorubicin-prednisone
VZV	Varicella zoster virus
WBC	white blood cell count

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International N.V. submitted to the European Medicines Agency on 12 June 2014 an application for a variation.

This application concerns the following medicinal product:

Centrally authorised Medicinal product(s): **For presentations: See Annex A**	**International non-proprietary name**
VELCADE	BORTEZOMIB

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication for the use of VELCADE in combination with rituximab, cyclophosphamide, doxorubicin and prednisone for the treatment of adult patients with previously untreated mantle cell lymphoma. Consequently, the MAH proposed updates of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC and the Package Leaflet.

The variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/78/2008 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The applicant received Scientific Advice from the CHMP on 24 April 2008. The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Daniela Melchiorri Co-Rapporteur: Outi Mäki-Ikola

Timetable	Actual dates
Submission date	12 June 2014
Start of procedure:	27 June 2014
CHMP Rapporteur Assessment Report	18 August 2014
CHMP Co-Rapporteur Assessment Report	18 August 2014
PRAC Rapporteur Assessment Report	25 August 2014
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	11 September 2014
CHMP Rapporteurs Joint Assessment Report	23 September 2014
Request for supplementary information (RSI)	25 September 2014
PRAC Rapporteur Assessment Report	17 November 2014
CHMP Rapporteurs Joint Assessment Report	21 November 2014
PRAC Rapporteur Updated Assessment Report	25 November 2014
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	4 December 2014
CHMP comments	8 December 2014
CHMP Rapporteurs updated Joint Assessment Report	15 December 2014
Opinion	18 December 2014

2. Scientific discussion

2.1. Introduction

Mantle Cell Lymphoma (MCL) is a B-cell Non-Hodgkin Lymphoma (NHL) and it accounts for about 6% of all NHL cases (1). In Europe, the annual incidence of MCL was similarly estimated as on average 0.45/100 000 persons based on cancer registry data from 20 countries in the beginning of the 21st century (2). For patients categorized as low-risk according to the Mantle Cell Lymphoma International Prognostic Index (MIPI), 5-year survival has been estimated to be 60%, while those in the intermediate- and high-risk groups have a median OS of 51 and 29 months, respectively (3).

In the European Union (EU) temsirolimus and ibrutinib are the approved treatments for relapsed or refractory MCL.

The applicant requested the approval for the following indication:

Velcade in combination with rituximab, cyclophosphamide, doxorubicin and prednisone is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma.

The final indication following CHMP review of this application is:

Velcade in combination with rituximab, cyclophosphamide, doxorubicin and prednisone is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation.

Bortezomib is a proteasome inhibitor. 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 ubiquitinated proteins. The ubiquitin proteasome pathway plays an essential role in regulating 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 (SmPC section 5.1).

The recommended dose is 1.3 mg/m^2 body surface area twice weekly for two weeks on days 1, 4, 8, and 11, followed by a 10 day rest period on days 12-21. This 3 week period is considered a treatment cycle. Six Velcade cycles are recommended, although for patients with a response first documented at cycle 6, two additional Velcade cycles may be given. At least 72 hours should elapse between consecutive doses of Velcade. The following medicinal products are administered on day 1 of each Velcade 3 week treatment cycle as intravenous infusions: rituximab at 375 mg/m^2, cyclophosphamide at 750 mg/m^2 and doxorubicin at 50 mg/m^2. Prednisone is administered orally at 100 mg/m^2 on days 1, 2, 3, 4 and 5 of each Velcade treatment cycle (SmPC section 4.2).

2.2. Non-clinical aspects

2.2.1. Introduction

The non-clinical data submitted by the applicant included literature data with a summary of the understanding of the mechanism of anti-cancer activity of bortezomib in MCL. An updated ERA was also submitted.

2.2.2. Pharmacology

Bortezomib is a proteasome inhibitor, specifically designed to inhibit the chymotrypsin like activity of the 26S proteasome in mammalian cells. The role of proteasome inhibitors in the treatment of MCL was recently reviewed [4]. Pham et al. [5] concluded that bortezomib inhibits MCL tumor cell growth through two control mechanisms: cell cycle arrest and induction of cell death. Multiple mechanisms may contribute to these effects, including inhibition of the NF-κB pathway by stabilization of IκB, stabilization and increased intracellular levels of cyclindependent kinase inhibitors, such as p27 and p21, and induction of mitochondrial depolarization and apoptosis by activation of the proapoptotic Bcl-2 family member, Noxa (Latin for damage) [5,6,7]. Activation of Noxa was shown to mediate bortezomib induced apoptosis in both bortezomib sensitive and resistant MCL cell lines, while down regulation of Noxa with siRNA protected the cell lines against bortezomib-induced apoptosis [5]. The findings suggested that Noxa may not contribute to the mechanisms of resistance to bortezomib. Bortezomib has been shown to cause cell cycle arrest in G1 with rapid induction of apoptosis. In addition, G1 cell cycle arrest has been associated with inhibition of cyclin D1 expression [6].

Reduced expression of p27 and loss of normal p53 function are both associated with a poor prognosis in MCL and the intracellular levels of p27 and p53 are both modulated by proteasomal degradation [9,10,11,12].

In one study, lysates were prepared from primary MCL tumors, and tested for proteasome-mediated degradation of p27 protein [9]. Lysates from patients with more rapidly progressive MCL tended to show more rapid degradation of p27. In another series of experiments in human MCL cell lines, treatment with the

proteasome inhibitor lactacystin resulted in accumulation of p21 and p53, inhibition of proliferation and induction of caspase-dependent apoptosis [11]. Therefore, it is possible that inhibition of the proteasome by bortezomib results in increased intracellular levels of p27, p21, and p53, and that this contributes to activity in MCL. More recently, transcription repressor PR domain zinc finger protein 1 (PRDM1) was also suggested to be an important regulator of apoptotic responses to bortezomib [13]. Bortezomib treatment of MCL cell lines rapidly induced PRDM1 expression leading to downregulation of the proliferation associated proteins MKI67 and proliferating cell nuclear antigen (PCNA). Expression of PRDM1 was also associated with apoptosis.

In preclinical studies, bortezomib has also been shown to be additive or synergistic with other clinically active agents in MCL. The combination of bortezomib and rituximab in MCL cell lines and primary cultures from patients with MCL produced additive apoptotic effects [14]. In a separate study, bortezomib combined with rituximab plus cyclophosphamide enhanced apoptosis in MCL cell lines and primary cultures established from patient samples *in vitro* [15]. *In vivo*, the combination of bortezomib with rituximab plus cyclophosphamide induced a marked regression of established Jeko-1 MCL tumor xenografts, which was not observed when the compounds were administered as single agents. Bortezomib was reported to have synergistic activity with cytarabine in three out of four MCL cell lines in vitro [16]. Enhanced activity was also reported for the combination of bortezomib and arsenic trioxide in MCL cell lines and MCL primary cultures explanted from patients [17].

2.2.3. Pharmacokinetics

No new pharmacokinetic data have been submitted.

2.2.4. Toxicology

No new toxicology data have been submitted.

2.2.5. Ecotoxicity / environmental risk assessment

Phase I

Screening for Persistence, Bioaccumulation and Toxicity (PBT)
The log Kow, of bortezomib is 2 (pH=7), which is lower than the trigger value of 4.5. Consequently, no PBT-assessment is performed.

Calculation of the predicted environmental concentration (PECsw)

The PECsw has been refined considering:

- the rarity of the new condition (MCL) for which the use of Velcade is being proposed,
- that since 2004 in EU bortezomib has been used in the treatment of Multiple Myeloma (MM), that although rare is significantly prevalent than MCL (MM=1-5 / 10 000; MCL=1-9 / 100 000 by Orphanet),
- the prevalence data is further limited when front line setting is considered,
- the use of Velcade in hospitals setting throughout Europe.

In conclusion no significant increase in environmental exposure is anticipated based on this extension of indication.

2.2.6. Discussion on non-clinical aspects

Literature based data from non-clinical studies of the mechanism of action of bortezomib supports its activity in MCL. Bortezomib inhibits MCL tumour cell growth through reversible inhibition of the proteasome activity. Multiple mechanisms may contribute to cell cycle arrest and induction of cell death; bortezomib inhibits the NF-κB pathway, upregulates important cell cycle inhibitors such as p27 and p21, and activates proapoptotic pathways such as Noxa. In nonclinical combination studies, bortezomib was additive or synergistic with other clinically active agents (such as rituximab, cyclophosphamide) in vitro in MCL patient cells and in vivo MCL tumor xenograft model.

2.2.7. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of active substance.

Considering the above data, bortezomib is not expected to pose a risk to the environment.

The non-clinical data submitted by the MAH support the sought indication.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1: Overview of the Efficacy Studies included in the submission

Study ID	No. of study centres / locations	Design	Study Posology	Number of Patients	Diagnosis Inclusion criteria	Primary Endpoint
LYM-3002	128 centers EU: Belgium, Poland, Czech Republic, Spain, Hungary, Romania, Austria, Italy, Germany, Portugal, France Non-EU: Canada, United States of America, Russia, China,	Randomized, open label, multicenter, prospective	Velcade 1.3 mg/m^2 IV days 1,4,8,11 as part of VcR-CAP administered every 21 days for 6-8 cycles	243	Previously untreated MCL	PFS

	Ukraine, Brazil, Thailand, Japan, India, Israel, Tunisia, Turkey, Colombia, S.Korea, Chile, Singapore, Taiwan					

2.4. Discussion and Conclusions on clinical pharmacology

No additional pharmacokinetic or pharmacodynamic studies were conducted in support of this application. The pharmacokinetics and pharmacodynamics have been evaluated and approved in the previous applications of Velcade. There is no need to conduct pharmacological analyses in order to support the new indication.

2.5. Clinical efficacy

2.5.1. Dose response study

No new dose-response study has been submitted with this application.

The selected dose and schedule of cyclophosphamide and doxorubicin are based on the dosing of these agents in the standard R-CHOP regimen. Regarding alternative Velcade dosing regimens in combination with an R-CHOP backbone, limited information is available in the medical literature. The MAH provided the results of a Phase 1/2 study in subjects with untreated Diffuse Large B-Cell Lymphoma (DLBCL) or MCL, in which standard R-CHOP was combined with one of 3 dose levels of Velcade (0.7 mg/m^2, 1.0 mg/m^2, and 1.3 mg/m^2) administered on Days 1 and 4 of each cycle. In the Phase 1 portion of the study Velcade 1.3 mg/m^2 was found to be tolerable with this schedule. The primary toxicities of Velcade with standard R-CHOP were neuropathy in addition to reversible myelosuppression. Velcade with standard R-CHOP resulted in an 86% CR/CRu rate for evaluable subjects with DLBCL, compared with historical rates of 75% to 86% for R-CHOP alone.

A study from the Wisconsin Oncology Network investigated the addition of Velcade to the R-CVAD regimen in MCL subjects. Velcade was given at a dose of 1.3 mg/m^2 on Days 1 and 4 of each cycle. The major toxicities from VcR-CVAD were myelosuppression (neutropenia, and thrombocytopenia) and peripheral neuropathy. The severity of myelosuppression did not appear to be altered by the addition of Velcade, however, there was clearly an increased risk for peripheral neuropathy when combining VELCADE and vincristine. The overall response rate (ORR) was 90% and the CR/CRu rate was 77%.

In a Phase 2 study from the French Adult Lymphoma Study Group (GELA), subjects were randomized to 1 of 2 schedules of Velcade, administered biweekly (Arm A; Days 1, 4, 8, and 11) or weekly (Arm B; Days 1 and 8), combined with 6 cycles of R-CHOP. The most common drug-related non-hematologic toxicities were neurologic toxicity (70% in biweekly and 71% in weekly) and more severe neurologic toxicity occurred in the biweekly Velcade arm. Grade 3 and 4 thrombocytopenia occurred in 14% of cycles and only among subjects in the biweekly arm. The two treatment arms could not be compared statistically; however, the investigators concluded that the biweekly schedule seems to lead to better efficacy results than the weekly schedule (CR/CRu rate, 90% versus 79%, respectively). However the peripheral neuropathy of the biweekly schedule in combination with vincristine was considered too high.

The MAH also provided an exploratory post-hoc analysis of LYM-3002 evaluating the impact of Velcade dose intensity on OS in newly diagnosed MCL patients receiving VcR-CAP. For this analysis, Velcade dose intensity

(total Velcade dose received per cycle) during Cycles 1–6 was calculated in Study LYM-3002. The median value was selected as a cut-off for dichotomization of patients to be included in lower or higher (<4.6 vs ≥4.6 mg/m^2/cycle) dose intensity groups. Overall survival was then compared between groups, among subjects who had received ≥6 cycles of Velcade (n=181). A landmark analysis (from the end of Cycle 6) was performed. From the landmark, OS was found to be significantly longer in the higher (n=93) versus lower (n=88) Velcade dose intensity group in univariate analysis (HR 0.43 [0.23, 0.80]; p=0.0059).

2.5.2. Main study

Study LYM-3002

Methods

Study LYM-3002 was a phase 3, randomized, open-label, multicenter, prospective study comparing the efficacy and safety of Rituximab, Cyclophosphamide, Doxorubicin, Velcade, and Prednisone (VcR-CAP) versus Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP) in subjects with newly diagnosed MCL who were ineligible or not considered for bone marrow transplantation.

Study participants

Inclusion criteria

The study included adult patients with MCL (stage II, III or IV) evidenced by histology and either expression of cyclin D1 (in association with CD20 and CD5) or evidence of t(11;14) such as cytogenetics, FISH or PCR. Patients must have had at least 1 measureable site of disease, no prior therapies for MCL and be assessed by the treating physician (Amendment 2) as ineligible for bone marrow transplantation. Furthermore, patients were required to have Eastern Cooperative Oncology Group (ECOG) status score of ≤2, absolute neutrophil count (ANC) ≥1500 cells/μL, platelet count ≥100,000 cells/μL (or ≥75,000 cells/μL if thrombocytopenia was considered by the investigator to be secondary to MCL), Alanine transaminase (ALT) ≤3 times the ULN, aspartate transaminase (AST) ≤3 times ULN, total bilirubin ≤1.5 times ULN, calculated creatinine clearance ≥20 mL/min.

Female subjects were required to be post-menopausal for at least 1 year, surgically sterile, or practicing an effective method of birth control and had a negative serum β–hCG or urine pregnancy test at screening. They also agreed to continue birth control measures for at least 6 months after terminating treatment; Male subjects agreed to use an acceptable method of contraception.

All subjects signed an informed consent document and, the ones of them who participated in the pharmacogenomics component of the study, an informed consent form (ICF) for pharmacogenomics research. Acquisition of tumor sample collections was required for all subjects (when available); all other sample collections were optional.

Exclusion criteria

Patients were excluded if they had: prior treatment with Velcade, antineoplastic (including unconjugated therapeutic antibodies), experimental or radiation therapy, radio-immunoconjugates, toxin immunoconjugates for the treatment of MCL; major surgery within 2 weeks before randomization; peripheral neuropathy or neuropathic pain of Grade 2 or higher; active systemic infection requiring treatment; history of allergic reaction attributable to compounds containing boron, mannitol, or

hydroxybenzoates; known anaphylaxis or immunoglobulin E-mediated hypersensitivity to murine proteins or to any component of rituximab; serious medical condition (eg, cardiac failure [New York Heart Association Class III or IV, or left ventricular ejection fraction {LVEF} <50%], active peptic ulceration, or uncontrolled diabetes mellitus), or psychiatric illness; concurrent treatment with another investigational agent.

If a subject received doxorubicin for any condition other than MCL, the maximum dose and exposure received prior to entry into this study may not have exceeded 150 mg/m^2. A short course (maximum of 10 days; ≤100 mg/day) of prednisone or equivalent steroids was allowed to treat symptoms in subjects with advanced disease who entered the Screening Phase and were awaiting randomization.

Treatments

Patients were randomised in ratio 1:1 to receive VcR CAP or R CHOP for 6 cycles (1 cycle: 21 days), or 8 cycles if a response is first documented at Cycle 6 assessment.

VcR CAP: Velcade 1.3 mg/m^2 IV on Days 1, 4, 8, and 11, in combination with rituximab 375 mg/m^2 IV on Day 1, cyclophosphamide 750 mg/m^2 IV on Day 1, doxorubicin 50 mg/m^2 IV on Day 1, prednisone 100 mg/m^2 per os on Day 1 to Day 5 of a cycle.

R CHOP: Rituximab 375 mg/m^2 IV on Day 1,cyclophosphamide 750 mg/m2 IV on Day 1, doxorubicin 50 mg/m2 IV on Day 1, vincristine 1.4 mg/m2 (maximum total of 2 mg) IV on Day 1, prednisone 100 mg/m^2 p.o. on Day 1 to Day 5 of a cycle.

Patients may receive less therapy or deviate from the planned treatment dose and schedule due to adverse events. Dose or schedule re-escalations were not permitted for Velcade after modification for neuropathic pain or peripheral sensory neuropathy.

Objectives

The primary objective of the study was to determine superiority of VcR-CAP versus R-CHOP treatment, in terms of progression-free survival (PFS), as assessed by an Independent Radiology Review Committee (IRC).

Secondary objectives were to evaluate Time to Progression (TTP), Time to Next Anti-Lymphoma treatment (TTNT), duration of Treatment-Free Interval (TFI), Overall Response Rate (ORR), Complete Response Rate (CRR= CR/complete response – unconfirmed [CRu]), Overall Survival (OS), duration of response (CR, CRu, or partial response [PR]), time to response and rate of durable response.

Exploratory Objectives included: identification of patient populations likely to respond to VcR-CAP or R-CHOP (through the evaluation of biomarker data); evaluation of patient-reported outcomes (PROs) utilizing the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30), the European Quality of Life-5 Dimension Questionnaire (EQ-5D) and Brief Fatigue Inventory (BFI) instruments.

Outcomes/endpoints

The primary objective of the study was to compare Progression-Free Survival (PFS) between patients treated with VcR-CAP and R-CHOP, as assessed by IRC, defined as the interval between the date of randomization and the date of PD or death, whichever occurred first, using the intent-to–treat (ITT) population. Subjects who withdrew from the study (ie, withdrawal of consent, lost to follow-up) or started anti-neoplastic therapy without documented PD, or who died >6 months after the last disease assessment, or without PD before clinical cut-off were censored at the time of the last adequate (CT scan available) disease assessment.

Secondary efficacy objectives included: Time to Progression (TTP: duration from the date of randomization until the date of first documented evidence of PD or relapse for subjects who experienced CR or CRu), Time to Next Anti-Lymphoma treatment (TTNT: time from the date of initiation of study treatment as per protocol to the start date of new anti-lymphoma treatment), duration of Treatment-Free Interval (TFI: time from the date of last dose plus 1 day to the start date of the new treatment), Overall Response Rate (or Overall Radiological Response, ORR: the proportion of subjects who achieved CR, CRu, or PR relative to the response-evaluable population, according to the modified IWRC), Complete Response Rate (the proportion of subjects who achieved CR or CRu relative to the response-evaluable population), Overall Survival (OS: time from the date of randomization to the date of the subject's death), duration of complete response (calculated from the date of initial documentation of a CR or CRu to the date of first documented evidence of PD or death due to PD), duration of response (calculated from the date of initial documentation of CR, Cru or PR to the date of first documented evidence of PD or death due to PD), time to response (from the date of randomization to the date of initial CR, CRu, or PR) and rate of durable response (defined as a CR, Cru or PR with a duration ≥6 months).

Sample size

The sample size calculation for the study population was based on the assumptions that the median PFS with R-CHOP treatment was 18 months and that VcR-CAP treatment would improve the median PFS by 40% (ie, from 18 to 25 months). It was estimated that 295 events (PD or death) would provide 80% power (alpha=0.05, 2-sided) to detect such an improvement. Assuming a 24-month accrual and 18-month follow-up, a total of 486 subjects was needed for the study (243 subjects per treatment group).

Randomisation

Subjects were assigned in a 1:1 ratio to one of the 2 treatment groups stratified by IPI (0-1, 2, 3, and 4-5) and stage of disease at diagnosis (II, III, and IV). Randomization was based on two stratification factors: International Prognostic Index (0-1, 2, 3, and 4-5) and stage of disease at diagnosis (II, III, and IV).

Blinding (masking)

N/A

Statistical methods

The primary population for efficacy analyses was the ITT population, with sensitivity analyses performed on the centrally confirmed MCL population and PP populations. All statistical tests were 2-sided. The primary hypothesis was tested at the 0.05 significance level (overall). The Kaplan-Meier method was used to estimate the distribution of the primary endpoint (PFS) for each treatment group. The primary treatment comparison was based on a stratified log-rank test. The hazard ratio (HR) and its 95% confidence interval (CI) were estimated based on a stratified Cox's model with treatment as the explanatory variable. The sensitivity analyses for PFS among centrally confirmed MCL subjects, for PFS without censoring subsequent therapy and for PFS censoring after more than 1 missing adequate disease assessment, were performed similarly. The unstratified log-rank test and the unstratified Cox regression model were performed as sensitivity analyses.

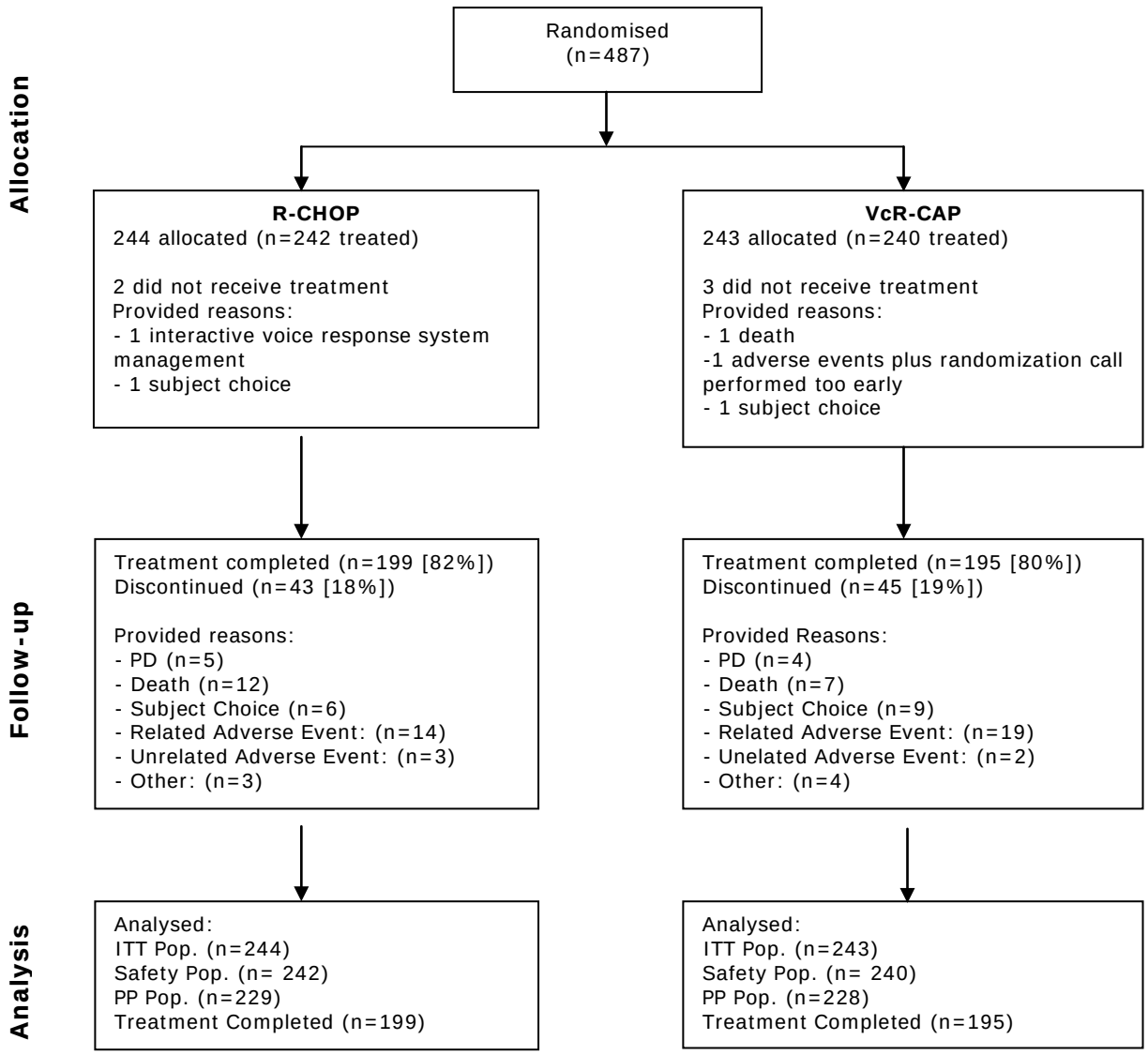
The secondary hypotheses were tested sequentially at the nominal 0.05 significance level in the following order: 1) TTP; 2) TTNT; 3) CR rate (CR+CRu) and 4) OS. A secondary hypothesis was tested only if the primary hypothesis was rejected along with all the secondary hypotheses that preceded it. However, OS was to be analyzed regardless of what happened to the other endpoints in the hierarchical test.

Three interim analyses were performed during the study and the significance level at an interim analysis was determined by the observed number of events at the time of the interim analysis using the O'Brien-Fleming spending function.

The first interim analysis was planned after the first 100 subjects had been randomized into the study in order to assess the safety and concordance rate of the diagnosis of MCL between central review and the investigator assessment of the diagnosis. The second interim analysis (review of safety data) was planned after 100 subjects per arm had either completed or discontinued study treatment. The third interim analysis (superiority and futility) was pre-specified after at least 148 events had occurred and the O'Brien-Fleming spending function method was used. The alpha allocated for the interim was 0.003 (2-sided) with 148 events and was 0.049 (2-sided) for the final analysis.

Results

Participant flow



Recruitment

The first subject was randomized on 26 May 2008 and the last on 05 December 2011. The last dose of study medication was given on 13 May 2012. Subjects were enrolled from 128 centers in 28 countries.

Conduct of the study

The original protocol was issued 13 December 2007. There were 5 amendments to the original protocol up to the cut-off date of the clinical study report (CSR) analysis.

Amendment 1 (01 October 2008: 18 subjects accrued): clarification was added that the IDMC would review data for interim analyses of safety, efficacy and the concordance rate of histological review; TFI added as a secondary objective; MRU added as an exploratory objective; subjects who withdrew could agree to provide information (ie, outcome of adverse events and survival status); subjects with initial response documented in Cycle 6 could receive 2 further cycles of therapy; central radiology review and assessments based on modified IWRC criteria; clarifications to definition of PFS, TTP. OS, TTNT, TFI; clarifications to definitions of measureable and assessable disease, criteria for response categories; ECG/ECHO/MUGA scans added to document baseline abnormalities; clarification that carriers of hepatitis B were allowed, but those with active hepatitis B or human immunodeficiency virus (HIV) were excluded; guidance on management of study drug toxicities added; defined minimum laboratory requirements at the beginning of each cycle (other than Cycle 1) before study drug administration; clarification was added that patients for whom bone marrow transplantation was not available and patients who refused a transplant as frontline treatment were eligible for the study; additional clarifications were made to other subject inclusion/exclusion criteria, dose adjustments, and statistical analyses.

Amendment 2 (26 February 2009: 74 subjects accrued): modification of inclusion criterion restricting enrollment to subjects deemed ineligible for transplantation as assessed by the treating physician based on clinical criteria (eg, age or presence of comorbidities); subjects who were eligible, but not considered for transplantation due to other than clinical reasons (e.g., cost or site not performing transplantation), were no longer eligible for the study.

Amendment 3 (16 September 2009: 179 subjects accrued): an additional (second) interim analysis for safety was added to allow review of cumulative toxicity once there was sufficient exposure data; confirmation of MCL could be made by an independent lymphoma expert, based on local diagnostic and clinical information if central review of pathology specimen was impossible because of insufficient tumor material; review of concordance rate between central pathology review and local pathology diagnosis to be repeated at 50% accrual; urinalysis, other than for pregnancy, removed; clarification of PFS sensitivity analysis, sampling for biomarker analysis, and procedures when a subject is reported to have PD; inclusion of prophylaxis for herpes zoster reactivation and granulocyte colony stimulating factor (G-CSF) for prevention and treatment of neutropenia/febrile neutropenia; guidance added on causality and dose adjustments for hematologic toxicity for study drugs added.

Amendment 4 (23 September 2010: 315 subjects accrued). The amendment was based on the feedback from IDMC on the second interim analysis for safety and to provide more clarity and guidance on some aspects of the study. Amendment 5 (09 August 2011: 450 subjects accrued). A futility stopping guideline was added for the prospectively planned interim analysis.

Protocol Deviations

The major protocol deviations are summarized in Table 2.

Table 2. Summary of Subjects with Major Protocol Deviations; Intent-to-treat Analysis Set (Study LYM-3002)

	R-CHOP	VcR-CAP	Total
Analysis set: intent-to-treat subjects	244	243	487
Total no. subjects with deviation	11 (4.5%)	46 (18.9%)	57 (11.7%)
Protocol deviation coded term			
Treatment deviation	4 (1.6%)	41 (16.9%)	45 (9.2%)
Selection criteria not met	4 (1.6%)	5 (2.1%)	9 (1.8%)
Violation of study procedures	3 (1.2%)	1 (0.4%)	4 (0.8%)
Excluded concomitant medication	1 (0.4%)	0	1 (0.2%)

Key: R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone;
VcR-CAP=VELCADE, rituximab, cyclophosphamide, doxorubicin, and prednisone.
Note: Percentages calculated with the number of subjects in each group as denominator.

Baseline data

Baseline demographic characteristics, factors of stratifications and disease characteristics are summarized in Table 3, Table 4 and Table 5, respectively.

Table 3. Demographic and Baseline Characteristics; Intent-to-treat Analysis Set (Study LYM-3002)

	R-CHOP	VcR-CAP	Total
Analysis set: intent-to-treat subjects	244	243	487
Age (years) [a]			
N	244	243	487
≤ 65	117 (48.0%)	124 (51.0%)	241 (49.5%)
> 65	127 (52.0%)	119 (49.0%)	246 (50.5%)
Mean (SD)	64.4 (8.78)	64.2 (9.68)	64.3 (9.23)
Median	66.0	65.0	66.0
Range	(34; 82)	(26; 88)	(26; 88)
Sex			
N	244	243	487
Male	182 (74.6%)	178 (73.3%)	360 (73.9%)
Female	62 (25.4%)	65 (26.7%)	127 (26.1%)
Race			
N	244	243	487
Asian	68 (27.9%)	88 (36.2%)	156 (32.0%)
White	172 (70.5%)	151 (62.1%)	323 (66.3%)
Black or African American	0	3 (1.2%)	3 (0.6%)
Other	4 (1.6%)	1 (0.4%)	5 (1.0%)
Weight (kg)			
N	243	243	486
Mean (SD)	69.98 (13.338)	71.20 (14.885)	70.59 (14.132)
Median	69.50	69.00	69.00
Range	(40.0; 108.9)	(38.5; 134.9)	(38.5; 134.9)
Height (cm)			
N	243	243	486
Mean (SD)	167.63 (8.255)	167.24 (8.786)	167.44 (8.518)
Median	168.00	167.00	168.00
Range	(144.0; 190.0)	(144.0; 192.0)	(144.0; 192.0)
BSA (m2)			
N	243	243	486
Missing	1	0	1
< 1.5	16 (6.6%)	12 (4.9%)	28 (5.8%)
1.5 – 2	199 (81.9%)	193 (79.4%)	392 (80.7%)
> 2	28 (11.5%)	38 (15.6%)	66 (13.6%)
Mean (SD)	1.79 (0.194)	1.80 (0.215)	1.80 (0.205)
Median	1.79	1.77	1.79
Range	(1.3; 2.3)	(1.3; 2.6)	(1.3; 2.6)
ECOG			
N	243	243	486
Missing	1	0	1
0:Asymptomatic	85 (35.0%)	111 (45.7%)	196 (40.3%)
1:Symptomatic, fully ambulatory	127 (52.3%)	101 (41.6%)	228 (46.9%)
2:Symptomatic, in bed < 50% of the day	31 (12.8%)	31 (12.8%)	62 (12.8%)

Key: R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone;
VcR-CAP=VELCADE, rituximab, cyclophosphamide, doxorubicin, and prednisone.
kg=kilogram; cm=centimeter; BSA=Body Surface Area; ECOG=Eastern Cooperative Oncology Group.
[a]Age at the date of randomization.

Table 4. Distribution of Stratification Factors Based on CRF; Intent-to-treat Analysis Set (Study LYM-3002)

	R-CHOP	VcR-CAP	Total
Analysis set: intent-to-treat subjects	244	243	487
IPI risk (IPI score)			
N	243	243	486
Low (0 - 1)	43 (17.7%)	43 (17.7%)	86 (17.7%)
Low-intermediate (2)	67 (27.6%)	71 (29.2%)	138 (28.4%)
High-intermediate (3)	91 (37.4%)	83 (34.2%)	174 (35.8%)
High (4 - 5)	42 (17.3%)	46 (18.9%)	88 (18.1%)
Stage of disease at diagnosis			
N	244	243	487
Stage II	16 (6.6%)	12 (4.9%)	28 (5.7%)
Stage III	42 (17.2%)	49 (20.2%)	91 (18.7%)
Stage IV	186 (76.2%)	182 (74.9%)	368 (75.6%)

Key: R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; VcR-CAP=VELCADE, rituximab, cyclophosphamide, doxorubicin, and prednisone; CRF=Case Report Form; IPI=International Prognostic Index.

Table 5. Disease Characteristics at Baseline; Intent-to-treat Analysis Set (Study LYM-3002)

	R-CHOP	VcR-CAP	Total
Analysis set: intent-to-treat subjects	244	243	487
Bone marrow aspirate or biopsy positive			
N	244	243	487
No	73 (29.9%)	72 (29.6%)	145 (29.8%)
Yes	171 (70.1%)	165 (67.9%)	336 (69.0%)
Indeterminate	0	6 (2.5%)	6 (1.2%)
Not evaluable	0	0	0
Bone marrow aspirate positive			
N	237	236	473
No	95 (40.1%)	93 (39.4%)	188 (39.7%)
Yes	137 (57.8%)	133 (56.4%)	270 (57.1%)
Indeterminate	4 (1.7%)	8 (3.4%)	12 (2.5%)
Not evaluable	1 (0.4%)	2 (0.8%)	3 (0.6%)
Bone marrow biopsy positive			
N	238	242	480
No	84 (35.3%)	85 (35.1%)	169 (35.2%)
Yes	153 (64.3%)	150 (62.0%)	303 (63.1%)
Indeterminate	0	5 (2.1%)	5 (1.0%)
Not evaluable	1 (0.4%)	2 (0.8%)	3 (0.6%)
Baseline LDH (U/L)			
N	244	243	487
Normal	158 (64.8%)	155 (63.8%)	313 (64.3%)
Elevated	86 (35.2%)	88 (36.2%)	174 (35.7%)
Mean (SD)	346.4 (279.58)	330.9 (210.37)	338.7 (247.35)
Median	269.7	270.0	270.0
Range	(93; 2852)	(88; 1398)	(88; 2852)
Reason for transplant ineligibility [a]			
N	244	243	487
Age	180 (73.8%)	175 (72.0%)	355 (72.9%)
Assessed as unable to tolerate high dose intensive chemo. [b]	14 (5.7%)	15 (6.2%)	29 (6.0%)
Co-morbidity	37 (15.2%)	37 (15.2%)	74 (15.2%)
Not considered for transplantation by investigator	17 (7.0%)	20 (8.2%)	37 (7.6%)
Other	26 (10.7%)	31 (12.8%)	57 (11.7%)

Key: R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone;
VcR-CAP=VELCADE, rituximab, cyclophosphamide, doxorubicin, and prednisone.
LDH=lactate dehydrogenase.
[a]A subject may have more than one reason per the case report form (CRF).
[b]Assessed as unable to tolerate high dose intensive chemotherapy regimens.

Based on medical monitor review of the 487 subjects in the ITT population after Amendment INT-2, 407 subjects were ineligible for transplant due to age (60 years or older) or medical reasons, and 80 subjects were eligible for transplant.

Numbers analysed

The primary efficacy analysis set was the Intent to Treat (ITT) population, which included all randomized subjects (N=487).

Secondary efficacy analyses were performed on the following sets:

-Per-protocol Population (N=457) defined as all randomized subjects who met all inclusion and exclusion criteria, who received at least 1 dose of study drug and underwent at least 1 post-baseline disease assessment (post-baseline tumor assessment by the IRC). Subjects in this population were analyzed according to the treatment to which they were randomized.

- Response-Evaluable Population (N=457) defined as all subjects in the ITT population, who received at least 1 dose of study drug, had at least 1 measurable tumor mass (>1.5 cm in the longest dimension and >1.0 cm in the short axis) at baseline and had at least 1 post-baseline tumor assessment by IRC, before any subsequent anti-lymphoma treatment.

- Biomarker Population (N[PSMB1]=271, N[PSMB5]=217, N[Ki67]=327) defined as all subjects in the ITT population whose biomaterial was available, who consented to participate in the biomarker and pharmacogenomics evaluations or future research, and had biomarker data generated for the biomarker evaluation.

- Safety Population (N=482) defined as all randomized subjects who received at least 1 dose of study drug.

- Centrally confirmed MCL Population (N=471) defined as all the subjects who had a central pathology review which confirmed the local diagnosis of MCL.

Outcomes and estimation

Primary objective: Progression free survival (IRC assessment)

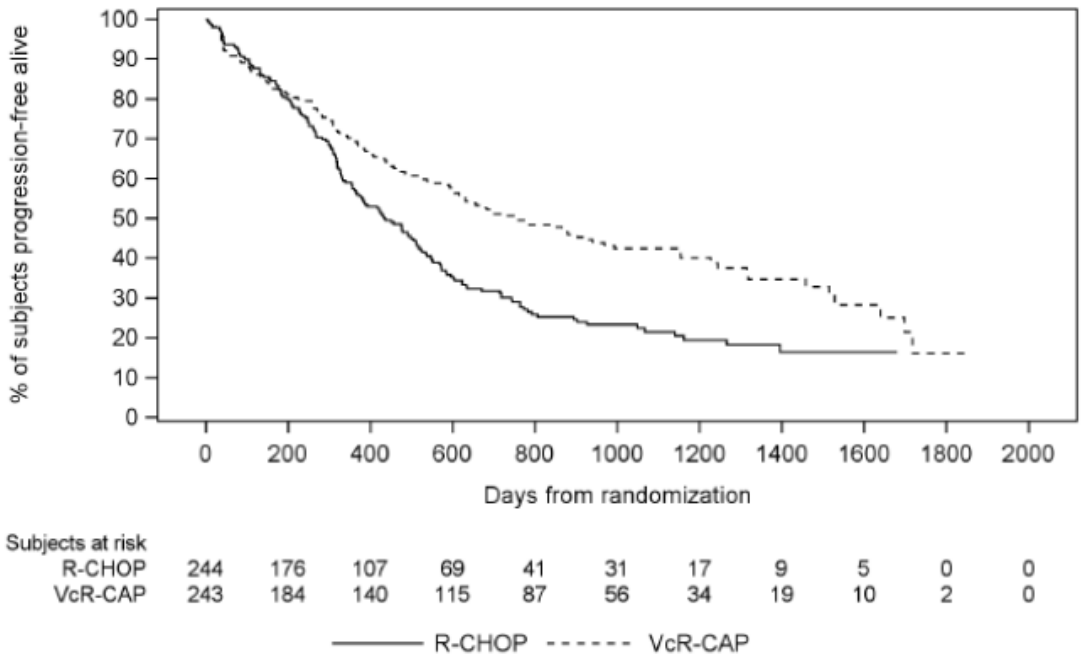
The efficacy results in terms of the primary endpoint of Progression free survival (cut-off date 02 December 2013), according to IRC assessment, are summarised in Table 6 and Figure 1.

Table 6. Summary of Progression-free Survival: per Independent Review Committee; Intent-to-treat Analysis Set (Study LYM-3002)

	R-CHOP	VcR-CAP
Analysis set: intent-to-treat subjects	244	243
Descriptive[a]		
Progression-free survival (days)		
Number of assessed	244	243
Number of censored (%)	79 (32.4%)	110 (45.3%)
Number of events (%)	165 (67.6%)	133 (54.7%)
25% quantile (95% CI)	248.0 (186.0; 298.0)	298.0 (214.0; 363.0)
Median (95% CI)	437.0 (365.0; 513.0)	751.0 (604.0; 969.0)
75% quantile (95% CI)	895.0 (714.0;1266.0)	1698.0 (1458.0;NE)
P-value[b]	<.001	
Hazard ratio (95% CI)[c]		0.63 (0.50; 0.79)

Key: R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone;
VcR-CAP=VELCADE, rituximab, cyclophosphamide, doxorubicin, and prednisone.
[a] Based on Kaplan-Meier product limit estimates.
[b] Based on Log rank test stratified with IPI risk and stage of disease.
[c] Hazards ratio estimate is based on a Cox´s model stratified by IPI risk and stage of disease. A hazard ratio < 1 indicates an advantage for VcR-CAP.
NE: Not estimable.

Figure 1. Kaplan-Meier Plot of Progression-free Survival: per Independent Review Committee; Intent-to-treat Analysis Set (Study LYM-3002)



Key: R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone;
VcR-CAP=VELCADE, rituximab, cyclophosphamide, doxorubicin, and prednisone.

Primary objective: Progression free survival (Investigator assessment)

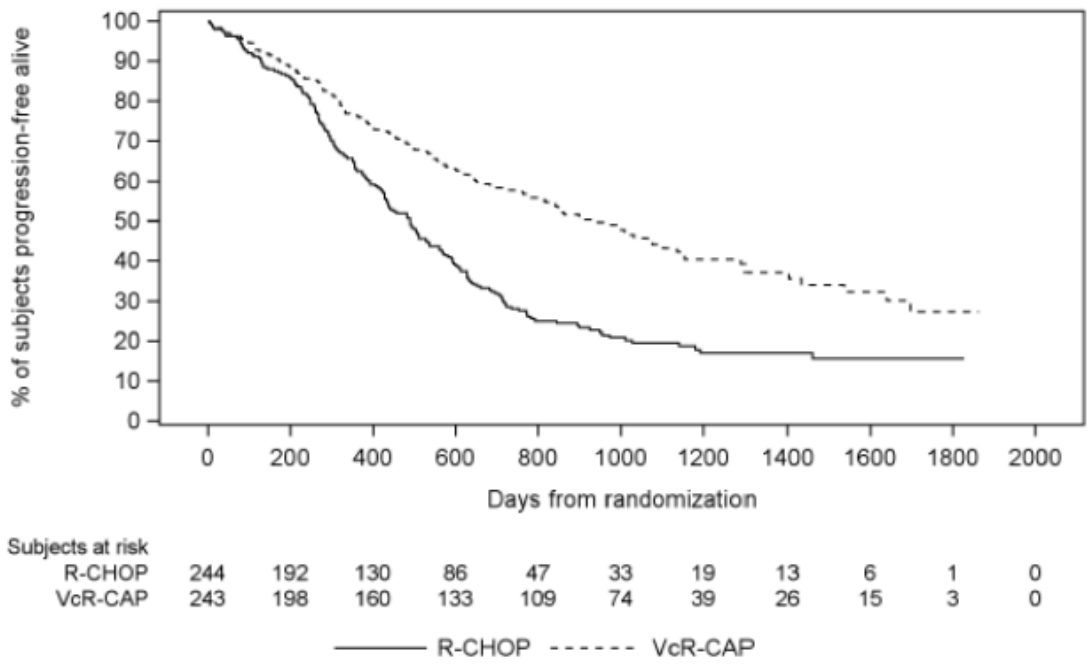
PFS results based on investigator assessment are reported in Table 7 and Figure 2.

Table 7. Summary of PFS per Investigator Assessment; Intent-to-treat Analysis Set (Study LYM-3002)

	R-CHOP	VcR-CAP
Analysis set: intent-to-treat subjects	244	243
Descriptive[a]		
Progression-free survival (days)		
Number of assessed	244	243
Number of censored (%)	65 (26.6%)	115 (47.3%)
Number of events (%)	179 (73.4%)	128 (52.7%)
25% quantile (95% CI)	271.0 (246.0; 304.0)	383.0 (308.0; 481.0)
Median (95% CI)	490.0 (427.0; 561.0)	934.0 (763.0;1136.0)
75% quantile (95% CI)	793.0 (710.0;1141.0)	NE (1538.0;NE)
P-value[b]	<.001	
Hazard ratio (95% CI)[c]		0.51 (0.41; 0.65)

Key: R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone;
VcR-CAP=VELCADE, rituximab, cyclophosphamide, doxorubicin, and prednisone.
[a] Based on Kaplan-Meier product limit estimates.
[b] Based on Log rank test stratified with IPI risk and stage of disease.
[c] Hazards ratio estimate is based on a Cox´s model stratified by IPI risk and stage of disease. A hazard ratio < 1 indicates an advantage for VcR-CAP.
NE: Not estimable.

Figure 2. Kaplan-Meier Plot of PFS per Investigator Assessment; Intent-to-treat Analysis Set (Study LYM-3002)



Key: R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone;
VcR-CAP=VELCADE, rituximab, cyclophosphamide, doxorubicin, and prednisone.

A summary of PFS results in subsets and sensitivity analyses is shown in Table 8.

Table 8. Summary of Primary and Sensitivity Analyses of PFS, All Subjects Analysis Set (Study LYM-3002)

	Total # of Events	Median (months)[a] R-CHOP	VcR-CAP	Difference	Hazard Ratio (95% CI)[b]	P-value[c]
IRC: ITT						
Primary Analysis	298	14.4	24.7	10.3	0.63 (0.50, 0.79)	<0.001
Unstratified Analysis	298	14.4	24.7	10.3	0.62 (0.50, 0.79)	<0.001
No Censoring for Subsequent Antineoplastic Therapy	302	14.4	24.0	9.6	0.63 (0.50, 0.80)	<0.001
Censoring for PD after More than 1 Missing Adequate Tumor Assessment	291	14.4	25.8	11.4	0.62 (0.49, 0.78)	<0.001
Using IRC Alternative Assessments of Transient Fluid Collection/Transient Lesion as Basis for PD	288	14.8	28.5	13.7	0.56 (0.44, 0.71)	<0.001
IRC: Per-protocol	282	14.8	27.9	13.1	0.59 (0.46, 0.75)	<0.001
IRC: Confirmation of MCL	287	14.8	24.0	9.2	0.64 (0.50, 0.81)	<0.001
Investigator: ITT	307	16.1	30.7	14.6	0.51 (0.41, 0.65)	<0.001

[a] Based on Kaplan-Meier product limit estimates.
[b] Hazards ratio estimate is based on a Cox's model. A hazard ratio < 1 indicates an advantage for VcR-CAP.
[c] Based on Log rank test.

Key Secondary endpoints

Overall Response Rate and Complete Response Rates

The efficacy results in terms of the secondary endpoint of Overall response rate (cut-off date 02 December 2013) are summarised in Table 9.

Table 9. Summary of Best Overall Response: per Independent Review Committee; Response-evaluable -Analysis Set (Study 26866138-LYM-3002)

	R-CHOP	VcR-CAP	P-value[c]	OR[d](95% CI)
Analysis set: response-evaluable subjects	228	229		
Overall complete response (CR+CRu)	95 (41.7%)	122 (53.3%)	0.007	1.688(1.148, 2.481)
CR	79 (34.6%)	106 (46.3%)		
CRu	16 (7.0%)	16 (7.0%)		
Overall radiological complete response (CR+CRu)[a]	162 (71.1%)	190 (83.0%)	0.002	2.037(1.294, 3.206)
Radiological CR	132 (57.9%)	163 (71.2%)		
Radiological CRu	30 (13.2%)	27 (11.8%)		
Partial response (PR)	42 (18.4%)	21 (9.2%)		
Overall response (CR+CRu+PR)[b]	204 (89.5%)	211 (92.1%)	0.275	1.428(0.749, 2.722)
Stable disease (SD)	15 (6.6%)	3 (1.3%)		
Progressive disease (PD)	9 (3.9%)	15 (6.6%)		

Key: R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; VcR-CAP=VELCADE, rituximab, cyclophosphamide, doxorubicin, and prednisone; OR=Odds Ratio; CR=Complete Response; PR=Partial Response; SD=Stable Disease; PD=Progressive Disease.
[a]Include all radiological CR+CRu, regardless the verification by bone marrow and LDH.
[b]Include all radiological CR+CRu+PR, regardless the verification by bone marrow and LDH.
[c] P-value from the Cochran Mantel-Haenszel Chi-Squared test, with IPI and Stage of Disease as stratification factors.
[d] Mantel-Haenszel estimate of the common odds ratio for stratified tables is used, with IPI risk and Stage of Disease as stratification factors. An odds ratio (OR) > 1 indicates an advantage for VcR-CAP.
Percentages calculated with the number of subjects in each group as denominator.

Other secondary endpoints

Based on IRC, median TTP was 490 days (16.1 months) in the R-CHOP group versus 929 days (30.5 months) in the VcR-CAP group (HR=0.58; p<0.001), median time to next anti-lymphoma treatment was 756 days (24.8 months) versus 1,353 days (44.5 months) (HR=0.50; p<0.001).

The TFI was 624 days (20.5 months) for the R-CHOP group, compared with 1,236 days (40.6 months) for the VcR-CAP group (HR=0.50; p<0.001).

The median time to initial response (CR, CRu or PR) by IRC assessment in the R-CHOP group was 50 days (1.6 months) compared with 42 days (1.4 months) in the VcR-CAP group (HR=1.54; p<0.001).

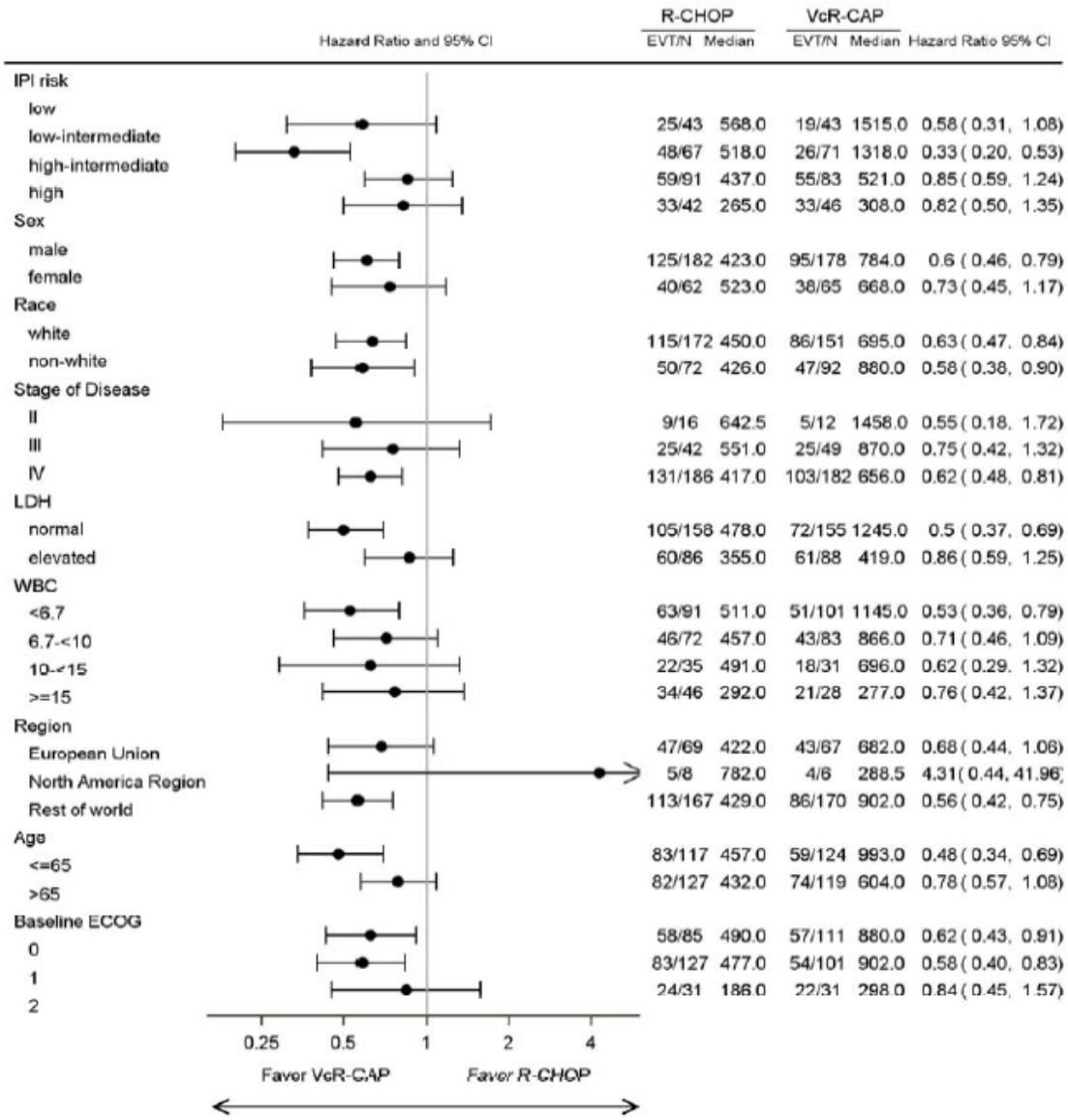
Based on IRC data, the median duration of overall response, median duration of response for complete responders and median duration of complete response in the VcR-CAP group versus R-CHOP group were as follows: 1,110 days (36.5 months) versus 459 days (15.1 months); 1,282 days (42.1 months) versus 563 days (18.5 months) and 1,282 days (42.1 months) versus 547 days (18.0 months), respectively.

Median OS was 1,714 days (56.3 months) in the R-CHOP group and not reached in the VcR-CAP group. The estimated HR was 0.80 (95% CI: 0.59, 1.10) (data not shown).

Ancillary analyses

Subgroup analyses for PFS in Study LYM-3002 are shown in Figure 3. Subgroups were stratified by IPI and stage of disease at diagnosis.

Figure 3 Forest plot for Progression-free Survival Subgroup Analyses: per Independent Review Committee; Intent-to-treat Analysis Set (Study LYM-3002)



Key: R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; VcR-CAP=VELCADE, rituximab, cyclophosphamide, doxorubicin, and prednisone.
Arrow in the plot represents that the confidence interval exceeds the display area.

Pre-specified additional subgroup analyses were performed for the subset of subjects in the United States + Canada + Western Europe (91 subjects in total, 18.7% of enrollment, 49 into the R-CHOP group and 42 into the VcR-CAP group) and for the EU subpopulation (136 subjects in total, 69 in the R-CHOP arm and 67 in the VcR-CAP group). For the first subgroup in the R-CHOP group, 49% of subjects had an IPI score of 3 (high-intermediate) and most (76%) had Stage IV disease. In the VcR-CAP group, 43% of subjects had an IPI score of 3 and 91% had Stage IV disease). The median PFS was 437 days (14.4 months) in the R-CHOP group and 592 days (19.4 months) in the VcR-CAP group, as IRC assessment. For the EU subgroup the

median PFS was 13.9 months in the R-CHOP group and 22.4 months in the VcR-CAP group (IRC assessment).

An ad hoc analysis has been performed for patients who underwent less than 6 cycles of VcR-CAP or R-CHOP: 63 subjects (R-CHOP: 31; VcR-CAP: 32) who received between 2 and 5 cycles of chemotherapy. As assessed by IRC, median PFS was 3.6 months for the VcR-CAP treatment group and 3.5 months for the R-CHOP treatment group. As assessed by investigator, median PFS was 5.7 months versus 3.5 months, respectively. Subjects included in this population very likely experienced some event that limited their exposure to between 2 and 5 cycles of treatment.

A post hoc subgroup analysis of PFS (per IRC assessment) by MIPIb risk category (low, intermediate, and high) was performed for the 327 subjects (164 subjects in the R-CHOP group and 163 subjects in the VcR-CAP group) with available Ki-67 biomarker results. The median PFS in the low-risk MIPIb subgroup was 504 days (16.6 months) in the R-CHOP group versus not estimable in the VcR-CAP (HR= 0.27; 95% CI: 0.10, 0.71); in the intermediate-risk subgroup was 526 days (17.3 months) versus 1,245 days (40.9 months), respectively (HR= 0.50; 95% CI: 0.32, 0.79); and in the high-risk subgroup was 362 days (11.9 months) versus 408 days (13.4 months), respectively (HR= 0.86; 95% CI: 0.57, 1.31)

Eighty-two (82) of subjects in the R-CHOP group (50%) and 84 (52%) of subjects in the VcR-CAP group were positive for Ki-67 (defined as Ki-67 >10%). For subjects who were Ki-67 negative, the median PFS in the R-CHOP group was 546 days [17.9 months] and in the VcR-CAP group was 1,245 days [40.9 months]; HR=0.60 (95% CI: 0.38, 0.94; p=0.024). For subjects who were Ki-67 positive, the median PFS in the R-CHOP group was 332 days [10.9 months] and in the VcR-CAP group was 604 days [19.8 months]; HR=0.59 (95% CI: 0.39, 0.88; p=0.009) (data not shown).

Summary of main study

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).

Table 10. Summary of Efficacy for trial LYM-3002

Title: A phase 3, randomized, open-label, multicenter, prospective study comparing the efficacy and safety of Rituximab, Cyclophosphamide, Doxorubicin, Velcade, and Prednisone (VcR-CAP) versus Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP) in subjects with newly diagnosed MCL who were ineligible or not considered for bone marrow transplantation.		
Study identifier	LYM-3002	
Design	Randomized, open-label, multicenter, prospective Phase 3 study	
	Duration of main phase Duration of Extension phase:	18 weeks 40 months follow-up
Hypothesis	Superiority	
Treatments groups	VcR-CAP	Velcade 1.3 mg/m^2 IV on Days 1, 4, 8, and 11, in combination with rituximab 375 mg/m^2 intravenous IV on Day 1, cyclophosphamide 750 mg/m^2 IV on Day 1, doxorubicin 50 mg/m2 IV on Day 1, prednisone 100 mg/m^2 per os (p.o.) on Day 1 to Day 5 of a 21 day (3 week) cycle for 6 cycles (or 8 cycles if a response is first documented at Cycle 6 assessment); 243 patients randomized

	R-CHOP		Rituximab 375 mg/m2 IV on Day 1,cyclophosphamide 750 mg/m^2 IV on Day 1, doxorubicin 50 mg/m2 IV on Day 1, vincristine 1.4 mg/m^2 (maximum total of 2 mg) IV on Day 1, prednisone 100 mg/m2 p.o. on Day 1 to Day 5 of a 21 day (3 week) cycle for 6 cycles (or 8 cycles if a response is first documented at Cycle 6 assessment); 244 patients randomized
Endpoints and definitions	Primary endpoint	Progression Free Survival (PFS) by IRC	The interval between the date of randomization and the date of PD or death, whichever occurred first, using the intent-to–treat (ITT) population, as assessed by IRC
	Primary endpoint	Progression Free Survival (PFS) by Investigator	The interval between the date of randomization and the date of PD or death, whichever occurred first, using the intent-to–treat (ITT) population, as assessed by Investigator
	Secondary endpoint	Overall Radiological Response (ORR)	The proportion of subjects who achieved CR, CRu, or PR relative to the response-evaluable population
	Secondary endpoint	Overall Complete Response (CRR)	The proportion of subjects who achieved CR or CRu relative to the response-evaluable population.
Database lock	10 January 2014		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent To Treat (ITT) Population by Independent Review Committee assessment (Clinical cut-off of 02 December 2013). N=487		
Descriptive statistics and estimate variability	Treatment group	VcR-CAP	R-CHOP
	Number of subject	243	244
	Median PFS by IRC (months)	24.7	14.4
	95% CI	(19.8, 31.8)	(12, 16.9)
	Median PFS by investigator (days)	934.0	490.0
	95% CI	(56.0, NE)	(47.2, NE)
	ORR N (%)	211 (92.1%)	204 (89.5%)
	95% CI	-	-
	CRR N (%)	122 (53.3%)	95 (41.7%)
	95% CI	-	-
Effect estimate per comparison	Primary endpoint: PFS by IRC	Comparison groups	VcR-CAP vs. R-CHOP
		hazard ratio	0.63
		95% CI	(0.50; 0.79)
		P-value	<.001
	Primary endpoint: PFS by Investigator	Comparison groups	VcR-CAP vs. R-CHOP
		hazard ratio	0.51
		95% CI	(0.41, 0.65)

		P-value	<.001
	Secondary endpoint: ORR	Comparison groups	VcR-CAP vs. R-CHOP
		odds ratio	1.428
		95% CI	(0.749, 2.722)
		P-value	0.275
	Secondary endpoint: CRR	Comparison groups	VcR-CAP vs. R-CHOP
		odds ratio	1.688
		95% CI	(1.148, 2.481)
		P-value	0.007
Notes	Stratification factors: International Prognostic Index (IPI) + stage of disease at diagnosis		

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

N/A

Clinical studies in special populations

N/A

Supportive study

Study M34103-053

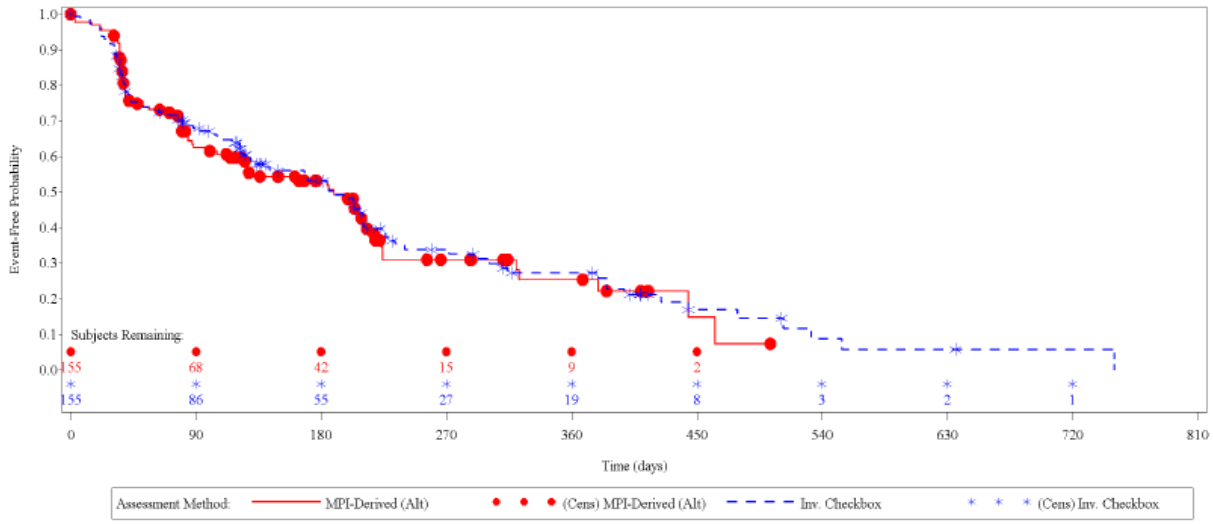
Study M34103-053 was a phase 2, single-arm, open-label, multicenter, 3-stage, prospective study in subjects with documented relapsed or refractory MCL, conducted at 50 centers in US and Europe.

A total of 155 patients with refractory/relapsed MCL were enrolled in this study and received single-agent Velcade 1.3 mg/m^2 at days 1, 4, 8, 11 of a 21-day treatment cycle up to 17 cycles. All patients were reported to have progressed during or relapsed following 1 (54%) or 2 (42%) prior line of therapy. Over 90% of the patients had previously received an alkylating agent, an anthracycline (or mitoxantrone), and rituximab, either in combination or as separate agents. More than one-third of patients (37%) had received prior high-intensity chemotherapeutics, including Hyper-CVAD, high-dose cytarabine, and SCT, with 30% of patients having received these high-intensity regimens as their last therapy prior to receiving single-agent Velcade.

The primary objective of this study was to determine if Velcade increases median TTP compared to historical controls in patients with MCL who have documented relapse or progression following 1 or 2 prior lines of antineoplastic therapy. The secondary objectives of this study included the response rate (CR/CRu/PR) to Velcade through the time of the first disease response evaluation, the overall CR rate (CR/CRu), the duration of response (DR) and the time to first response. Additional endpoints included OS and PFS.

Median TTP across all patients in the All-treated population (ATP) was 6.7 months (Figure #) and 6.9 months for patients in the PP population (ie, patients with documented MCL who had received an anthracycline/ mitoxantrone, an alkylating agent and rituximab prior to study entry).

Figure 4 - Kaplan-Meier Curve of Time to Progression in ATP Population (Study M34103-053)



Eleven patients (8%) experienced CR or CRu as best response on treatment, including 9 patients with CR and 2 patients with CRu and an additional 34 (24%) patients experienced PR. Patients who achieved CR or CRu had longer TTP compared to patients in other response categories.

With a median duration of follow-up of more than 26 months, median survival for both the ATP and the PP population was 23.5 months. Median survival for responders (CR+CRu+PR) was 35.4 months. At the time of database-lock, 62 (40%) of 155 ATP patients were alive, including 50 (39%) of 128 patients in the PP population and the Kaplan-Meier estimate of 1-year survival in all patients was 69% in both populations.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study LYM-3002 was a Phase III, randomised, open-label study comparing the efficacy and safety of the combination of velcade, rituximab, cyclophosphamide, doxorubicin and prednisone (VcR-CAP; n=243) to that of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP; n=244) in adult patients with previously untreated MCL (Stage II, III or IV). Patients in the VcR-CAP treatment arm received velcade (1.3 mg/m^2; on days 1, 4, 8, 11, rest period days 12-21), rituximab 375 mg/m^2 IV on day 1; cyclophosphamide 750 mg/m^2 IV on day 1; doxorubicin 50 mg/m^2 IV on day 1; and prednisone 100 mg/m^2 orally on day 1 through day 5 of the 21 day of velcade treatment cycle. For patients with a response first documented at cycle 6, two additional treatment cycles were given (see SmPC section 5.1).

No new dose-response study has been submitted with this application. The phase 1/2 studies summarized have shown the additive neurotoxicity of vincristine and Velcade, which justified the replacement of vincristine by Velcade in the VcR-CAP approach. While weekly Velcade led to improvement of efficacy, the GELA study suggested that it may be less effective than biweekly dosing, with fewer subjects achieving CR. In Study LYM-3002, the use of biweekly Velcade for only a brief treatment period (median 4 months) led to substantial improvements in long-term disease control as assessed by duration of response and time to next treatment. Such improvements may be difficult to achieve with once-weekly Velcade treatment. The selected dose and schedule of cyclophosphamide and doxorubicin are based on the dosing of these agents in the standard R-CHOP regimen.

Based on the above, the study is considered adequate with regard to drugs scheduling and dosing. Since blinding was problematic due to the different dose schedules for Velcade and Vincristine the open label design of the study was acceptable. Velcade was administered exclusively by IV route; however, the sought indication in MCL includes both Velcade IV and SC administration. This is considered acceptable since no relevant Velcade PK/PD differences were observed between Velcade administered IV and SC in the MM setting, and no significant differences on the Velcade SC bioavailability are expected between MM and MCL patients.

The study inclusion/exclusion criteria were considered appropriate to define a population of previously untreated MCL patients. The exclusion of stage I MCL patients was acceptable since these patients should receive a different, integrated therapeutic approach.

The demographic and baseline disease characteristics were generally well balanced between the two treatment arms: median patient age was 66 years, 74% were male, 66% were Caucasian and 32% Asian, 69% of patients had a positive bone marrow aspirate and/or a positive bone marrow biopsy for MCL, 54% of patients had an International Prognostic Index (IPI) score of $\geqslant$ 3, and 76% had Stage IV disease (SmPC section 5.1).

The validity of PFS as primary endpoint has been discussed and endorsed during the EMA scientific advice procedure. The choice of TTP, TTNT and TFI as secondary endpoints is deemed valid, since at present MCL is a chronic incurable disease, and treatment-free intervals are very valuable for the patient's quality of life. The estimate of ORR, CR and CR+CRu rates is also appropriate, primarily in the evaluation of the small set of transplant-fit patients.

Study LYM-3002 was in conclusion adequately designed to investigate the superior efficacy of VcR-CAP in previously untreated MCL patients unsuitable for haematopoietic stem cell transplantation.

Efficacy data and additional analyses

The primary efficacy endpoint was met in this study. Results from study LYM-3002 showed a clear superiority of VcR-CAP over R-CHOP in untreated MCL patients with regard to PFS by IRC assessment (24.7 vs 14.4 months respectively, HR 0.63, 95% [CI 0.50-0.79]; p<0.001). There was a good concordance between IRC and investigator assessment of PFS and the findings of primary analysis were supported by all relevant sensitivity analyses. Thus, the efficacy results were considered robust.

Secondary endpoints including time to progression, time to new treatment, treatment-free interval, complete response rates, duration of response and overall response rate supported the primary efficacy endpoint and favoured the VcR-CAP arm compared to the R-CHOP arm.

During the evaluation, the CHMP raised a major objection about the indication needing to be further discussed, with reference to the patients who were ineligible to transplantation. Further to amendments 1 and 2 of the original protocol, the majority of patients included were ineligible to transplantation for medical reasons and only 80 subjects by medical monitor assessment (42 subjects in the R-CHOP group and 38 subjects in the VcR-CAP group) would have been considered suitable for transplantation out of this trial. In the small transplant-fit population, CR (52.8%) and CR+CRu (66.7%) rates observed in VcR-CAP arm were lower comparing to those obtained with more intensive chemotherapy regimens, according to recent scientific literature, despite the favourable baseline characteristics (18). The broad indication initially proposed by the MAH: ”adult patients with untreated mantle cell lymphoma”, which could possibly include transplant-fit patients, was therefore not justified considering also that feasibility of bone marrow transplantation procedures after VcR-CAP was not specifically addressed by the study. Taking into account that patients should always receive the best available therapy and that at present there is no evidence that VcR-CAP should be preferred to more intensive treatments (i.e. R-hyperCVAD/HD-Cytarabine plus Methotrexate) in the first-line setting, VcR-CAP can be considered nonetheless a valuable treatment option

for patients not suitable for intensive chemotherapy regimens. To reflect this, the indication (see SmPC, section 4.1) has been restricted to treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation.

Overall, the baseline demographics and prognostic factors were well balanced although some imbalances were noted. It seems unlikely that such imbalances should influence the overall very convincing efficacy results.

2.5.4. Conclusions on the clinical efficacy

Study LYM-3002 has provided convincing evidence of clinical efficacy of bortezomib in combination with rituximab, cyclophosphamide, doxorubicin and prednisone in terms of the primary endpoint PFS compared with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone in adult patients with previously untreated mantle cell lymphoma. The combination with bortezomib resulted in a clinically meaningful and statistically significant improvement in the primary endpoint of PFS.

2.6. Clinical safety

Introduction

The evaluation of safety of the VcR-CAP combination derives from the studies reported in Table 11.

Table 11 Studies Included in the Summary of Clinical Safety Analysis

Study Number	Study Treatments[a]	Subjects in the Study Safety Analysis Set	Subjects in the Pooled Safety Analysis Set
Pooled Studies			
LYM-3002	R-CHOP	242	242
	VcR-CAP	240	240
LYM-2034	R-CHOP	79	79
	VcR-CAP	82	82
Non-pooled Study			
M34103-053	VELCADE monotherapy	155	0
Grand Total		798	Pooled R-CHOP: 321 Pooled VcR-CAP: 322

R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; VcR-CAP=VELCADE, rituximab, cyclophosphamide, doxorubicin, and prednisone

[a] Starting VELCADE regimen for all studies was 1.3 mg/m^2 administered on Days 1, 4, 8, and 11 of a 21–day treatment cycle. Subjects in LYM-3002 could receive up to 6 cycles of treatment (up to 8 cycles if response was first documented at Cycle 6). Subjects in LYM-2034 could receive up to 6 cycles of treatment. Subjects in M34103-053 were to receive 4 cycles of treatment beyond the date of initial documentation of complete response or unconfirmed complete response up to a maximum of 17 cycles.

Data from LYM-3002 and LYM-2034 were pooled by treatment group (R-CHOP or VcR-CAP), while data from Study M34103-053 (Velcade monotherapy) were presented alongside the pooled data.

Study LYM-2034 enrolled subjects with previously untreated non-GCB subtype DLBCL. The maximum allowable number of treatment cycles was up to 6 cycles. Velcade administration and regimen of the 2 arms were the same as in Study LYM-3002.

Patient exposure

The median duration of treatment with Velcade was 17.1 weeks for the pooled VcR-CAP treatment group and 11.9 for the Velcade monotherapy group. The distribution of number of Treatment Cycles for the pooled studies LYM-3002 and LYM-2034 and for the supportive study M34103-053 is showed in Table 12.

Table 12 Distribution of Number of Treatment Cycles; Safety Analysis Set (Studies LYM-3002, LYM-2034, M34103-053)

	Previously Untreated ----LYM-3002+LYM-2034----		Previously Treated -M34103-053-
	R-CHOP	VcR-CAP	Vc Monotherapy
Analysis set: safety subjects	321	322	155
1 Cycle	10 (3.1%)	7 (2.2%)	18 (11.6%)
2 Cycles	7 (2.2%)	8 (2.5%)	36 (23.2%)
3 Cycles	10 (3.1%)	12 (3.7%)	10 (6.5%)
4 Cycles	11 (3.4%)	10 (3.1%)	17 (11.0%)
5 Cycles	7 (2.2%)	10 (3.1%)	7 (4.5%)
6 Cycles	234 (72.9%)	242 (75.2%)	17 (11.0%)
7 Cycles	0	1 (0.3%)	2 (1.3%)
8 Cycles	42 (13.1%)	32 (9.9%)	9 (5.8%)
9 Cycles	0	0	3 (1.9%)
10 Cycles	0	0	10 (6.5%)
11 Cycles	0	0	3 (1.9%)
12 Cycles	0	0	5 (3.2%)
14 Cycles	0	0	5 (3.2%)
15 Cycles	0	0	1 (0.6%)
16 Cycles	0	0	2 (1.3%)
17 Cycles	0	0	9 (5.8%)
21 Cycles	0	0	1 (0.6%)
Categories			
1-6 Cycles	279 (86.9%)	289 (89.8%)	105 (67.7%)
7-8 Cycles	42 (13.1%)	33 (10.2%)	11 (7.1%)
9 or Higher Cycles	0	0	39 (25.2%)

Key: R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; VcR-CAP=VELCADE, rituximab, cyclophosphamide, doxorubicin, and prednisone; Vc=VELCADE.
Note: Subjects received up to 8 cycles of study treatment in studies LYM-2034 and LYM-3002. Subjects in study M34103-053 received up to 17 cycles (except subject 002002 who received 21 cycles) of study treatment.
Percentages calculated with the number of subjects in each group as denominator.

Adverse events

An overview of treatment-emergent adverse events in study LYM-3002 and in Studies: LYM-3002, LYM-2034, and M34103-053) is presented in Table 13 and Table 14 respectively.

Table 13 Overview of Treatment-emergent Adverse Events; Safety Analysis Set (Study LYM-3002)

	R-CHOP	VcR-CAP
Analysis set: safety subjects	242	240
Any treatment-emergent adverse event	238 (98.3%)	238 (99.2%)
At least one related [a]	226 (93.4%)	231 (96.3%)
None related	12 (5.0%)	7 (2.9%)
Any serious adverse event	72 (29.8%)	90 (37.5%)
At least one related [a]	50 (20.7%)	78 (32.5%)
None related	22 (9.1%)	12 (5.0%)
Maximum severity of any AE	238 (98.3%)	238 (99.2%)
Grade 1	6 (2.5%)	2 (0.8%)
Grade 2	26 (10.7%)	13 (5.4%)
Grade 3	53 (21.9%)	31 (12.9%)
Grade 4	136 (56.2%)	176 (73.3%)
Grade 5	17 (7.0%)	16 (6.7%)
Treatment discontinuation due to AEs	17 (7.0%)	21 (8.8%)
At least one related [a]	14 (5.8%)	19 (7.9%)
None related	3 (1.2%)	2 (0.8%)

Key: R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone;
VcR-CAP=VELCADE, rituximab, cyclophosphamide, doxorubicin, and prednisone; AE=adverse event.
[a] Related to any study drug.
Note: Percentages calculated with the number of subjects in each group as denominator.
Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Adverse events with missing toxicity grade are not included in the table.

Table 14 Overview of Treatment-emergent Adverse Events; Safety Analysis Set (Studies: LYM-3002, LYM-2034 and M34103-053)

	Previously Untreated ----LYM-3002+LYM-2034----		Previously Treated -M34103-053-
	R-CHOP	VcR-CAP	Vc Monotherapy
Analysis set: safety subjects	321	322	155
Any treatment-emergent adverse event	317 (98.8%)	319 (99.1%)	152 (98.1%)
At least 1 related [a]	301 (93.8%)	311 (96.6%)	145 (93.5%)
None related	16 (5.0%)	8 (2.5%)	7 (4.5%)
Any serious adverse event	99 (30.8%)	121 (37.6%)	61 (39.4%)
At least 1 related [a]	71 (22.1%)	101 (31.4%)	32 (20.6%)
None related	28 (8.7%)	20 (6.2%)	29 (18.7%)
Maximum severity of any adverse event [b]	317 (98.8%)	319 (99.1%)	152 (98.1%)
Grade 1	10 (3.1%)	5 (1.6%)	7 (4.5%)
Grade 2	31 (9.7%)	19 (5.9%)	36 (23.2%)
Grade 3	64 (19.9%)	45 (14.0%)	83 (53.5%)
Grade 4	191 (59.5%)	231 (71.7%)	21 (13.5%)
Grade 5	21 (6.5%)	19 (5.9%)	5 (3.2%)
Treatment discontinuation due to AEs	19 (5.9%)	27 (8.4%)	41 (26.5%)
At least 1 related [a]	16 (5.0%)	24 (7.5%)	35 (22.6%)
None related	3 (0.9%)	3 (0.9%)	6 (3.9%)

Key: R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone;
VcR-CAP=VELCADE, rituximab, cyclophosphamide, doxorubicin, and prednisone; Vc=VELCADE;
AE=adverse event.
[a]Related to any study medication.
[b]In Study LYM-3002 and Study M34103-053, NCI CTCAE Version 3.0 was used; in Study LYM-2034, NCI CTCAE Version 4.0 was used; Adverse events with missing toxicity grade are not included in the table;
Note:Adverse events were coded using MedDRA Version 16.0; Percentages calculated with the number of subjects in each group as denominator.

Adverse reactions

The incidence of most frequent (at Least 5 Percent in either Treatment Group) TEAE-related with the medication that were reported in Study LYM-3002 are presented by grade in Table 15.

Table 15. Incidence of Most Frequent (at Least 5 Percent in either Treatment Group) Study Medication-related Treatment-emergent Adverse Events; Safety Analysis Set (Study 26866138-LYM-3002)

	VcR-CAP			R-CHOP		
	Total	Grade 3	Grade >=4	Total	Grade 3	Grade >=4
Analysis set: safety subjects	240			242		
MedDRA system organ class/preferred term						
Blood and lymphatic system disorders	223 (93%)	29 (12%)	187 (78%)	196 (81%)	42 (17%)	135 (56%)
Neutropenia	209 (87%)	32 (13%)	168 (70%)	172 (71%)	31 (13%)	125 (52%)
Leukopenia	116 (48%)	34 (14%)	69 (29%)	87 (36%)	39 (16%)	27 (11%)
Anaemia	106 (44%)	27 (11%)	4 (2%)	71 (29%)	23 (10%)	4 (2%)
Thrombocytopenia	172 (72%)	59 (25%)	76 (32%)	42 (17%)	9 (4%)	3 (1%)
Febrile neutropenia	41 (17%)	24 (10%)	12 (5%)	33 (14%)	17 (7%)	15 (6%)
Lymphopenia	68 (28%)	25 (10%)	36 (15%)	28 (12%)	15 (6%)	2 (1%)
Nervous system disorders	105 (44%)	31 (13%)	1 (< 1%)	94 (39%)	11 (5%)	2 (1%)
Peripheral sensory neuropathy	53 (22%)	11 (5%)	1 (< 1%)	45 (19%)	6 (2%)	0
Neuropathy peripheral	18 (8%)	4 (2%)	0	18 (7%)	2 (1%)	0
Hypoaesthesia	14 (6%)	3 (1%)	0	13 (5%)	0	0
Paraesthesia	14 (6%)	2 (1%)	0	11 (5%)	0	0
Neuralgia	25 (10%)	9 (4%)	0	1 (< 1%)	0	0
General disorders and administration site conditions	109 (45%)	22 (9%)	2 (1%)	84 (35%)	13 (5%)	0
Fatigue	43 (18%)	11 (5%)	1 (< 1%)	38 (16%)	5 (2%)	0
Pyrexia	48 (20%)	7 (3%)	0	23 (10%)	5 (2%)	0
Asthenia	29 (12%)	4 (2%)	1 (< 1%)	18 (7%)	1 (< 1%)	0
Oedema peripheral	16 (7%)	1 (< 1%)	0	13 (5%)	0	0
Chills	11 (5%)	0	0	4 (2%)	0	0
Gastrointestinal disorders	119 (50%)	20 (8%)	1 (< 1%)	78 (32%)	7 (3%)	2 (1%)
Nausea	54 (23%)	1 (< 1%)	0	28 (12%)	0	0
Constipation	42 (18%)	1 (< 1%)	0	22 (9%)	2 (1%)	0
Stomatitis	20 (8%)	2 (1%)	0	19 (8%)	0	1 (< 1%)
Dyspepsia	11 (5%)	0	0	12 (5%)	0	0
Diarrhoea	59 (25%)	11 (5%)	0	11 (5%)	3 (1%)	1 (< 1%)
Vomiting	24 (10%)	1 (< 1%)	0	8 (3%)	0	0
Abdominal distension	13 (5%)	0	0	4 (2%)	0	0
Infections and infestations	74 (31%)	25 (10%)	9 (4%)	55 (23%)	15 (6%)	7 (3%)
Pneumonia	20 (8%)	8 (3%)	5 (2%)	11 (5%)	5 (2%)	3 (1%)
Herpes zoster	11 (5%)	6 (3%)	0	2 (1%)	0	0
Skin and subcutaneous tissue disorders	51 (21%)	2 (1%)	1 (< 1%)	50 (21%)	4 (2%)	0
Alopecia	31 (13%)	1 (< 1%)	1 (< 1%)	33 (14%)	4 (2%)	0
Metabolism and nutrition disorders	63 (26%)	12 (5%)	3 (1%)	49 (20%)	16 (7%)	3 (1%)
Hyperglycaemia	10 (4%)	1 (< 1%)	0	17 (7%)	10 (4%)	0
Decreased appetite	36 (15%)	2 (1%)	0	15 (6%)	1 (< 1%)	0
Hypokalaemia	11 (5%)	3 (1%)	1 (< 1%)	6 (2%)	1 (< 1%)	0
Respiratory, thoracic and mediastinal disorders	36 (15%)	5 (2%)	3 (1%)	28 (12%)	0	3 (1%)
Cough	11 (5%)	2 (1%)	0	6 (2%)	0	0
Vascular disorders	29 (12%)	6 (3%)	0	16 (7%)	1 (< 1%)	2 (1%)
Hypertension	15 (6%)	1 (< 1%)	0	3 (1%)	0	0
Injury, poisoning and procedural complications	6 (3%)	0	0	15 (6%)	3 (1%)	0
Infusion related reaction	4 (2%)	0	0	11 (5%)	2 (1%)	0
Psychiatric disorders	18 (8%)	2 (1%)	0	9 (4%)	0	0
Insomnia	16 (7%)	1 (< 1%)	0	8 (3%)	0	0

Adverse Events of special interest

Hepatitis B

In the pooled analysis 4 (1%) subjects in the pooled R-CHOP group and 2 (1%) subjects in the VcR-CAP group experienced a hepatitis B event. With the exception of 1 subject in the pooled R-CHOP group, all cases of hepatitis B occurred in study LYM-3002. Three subjects (2 in the R-CHOP group and 1 in the VcR-CAP group) died due to hepatitis B infection. In study LYM-3002 for the 191 subjects with hepatitis B testing at baseline hepatitis B reactivations were seen in 3 subjects. In the 291 subjects (R-CHOP: 152; VcR-CAP: 139) without Hepatitis B testing at baseline in Study LYM-3002, events of Hepatitis B were seen in 2 subjects not treated with prophylactic anti-virals: one subject in the R-CHOP group and one in the VcR-CAP group.

The overall incidence of Hepatitis B infection in Study LYM-3002 was 0.8% in the VcR-CAP group (incidence of Hepatitis B reactivation: 8.3% [1/12] for those not administered antiviral prophylaxis) and 1.2% in the R-CHOP group (incidence of Hepatitis B reactivation: 0% [0/4] for those administered antiviral prophylaxis). Three subjects (2 in the R-CHOP group and 1 in the VcR-CAP group) died due to Hepatitis B infection during treatment; of these, 2 subjects (1 in each group) had received antiviral prophylaxis.

Cardiac events

Cardiac rhythm and conduction abnormality adverse events were reported in 11% of subjects in the pooled R-CHOP group and 10% in VcR-CAP group. Five (2%) subjects in the pooled R-CHOP treatment group and 11 (3%) subjects in the pooled VcR-CAP treatment group experienced a cardiac disorder adverse event; cardiac failure was experienced by no subject in the pooled R-CHOP treatment group and 5 (2%) subjects in the pooled VcR-CAP treatment group. In the Study LYM-3002 myocardial ischemia was reported in 3 subjects (1.3%) in the VcR-CAP treatment group.

Peripheral Neuropathies

Subjects in the pooled VcR-CAP treatment group experienced peripheral neuropathy adverse events in 31% of cases versus 27% of R-CHOP group. Grade 2 or higher peripheral neuropathy was reported for 8% of subjects in the R-CHOP treatment group and 17% of subjects in the VcR-CAP treatment group. Grade 3 or higher peripheral neuropathy was reported for 4% of subjects in the R-CHOP treatment group and 7% of subjects in the VcR-CAP treatment group. Two (1%) subjects in the pooled VcR-CAP treatment group reported serious peripheral neuropathy versus none in the pooled R-CHOP treatment group, and 6 (2%) subjects in the pooled VcR-CAP treatment group discontinued all study treatment due to a peripheral neuropathy compared with 1 (<1%) subject in the pooled RCHOP treatment group. Velcade discontinuation due to peripheral neuropathy occurred in 5% of subjects in the pooled VcR-CAP treatment group versus a 3% vincristine discontinuation in the pooled R-CHOP treatment group. Subjects in Study M34103-053 experienced all grade peripheral neuropathy adverse events in 56% of cases versus 31% of the pooled VcR-CAP treatment group. Grade 2 or higher peripheral neuropathy was reported in 32% of subjects in the VELCADE monotherapy treatment group; Grade 3 and higher in 13% of subjects. Median time to onset of any grade peripheral neuropathy event was 49.5 days (range 1 to 197). Nineteen percent of peripheral neuropathies occurred in VcR-CAP patients and 25% in R-CHOP patients were not resolved. Median time to improvement of peripheral neuropathy in the pooled analysis was 145 days (95% CI: 86, 196) in R-CHOP patients versus 46 days (95% CI: 28, 62) in VcR-CAP patients, and median time to resolution was 168 days (95% CI: 119, 247) in the R-CHOP group versus 91 days (95% CI: 50, 144) in the VcR-CAP group.

The results of the assessment of peripheral neuropathies in Study LYM-3002 demonstrated similar rates of peripheral neuropathy adverse events (R-CHOP: 29%; VcR-CAP 30%), with most of these considered related to study treatment in both treatment groups (R-CHOP: 27%; VcR-CAP 30%). Grade 2 or higher

peripheral neuropathy adverse events occurred in 9% of subjects in the R-CHOP group and 18% of subjects in the VcR-CAP group. Grade 3 or higher peripheral neuropathy was reported in 4% of subjects in the R-CHOP treatment group and 8% of subjects in the VcR CAP treatment group. Two (1%) subjects in the VcR-CAP treatment group reported serious peripheral neuropathy adverse events versus none in the R-CHOP treatment group, and 4 (2%) subjects in the VcR-CAP treatment group discontinued treatment due to a peripheral neuropathy compared with 1 subject (<1%) in the R-CHOP treatment group.

Thrombocytopenia and Bleeding Events

In study LYM–3002 Grade ≥3 thrombocytopenia occurred in 57% of subjects in the VcR-CAP group and in 5.8% of subjects in the R-CHOP group. In the pooled analysis Grade ≥3 thrombocytopenia occurred in 52% of subjects in the pooled VcR-CAP group and in 5% of the pooled R-CHOP group. Sixteen (5%) subjects in the pooled R-CHOP treatment group and 24 (8%) subjects in the pooled VcR-CAP treatment group experienced a bleeding event of any grade. The majority of all-grade bleeding adverse events occurred in Study LYM-3002, in which bleeding events were reported for 12 (5%) subjects in the R-CHOP treatment group and 15 (6.3%) subjects in the VcR-CAP treatment group. Grade 3 or higher bleeding events were reported for 3 (1.2%) subjects in the R-CHOP treatment group and 4 (1.7%) subjects in the VcR-CAP treatment group. In study LYM–3002 the incidence of all grade bleeding events (5% and 6%, respectively) and Grade 3 or higher bleeding events (3 subjects versus 4 subjects) was low and similar in both groups. No subject died in this study due to a bleeding adverse event or due to a bleeding event related to study drug. In the VcR-CAP group, 22.5% of patients received platelet transfusions compared to 2.9% of patients in the R-CHOP group.

Neutropenia and Infection Events

In the pooled VcR-CAP group the incidence of infections was 59% versus 44% of R-CHOP group (in study LYM–3002: 60% and 46% of subjects respectively). The most frequently reported infection adverse event was pneumonia (R-CHOP: 7%; VcR-CAP: 11%). In the pooled VcR-CAP group Grade ≥3 infection events and serious adverse events were reported in 20% and 17% of subjects versus 13 and 12% of the pooled R-CHOP treatment group, respectively. Pneumonia/lung infection was the most commonly reported Grade 3 or higher event in both treatment groups. Antibacterials for systemic use were used in 70% of subjects in the R-CHOP group versus 79 in the VcR-CAP group.

Eight (3%) subjects in the pooled R-CHOP treatment group and 7 (2%) subjects in the pooled VcR-CAP group had infection adverse events leading to death. In the pooled R-CHOP arm 2 subjects died of pneumonia, 2 of hepatitis B, 1 of septic shock, 1 of sepsis, 1 of bronchopneumonia, 1 of non-specified viral hepatitis. In the pooled VcR-CAP arm 4 subjects died of pneumonia, 2 of septic shock, 1 of hepatitis, 1 of non-specified lung infection, 1 of sepsis.

In the Study LYM- 3002 15% of subjects in the R-CHOP group and 21% of subjects in the VcR-CAP group experienced a Grade 3 or higher infection (regardless of neutropenia); in 3 subjects in the R-CHOP group and 4 subjects in the VcR-CAP group the infection adverse event resulted in death within 30 days of the last dose of study medication. Infection adverse events were considered as serious in 29 subjects (12%) in the R-CHOP group and 42 subjects (18%) in the VcR-CAP group. The use of colony stimulating factors during study treatment (61% in the R-CHOP group and 78% in the VcR-CAP group) was consistent with the incidence of Grade 3 or higher neutropenia (67% in the R-CHOP group and 85% in the VcR-CAP group). In the 3 groups that required CSF support – primary prophylactic, secondary prophylactic, and non-prophylactic – there was a trend for a lower rate of cycle delays (50%, 59%, and 65%, respectively) with prophylactic use of CSF, and a similar need for Velcade dose modifications (96%, 95%, and 98%, respectively).

Serious adverse event / deaths / other significant events

Serious adverse events

Treatment-emergent serious adverse events that occurred with an incidence of 1% or more are summarized by system organ class and preferred term in Table 16 (for Pooled Set and Study M34103-053)

Table 16 Incidence of Most Frequent (at Least 1 Percent of Subjects in Any Treatment Group) Treatment-emergent Serious Adverse Events by MedDRA SOC and Preferred Term; Safety Analysis Set (Studies: LYM-3002, LYM-2034, and M34103-053)

	Previously Untreated ----LYM-3002+LYM-2034----		Previously Treated -M34103-053-
	R-CHOP	VcR-CAP	Vc Monotherapy
Analysis set: safety subjects	321	322	155
Total no. subjects with serious TEAEs	99 (30.8%)	121 (37.6%)	61 (39.4%)
MedDRA SOC/preferred term			
Blood and lymphatic system disorders	43 (13.4%)	56 (17.4%)	4 (2.6%)
Febrile neutropenia	27 (8.4%)	33 (10.2%)	1 (0.6%)
Neutropenia	18 (5.6%)	16 (5.0%)	1 (0.6%)
Thrombocytopenia	1 (0.3%)	9 (2.8%)	0
Leukopenia	3 (0.9%)	7 (2.2%)	0
Anaemia	5 (1.6%)	4 (1.2%)	2 (1.3%)
Infections and infestations	37 (11.5%)	54 (16.8%)	18 (11.6%)
Pneumonia	10 (3.1%)	23 (7.1%)	10 (6.5%)
Lung infection	1 (0.3%)	4 (1.2%)	0
Sepsis	2 (0.6%)	4 (1.2%)	4 (2.6%)
Herpes zoster	1 (0.3%)	2 (0.6%)	3 (1.9%)
General disorders and administration site conditions	14 (4.4%)	20 (6.2%)	21 (13.5%)
Pyrexia	4 (1.2%)	15 (4.7%)	3 (1.9%)
Asthenia	1 (0.3%)	1 (0.3%)	4 (2.6%)
Disease progression	0	0	10 (6.5%)
Pain	0	0	2 (1.3%)
Respiratory, thoracic and mediastinal disorders	14 (4.4%)	18 (5.6%)	10 (6.5%)
Pleural effusion	1 (0.3%)	5 (1.6%)	0
Dyspnoea	5 (1.6%)	4 (1.2%)	3 (1.9%)
Pulmonary embolism	1 (0.3%)	4 (1.2%)	1 (0.6%)
Respiratory failure	1 (0.3%)	1 (0.3%)	2 (1.3%)
Gastrointestinal disorders	17 (5.3%)	17 (5.3%)	12 (7.7%)
Diarrhoea	3 (0.9%)	6 (1.9%)	1 (0.6%)
Vomiting	2 (0.6%)	3 (0.9%)	4 (2.6%)
Abdominal pain	1 (0.3%)	1 (0.3%)	5 (3.2%)
Nausea	1 (0.3%)	1 (0.3%)	4 (2.6%)
Abdominal distension	0	0	2 (1.3%)
Vascular disorders	5 (1.6%)	14 (4.3%)	7 (4.5%)
Hypotension	1 (0.3%)	5 (1.6%)	2 (1.3%)
Orthostatic hypotension	0	3 (0.9%)	2 (1.3%)
Deep vein thrombosis	4 (1.2%)	1 (0.3%)	2 (1.3%)
Nervous system disorders	5 (1.6%)	11 (3.4%)	13 (8.4%)
Dizziness	0	1 (0.3%)	3 (1.9%)
Peripheral sensory neuropathy	0	1 (0.3%)	2 (1.3%)
Syncope	1 (0.3%)	1 (0.3%)	7 (4.5%)
Metabolism and nutrition disorders	4 (1.2%)	7 (2.2%)	7 (4.5%)
Dehydration	1 (0.3%)	0	3 (1.9%)

Key: R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone;
VcR-CAP=VELCADE, rituximab, cyclophosphamide, doxorubicin, and prednisone; Vc=VELCADE;
TEAE=treatment-emergent adverse event; SOC=System Organ Class.
Note:Adverse events were coded using MedDRA Version 16.0
Percentages calculated with the number of subjects in each group as denominator.

Deaths

The summary of deaths and causes of death are summarized in Table17.

Table 17 Summary of Deaths and Causes of Death; Safety Analysis Set (Studies: LYM-3002, LYM-2034, and M34103-053)

	Previously Untreated ----LYM-3002+LYM-2034----		Previously Treated -M34103-053-
	R-CHOP	VcR-CAP	Vc Monotherapy
Analysis set: safety subjects	321	322	155
Deaths of all causes	103 (32.1%)	84 (26.1%)	93 (60.0%)
Progressive disease	64 (19.9%)	57 (17.7%)	71 (45.8%)
Adverse events	23 (7.2%)	19 (5.9%)	4 (2.6%)
At least 1 related TEAE	11 (3.4%)	9 (2.8%)	3 (1.9%)
Unrelated TEAE	10 (3.1%)	7 (2.2%)	1 (0.6%)
Unrelated non treatment-emergent AE	2 (0.6%)	3 (0.9%)	0
Other	16 (5.0%)	8 (2.5%)	18 (11.6%)
Deaths of all causes within 30 days of first dose	6 (1.9%)	4 (1.2%)	6 (3.9%)
Progressive disease	1 (0.3%)	1 (0.3%)	4 (2.6%)
Adverse events	5 (1.6%)	3 (0.9%)	2 (1.3%)
At least 1 related TEAE	2 (0.6%)	2 (0.6%)	1 (0.6%)
Unrelated TEAE	3 (0.9%)	1 (0.3%)	1 (0.6%)
Deaths of all causes within 60 days of first dose	9 (2.8%)	8 (2.5%)	16 (10.3%)
Progressive disease	1 (0.3%)	3 (0.9%)	12 (7.7%)
Adverse events	8 (2.5%)	5 (1.6%)	4 (2.6%)
At least 1 related TEAE	2 (0.6%)	2 (0.6%)	3 (1.9%)
Unrelated TEAE	5 (1.6%)	3 (0.9%)	1 (0.6%)
Unrelated non treatment-emergent AE	1 (0.3%)	0	0
Deaths of all causes within 30 days of last dose	17 (5.3%)	14 (4.3%)	12 (7.7%)
Progressive disease	1 (0.3%)	3 (0.9%)	8 (5.2%)
Adverse events	15 (4.7%)	10 (3.1%)	4 (2.6%)
At least 1 related TEAE	7 (2.2%)	5 (1.6%)	3 (1.9%)
Unrelated TEAE	8 (2.5%)	5 (1.6%)	1 (0.6%)
Other	1 (0.3%)	1 (0.3%)	0

Key: R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone;
VcR-CAP=VELCADE, rituximab, cyclophosphamide, doxorubicin, and prednisone; Vc=VELCADE;
AE=adverse event; TEAE=treatment-emergent adverse event.
Note: Cause of death category 'Other' may include some subjects with unknown cause of death.
Percentages calculated with the number of subjects in each group as the denominator.
Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

In the Study LYM3002, death incidence was 36% in the R-CHOP treatment group and 29% in the VcR-CAP group; in R–CHOP arm 23% of patients died to disease progression as compared to VcR-CAP arm (18.%). In both arms, fatal cases occurred mostly after 60 days of treatment. Adverse events were reported as the cause of death for 18 subjects (7%) in the R-CHOP group and 17 subjects (7%) in the VcR-CAP group. Twelve subjects, 7 (3%) in the R-CHOP group and 5 (2%) in the VcR-CAP group, died due to a drug-related adverse event that occurred within 30 days of the last dose of study treatment mainly due to cardiac or infection-related causes. Fourteen subjects (6%) in the R-CHOP group and 11 subjects (5%) in the VcR-CAP group died within 30 days of last dose, most due to adverse events, 12 (5%) and 8 (3%), respectively. Seven subjects in the R-CHOP group died due to a drug-related adverse event: of infectious origin (3), of cardiac origin (2), due to hypotension, diarrhea and renal failure (1), and tumor lysis syndrome (1). Five subjects in the VcR-CAP group died due to a drug-related adverse event of infectious origin (3), of cardiac origin (1) and due to pulmonary embolism (1).

Laboratory findings

The proportions of subjects with Grade 3 or higher laboratory values were as follows: leukocytes: 76% R-CHOP versus 88% VcR-CAP (Grade 3 or higher adverse events of leukopenia were 29% versus 44%, respectively); lymphocytes: 59% R-CHOP versus 86% VcR-CAP (Grade 3 or higher adverse events of lymphopenia were 9% versus 28%, respectively); hemoglobin: 19% R-CHOP versus 20% VcR-CAP (Grade 3 or higher adverse events of anemia were 14% versus 15%, respectively); supportive treatment with RBC transfusions: 17% in the R-CHOP group and 22% in the VcR-CAP group; supportive treatment with erythropoiesis-stimulating agents: 9% in the R-CHOP group and 10% in the VcR-CAP group. Neutrophils: 83% R-CHOP versus 89% VcR-CAP (Grade 3 or higher adverse events of febrile neutropenia were 14% and 15%, respectively); supportive treatment with colony-stimulating factors was 78% in the VcR-CAP group and 61% in the R-CHOP group.

During study treatment, Grade 2 or higher laboratory abnormalities were reported for 5% or more subjects in either pooled treatment group for the following: hypoalbuminemia (R-CHOP: 13%; VcR-CAP: 18%); hyperglycemia (R-CHOP: 15%; VcR-CAP: 12%); hypocalcemia (R-CHOP: 11%; VcR-CAP: 16%); hyperkalemia (R-CHOP: 10%; VcR-CAP: 7%); hypokalemia (R-CHOP: 6%; VcR-CAP: 10%); ALT (R-CHOP: 6%; VcR-CAP: 3%); hyponatremia (R-CHOP: 3%; VcR-CAP: 6%). For all other clinical chemistry assessments, the difference in incidence of Grade 2 or higher laboratory abnormalities was 3% or less between the pooled R-CHOP and pooled VcR-CAP treatment groups.

Safety in special populations

Adverse events by sex

Women in both pooled treatment groups experienced higher rates of Grade 4 adverse events compared with men (R-CHOP: men: 63%, women: 74%; VcR-CAP: men: 74%, women: 85%), the large majority of which were hematologic adverse events, primarily neutropenia, and in the pooled VcR-CAP treatment group, thrombocytopenia. At the SOC level for all-grade adverse events, in the pooled analysis women experienced 10% or higher rates of Gastrointestinal disorders (men 57%, women 67%) and Skin and subcutaneous tissue disorders (men 26%, women 39%). In the pooled R-CHOP group women experienced higher rates of Nervous system disorders (men 44%, women 55%) and Metabolism and nutrition disorders (men 25%, women 37%).

Adverse events by race

In the pooled VcR-CAP treatment group, non-white subjects experienced higher rates of Grade 3 or higher adverse events (white: 88%; non-white 98%) and Grade 4 or higher adverse events (white: 72%, non-white: 89%). A similar trend was found in the pooled R-CHOP treatment group for Grade 3 or higher adverse events (white: 84%; non-white: 90%) and Grade 4 or higher adverse events (white: 63%; non-white: 74%). Non-white subjects in the pooled R-CHOP treatment group also experienced higher incidence of serious adverse events (white: 27%; nonwhite: 40%); a finding not observed in the pooled VcR-CAP treatment group (white: 38%; nonwhite: 37%). White subjects experienced higher rates of all-grade and higher-grade peripheral neuropathy (R-CHOP: white 30.6%, non-white: 18.2%; VcR-CAP: white 36.0%, non-white 21.6%).

Adverse events by age

In the pooled VcR-CAP treatment group, subjects >65 years old experienced 5% or higher incidence of serious adverse events compared with younger subjects (≤65 years: 33%; >65 years: 44%). Older and

younger subjects experienced similar rates of Grade 3 or higher adverse events; however, older subjects experienced a 5% or greater incidence of Grade 4 or higher adverse events (≤65 years: 73%; >65 years: 83%). Older subjects also experienced a 5% or higher rate of treatment discontinuation compared with younger subjects (≤65 years: 6%; >65 years: 11%). In the pooled R-CHOP treatment group, in addition to experiencing a 5% or greater rate of serious adverse events (≤65 years: 27%; >65 years: 35%), older subjects reported a higher rate of Grade 4 or higher adverse events (≤65 years: 61%; >65 years: 72%) and treatment discontinuation (≤65 years: 3%; >65 years: 9%). Eighty-four percent of subjects ≤65 years experienced Grade 3 or higher adverse events compared with 88% of subjects >65 years old. Older (>65 years) subjects treated with VcR-CAP also experienced a higher incidence of adverse events leading to death (9%) compared to younger subjects (3%). Most of the Grade 5 adverse events leading to death among older (>65 years) subjects treated with VcR-CAP were respiratory, infectious or cardiac in nature; A similar pattern was also observed in the R-CHOP group.

Adverse events by region

In the pooled VcR-CAP treatment group, differences of 5% or greater were noted for incidence of serious adverse events (EU: 50%; USA/Canada: 22%; ROW: 33%), Grade 3 and higher adverse events (EU: 93%; USA/Canada: 78%; ROW: 92%), and Grade 4 and higher adverse events (EU: 79%; USA/Canada: 56%; ROW: 78%). In the pooled R-CHOP treatment group, differences of 5% or greater were noted for incidence of serious adverse events (EU: 27%; USA/Canada: 9%; ROW: 34%), Grade 3 and higher adverse events (EU: 83%; USA/Canada: 82%; ROW: 88%), Grade 4 and higher adverse events (EU: 62%; USA/Canada: 55%; ROW: 69%), and discontinuation due to adverse events (EU: 6%; USA/Canada: 0%; ROW: 6%).

Renal impairment

In the Study LYM-3002, in the VcR-CAP treatment group, the incidence of Grade 4 adverse events was 81% for subjects with impaired renal function versus 71% for those with normal renal function. For subjects in the R-CHOP group the incidence of Grade 4 adverse events was 66% for subjects with impaired renal function and 53% for subjects with normal renal function.

Hepatic impairment

In the pooled VcR-CAP treatment group subjects with impaired liver function had 5% or higher rates of Grade 3 or higher adverse events (<1.5xULN: 92%; ≥1.5xULN: 80%) and discontinuation due to adverse events (<1.5xULN: 8%; ≥1.5xULN: 20%). Also In pooled R-CHOP treatment group subjects with impaired liver function had 5% or higher rates of all grade adverse events (<1.5xULN: 99%; ≥1.5xULN: 94%), serious adverse events (<1.5xULN: 31%; ≥1.5xULN: 24%), and Grade 4 and higher adverse events (<1.5xULN: 66%; ≥1.5xULN: 77%).

Safety related to drug-drug interactions and other interactions

No safety data related to drug-drug interactions have been submitted.

Discontinuation due to adverse events

Nineteen (6%) subjects in the pooled R-CHOP treatment group and 27 (8%) of subjects in the pooled VcR-CAP treatment group experienced adverse events that led to permanent discontinuation of all study treatment. For the pooled treatment groups adverse events in the Nervous system disorders (R-CHOP: 4 [2%]; VcR-CAP: 9 [3%]), Blood and lymphatic system disorders (R-CHOP: 2 [1%]; VcR-CAP: 7 [2%]), and Infections and infestations (R-CHOP: 6 [2%]; VcR-CAP: 7 [2%]) system organ classes were identified most

often as leading to treatment discontinuation.

In the Study LYM-3002 a dose withholding has been reported in 25 subjects in the R-CHOP arm and in 205 subjects in VcR-CAP arm. The most common adverse events that led to a dose withholding were peripheral sensory neuropathy (7 subjects; 3%) in the R-CHOP group and thrombocytopenia, leukopenia and neutropenia in VcR-CAP. In particular, 180 subjects (75%) had a dose of VELCADE withheld (most commonly for neutropenia [143 subjects; 60%]. Eighty (33%) of the subjects in the R-CHOP group and 121 (50%) of the subjects in the VcR-CAP group experienced at least 1 adverse events that led to a cycle delay.

Post marketing experience

The review of post marketing experience (to identify cases in which Velcade was administered to patients with MCL alone or in combination) included retrieval of data from the following report types (number of cases) in the safety database: compassionate use (3), literature spontaneous (76), post-marketing survey (25), regulatory authority (7), and spontaneous (295). The database search criteria included any patient who was reported to have received Velcade for the treatment of MCL, in addition to any patient who reported a concurrent condition or past medical history of MCL and who received Velcade treatment for any indication. The search retrieved 406 cases reporting a total of 1,022 adverse events. The adverse events were reported from 29 countries, with the majority reported from the United States (170 [42%]), Japan (49 [12%]), and Switzerland (30 [7%]), in which Velcade is authorised in the relapsed/refractory setting. The most common adverse events were neuropathy peripheral (59 of 1,022 events [5.8%]), thrombocytopenia (51 events [5.0%]), platelet count decreased (45 events [4.4%]), disease progression (30 events [2.9%]), fatigue (22 events [2.2%]), and diarrhea (21 events [2.1%]). All other adverse events occurred at a reporting frequency of <2%.

2.6.1. Discussion on clinical safety

The evaluation of VcR-CAP safety derives primarily from the pooled analysis of the 2 studies LYM-3002 and LYM-2034. Data from Study M34103-053 were only partially informative due to the different schedule and prolonged administration of Velcade in monotherapy compared to the VcR-CAP regimen.

The safety profile of 240 patients treated with Velcade at 1.3 mg/m^2 in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (VcR-CAP) versus 242 patients treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP], was relatively consistent to that observed in patients with multiple myeloma with main differences described below. Additional adverse drug reactions identified associated with the use of the combination therapy (VcR-CAP) were hepatitis B infection (< 1%) and myocardial ischaemia (1.3%). The similar incidences of these events in both treatment arms indicated that these adverse drug reactions are not attributable to Velcade alone. Notable differences in the MCL patient population as compared to patients in the multiple myeloma studies were a ≥ 5% higher incidence of the haematological adverse reactions (neutropenia, thrombocytopenia, leukopenia, anemia, lymphopenia), peripheral sensory neuropathy, hypertension, pyrexia, pneumonia, stomatitis, and hair disorders (See SmPC section 4.8).

Neurotoxicity is a known adverse reaction of bortezomib and a frequent event in the treatment of patients with multiple myeloma. Neurotoxicity is also a known adverse reaction of Vincristine. Peripheral sensory neuropathy was confirmed to be associated with Velcade and Vincristine treatment. Vincristine-related neuropathy is characterized by an earlier onset compared to Velcade-related neuropathy (49.5 vs 81.5 days respectively). This finding confirmed that Velcade-related neuropathy is dependent on the cumulative Velcade dose. Usually more prolonged Velcade exposures, as shown in Study M34103-053, are associated with higher rates of neuropathy. Velcade-related neuropathy is also more often reversible than

Vincristine-related neuropathy: 19% of peripheral neuropathies occurred in VcR-CAP patients vs 25% in R-CHOP patients were not resolved at the end of follow-up. Velcade discontinuation due to peripheral neuropathy occurred in 5% of subjects in the pooled VcR-CAP treatment group while Vincristine discontinuation in the pooled R-CHOP treatment group was slightly less frequent (3%). Section 4.4 of the SmPC includes a warning that treatment with Velcade is very commonly associated with peripheral neuropathy, which is predominantly sensory. However, cases of severe motor neuropathy with or without sensory peripheral neuropathy have been reported. In addition, the SmPC provides a recommendation that patients should be carefully monitored for symptoms of neuropathy and those patients experiencing new or worsening peripheral neuropathy may require the dose and schedule of Velcade to be modified (See sections 4.2 and 4.4 of the SmPC and Risk Management Plan).

In the VcR-CAP arm, one of the most common haematologic toxicity was transient thrombocytopenia. Platelets were lowest at Day 11 of each cycle of Velcade treatment and typically recovered to baseline by the next cycle. The mean platelet count nadir measured was 50% in the MCL study (See SmPC section 4.4).

In study LYM-3002, there was a higher incidence (56.7% versus 5.8%) of Grade ≥ 3 thrombocytopenia in the Velcade treatment group (VcR-CAP) as compared to the non-Velcade treatment group (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]). The two treatment groups were similar with regard to the overall incidence of all-grade bleeding events (6.3% in the VcR-CAP group and 5.0% in the R-CHOP group) as well as Grade 3 and higher bleeding events (VcR-CAP: 4 patients [1.7%]; R-CHOP: 3 patients [1.2%]). In the VcR-CAP group, 22.5% of patients received platelet transfusions compared to 2.9% of patients in the R-CHOP group (SmPC section 4.4). In order to improve the haemorrhagic risk control section 4.2 of the SmPC has been updated to include that platelet transfusion for the treatment of thrombocytopenia should be considered when clinically appropriate.

In patients with MCL, transient neutropenia that was reversible between cycles was observed, with no evidence of cumulative neutropenia. Neutrophils were lowest at Day 11 of each cycle of Velcade treatment and typically recovered to baseline by the next cycle. In study LYM-3002, colony stimulating factor support was given to 78% of patients in the VcR-CAP arm and 61% of patients in the R-CHOP arm. Since patients with neutropenia are at increased risk of infections, they should be monitored for signs and symptoms of infection and treated promptly. Granulocyte colony stimulating factors may be administered for haematologic toxicity according to local standard practice. Prophylactic use of granulocyte colony stimulating factors should be considered in case of repeated delays in cycle administration (See SmPC sections 4.2 and 4.4).

As for neutropenia, in spite of an intensive use of granulocyte colony-stimulating factor and antibacterial agents for prophylaxis, subjects in the VcR-CAP treatment group were nevertheless more likely to experience higher-grade infective adverse events compared to subjects in the R-CHOP treatment group. The increased number of pneumonia in the VcR-CAP group was of concern. However the MAH conducted an internal analysis in this patient population based on health insurance claims databases that provided further evidence that pneumonia is a well-recognized medical complication in patients with newly diagnosed MCL often treated with immunosuppressive medication. In addition, since the majority of the pneumonia events in study occurred within the context of neutropenia, the use of colony stimulating factors is strongly supported whenever necessary during the treatment of patients with MCL. Instructions regarding the use of colony stimulating factors in the SmPC section 4.2 have been included and the MAH will continue to monitor pneumonia cases as part of the important identified risk of “Neutropenia and neutropenia with associated infection” (see Risk Management Plan).

In study LYM 3002, Hepatitis B virus (HBV) infection with fatal outcomes occurred in 0.8% (n=2) of patients in the non -Velcade treatment group (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R CHOP) and 0.4% (n=1) of patients receiving Velcade in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (VcR CAP). The overall incidence of hepatitis B infections

was similar in patients treated with VcR CAP or with R CHOPS (0.8% vs 1.2% respectively). When rituximab is used in combination with Velcade, HBV screening must always be performed in patients at risk of infection with HBV before initiation of treatment. Carriers of hepatitis B and patients with a history of hepatitis B must be closely monitored for clinical and laboratory signs of active HBV infection during and following rituximab combination treatment with Velcade. Antiviral prophylaxis should be considered. Refer to the Summary of Product Characteristics of rituximab for more information (See SmPC, section 4.4).

In study LYM 3002, the incidence of herpes zoster infection was 6.7% in the VcR CAP arm and 1.2% in the R CHOP arm (See SmC section 4.4). Antiviral prophylaxis was administered to 137 of 240 patients (57%) in the VcR-CAP arm. The incidence of herpes zoster among patients in the VcR-CAP arm was 10.7% for patients not administered antiviral prophylaxis compared to 3.6% for patients administered antiviral prophylaxis (See SmPC section 4.8).

10.7% and 5.4% of patients in the VcR-CAP arm were in the range 65-74 and ≥75 years of age, respectively. Although in patients aged ≥ 75 years both VcR-CAP and R-CHOP were less tolerated, the serious adverse event rate in the VcR-CAP groups was 68%, compared to 42% in the R-CHOP group (See SmPC section 4.8).

2.6.2. Conclusions on clinical safety

The overall safety of the VcR-CAP combination is consistent with the known single safety profiles of Velcade, rituximab, cyclophosphamide, doxorubicin and prednisone. Additional adverse drug reactions identified associated with the use of the combination therapy (VcR-CAP) were hepatitis B infection and myocardial ischaemia.

2.6.3. PSUR cycle

The PSUR cycle remains unchanged.

2.7. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 29.1 is acceptable. The PRAC advice is attached.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 29.1 with the following content:

Safety concerns

Table 18: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Peripheral motor neuropathy (including paralysis) Autonomic neuropathy Thrombocytopenia and thrombocytopenia with associated bleeding Neutropenia and neutropenia with associated infection Herpes zoster infection

	Heart failure Acute diffuse infiltrative pulmonary disease Acute hypersensitivity reaction Tumour lysis syndrome Posterior reversible encephalopathy syndrome Optic neuropathy and different degrees of visual impairment (up to blindness) Hepatotoxicity Pulmonary hypertension Pericardial disease
Important potential risks	Progressive multifocal leukoencephalopathy Ventricular rhythm abnormalities Guillain-Barré syndrome Other central nervous system disorders Medication/dispensing errors
Missing information	Safety in patients with cardiac impairment or with NYHA Class III or IV impairment Safety in patients with ECOG>2 Second primary malignancies with VcTD induction therapy

Pharmacovigilance plan

A survey is being conducted by the MAH within 18 months of the launch of the VELCADE 3.5 mg new dual route of administration (subcutaneous and intravenous). The survey targeted HCPs and other specialised personnel involved in the prescription, dispensing, and preparation and/or administration of VELCADE, and entailed questions regarding the utility and effectiveness of various tools provided as part of the educational materials.

The PRAC, having considered the data submitted, was of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The PRAC also considered that the study in the post-authorisation development plan is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table 19: Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Peripheral motor neuropathy (including paralysis)	The SmPC, Section 4.4 Special Warnings and Precautions for Use, warns that treatment with VELCADE is very commonly associated with peripheral neuropathy, which is predominantly sensory. However, cases of severe motor neuropathy with or without sensory peripheral neuropathy have been reported. The SmPC provides a recommendation that patients be carefully monitored for symptoms of neuropathy and those patients experiencing new or worsening peripheral neuropathy may require the dose and schedule of	None

	VELCADE to be modified. Recommendations for dose modification in patients with neuropathy are provided in the SmPC, Section 4.2, Posology and Method of Administration. SmPC: Labelled in Section 4.8 Undesirable Effects.	
Autonomic neuropathy	The SmPC, Section 4.4 Special Warnings and Precautions for Use, warns that in addition to peripheral neuropathy, there may be a contribution of autonomic neuropathy to some adverse reactions such as postural hypotension and severe constipation with ileus.	None
Thrombocytopenia and Thrmbocytopenia with Associated Bleeding	The SmPC, Sections 4.4 and 4.8, states that in studies in patients with relapsed multiple myeloma treated with VELCADE and in patients with previously untreated MCL treated with VELCADE in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (VcR-CAP), transient thrombocytopenia was one of the most common haematologic toxicities. Platelets were lowest at Day 11 of each cycle of VELCADE treatment and typically recovered to baseline by the next cycle. In MCL patients, 22.5% of patients receiving VcR-CAP received platelet transfusions compared to 2.9% of patients receiving R-CHOP. Platelet transfusion for the treatment of thrombocytopenia should be considered when clinically appropriate. Dose toxicity management for thrombocytopenia within the different indications (MCL and multiple myeloma) are slightly different depending on the indication. The SmPC Section 4.2 provides guidance on all dose modifications. When VELCADE is given in combination with other chemotherapeutic medicinal products, appropriate dose reductions for these medicinal products should be considered in	None

	the event of toxicities, according to the recommendations in the respective SmPCs. For MCL patients receiving VcR-CAP, the SmPC Section 4.2 provides guidance on dose modifications of cyclophosphamide and doxorubicin for haematologic toxicities. The SmPC Section 4.9 (Overdose) states that overdosage more than twice the recommended dose has been associated with acute onset of thrombocytopenia with fatal outcomes.	
Neutropenia and Neutropenia with Associated Infection	The SmPC Section 4.2 provides pretreatment criteria and dose modification guidance, including adjustments for ≥ Grade 3 neutropenia with fever and Grade 4 neutropenia lasting more than 7 days. The SmPC, Sections 4.4 and 4.8, states that in studies in patients with relapsed multiple myeloma treated with VELCADE and in patients with previously untreated MCL treated with VELCADE in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (VcR-CAP), transient neutropenia was one of the most common haematologic toxicities. When VELCADE is given in combination with other chemotherapeutic medicinal products, appropriate dose reductions for these medicinal products should be considered in the event of toxicities, according to the recommendations in the respective SmPCs. For MCL patients receiving VcR-CAP, the SmPC Section 4.2 provides guidance on dose modifications of cyclophosphamide and doxorubicin for haematologic toxicities.	None
Herpes zoster infection	Section 4.4 of the SmPC indicates that antiviral prophylaxis is recommended in patients being treated with VELCADE. The SmPC, Section 4.8 Undesirable Effects, identifies herpes zoster (including disseminated) as a common adverse reaction during treatment with VELCADE.	None
Heart failure	The SmPC, Section 4.4 Special Warnings and Precautions for Use,	None

	warns that acute development or exacerbation of congestive heart failure, and/or new onset of decreased left ventricular ejection fraction has been reported during bortezomib treatment. Fluid retention may be a predisposing factor for signs and symptoms of heart failure. Patients with risk factors for or existing heart disease should be closely monitored. SmPC: Labelled in Section 4.8 Undesirable Effects.	
Acute diffuse infiltrative pulmonary disease	The use of VELCADE is contraindicated in patients with acute diffuse infiltrative pulmonary disease in Section 4.3 of the SmPC. TheSmPC, Section 4.4 Special Warnings and Precautions for Use, warns that there have been rare reports of acute diffuse infiltrative pulmonary disease of unknown aetiology in patients receiving VELCADE and that some of these events have been fatal. The SmPC recommends that a pretreatment chest radiograph be performed to determine if any additional diagnostic measures are necessary and to serve as a baseline for potential post-treatment pulmonary changes. SmPC: Labelled in Section 4.8 Undesirable Effects.	None
Acute hypersensitivity reaction	The SmPC, Section 4.3 Contraindications includes hypersensitivity to bortezomib, boron, or to any of the excipients. The SmPC, Section 4.8 Undesirable Effects, identifies hypersensitivity, anaphylactic shock, Type III immune complex mediated reaction as uncommon or rare adverse reactions.	None
Tumour lysis syndrome	The SmPC, Section 4.4 Special Warnings and Precautions for Use, warns that because bortezomib is a cytotoxic agent and can rapidly kill malignant plasma cells and MCL cells, the complications of TLS may occur. The SmPC indicates that patients at risk of TLS are those	None

	with high tumour burden prior to treatment and suggests that these patients should be monitored closely and appropriate precautions taken. SmPC: Labelled in Section 4.8 Undesirable Effects.	
Posterior reversible encephalopathy syndrome	The SmPC, Section 4.4 Special Warnings and Precautions for Use, warns that there have been reports of PRES in patients receiving VELCADE. Section 4.4 of the SmPC describes PRES as a rare, often reversible, rapidly evolving neurological condition which can present with seizure, hypertension, headache, lethargy, confusion, blindness, and other visual and neurological disturbances. Brain imaging, preferably Magnetic Resonance Imaging, is used to confirm the diagnosis. The SmPC indicates that in patients developing PRES, VELCADE should be discontinued. The safety of reinitiating VELCADE treatment in patients previously experiencing PRES is not known. SmPC: Labelled in Section 4.8 Undesirable Effects.	None
Optic neuropathy and different degrees of visual Impairment (up to blindness)	The proposed SmPC, Section 4.8 Undesirable Effects, identifies optic neuropathy, different degrees of visual impairment (up to blindness) as an adverse reaction based on reports from clinical trial and postmarketing sources.	None
Hepatotoxicity	The SmPC, Section 4.4 Special Warnings and Precautions for Use, warns that rare cases of hepatic failure have been reported in patients receiving multiple concomitant medicinal products and with serious underlying medical conditions. Other reported hepatic reactions include increases in liver enzymes, hyperbilirubinaemia, and hepatitis. Such changes may be reversible upon discontinuation of bortezomib. SmPC: Labelled in Section 4.8 Undesirable Effects.	None
Pulmonary hypertension	The SmPC, Section 4.8 Undesirable Effects, identifies pulmonary hypertension as a	None

	serious adverse reaction uncommonly reported during treatment with VELCADE.	
Pericardial disease	As stated in Section 4.3 of the SmPC, the use of VELCADE is contraindicated in patients with pericardial disease. The SmPC, Section 4.8 Undesirable Effects, identifies pericarditis as adverse reactions based on reports from postmarketing sources.	None
Important potential risks:		
Progressive multifocal leukoencephalopathy	In Section 4.4 of the SmPC, managing physicians are advised to monitor patients regularly for any new or worsening neurological symptoms or signs that may be suggestive of PML, and refer appropriately.	None
Ventricular rhythm abnormalities	The SmPC, Section 4.4 Special Warnings and Precautions for Use warns that isolated cases of QT-prolongation have been reported during treatment with VELCADE. Arrhythmia and ventricular dysfunction are identified as uncommon adverse drug reactions on the basis of postmarketing reports in Section 4.8 (Undesirable Effects) of the SmPC.	None
Guillain-Barré Syndrome	None	None
Other central nervous system disorders	The SmPC, Section 4.8 Undesirable Effects, identifies encephalopathy as an adverse reaction based on reports from postmarketing sources.	None
Medication/Dispensing errors	<u>Subcutaneous administration</u> The proposed SmPC, Section 6.6 Special Precautions for Disposal and Other Handling, provides instructions for HCPs on reconstitution of the 10 mL vial of VELCADE for either IV or SC injection. Additionally, warnings regarding the danger of intrathecal administration are included in Sections 4.2, 4.4 and 6.6 of the proposed SmPC. There is also single vial packaging with an additional warning statement, and single labelling for IV and SC administrations of	Additional risk-minimisation activities, including: Education of HCPs Reconstitution poster, A dosing slide rule Training of medical representative, medical and scientific liaisons.

	VELCADE. <u>Confusion with administering the incorrect regimens in the transplant induction setting.</u> Refer to the proposed SmPC (Sections 4.2 and 4.8) for the correct use of the 2 regimens (VELCADE with dexamethasone and with dexamethasone and thalidomide) and for additional information concerning ADRs.	Proposed actions/components and rationale include: The company will ensure proper training of all MSLs on the different VELCADE treatment schedules approved for transplant induction. MSLs will be able to offer on-site training and relevant recommendations. Have the schedules, doses and number of cycles for each of the 2 combinations clearly described and graphically represented in educational materials. Include detailed discussions on the dosing regimens in the transplant induction setting in all future regional and local medical education (programme) whenever the use of VELCADE in the Transplant settings is addressed.
Missing information		
Safety in patients with cardiac impairment or with NYHA Class III or IV impairment	The SmPC, Section 4.4 Special Warnings and Precautions for Use, states that acute development or exacerbation of congestive heart failure, and/or new onset of decreased LVEF has been reported during bortezomib treatment. In a single agent Phase 3 randomised, comparative trial the incidence of heart failure in the VELCADE (injected intravenously) group was similar to that in the dexamethasone group. Fluid retention may be a predisposing factor for signs and symptoms of heart failure. Patients with risk factors for or existing heart disease should be closely monitored.	
Safety in patients with ECOG>2	None	None
Second primary malignancies with VcTD induction therapy	Section 4.4 of the SmPC warns that when VELCADE is given in combination with other medicinal products. The prescriber should refer to the SmPC for these other products.	None

2.8. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC have been updated. Particularly, a new warning with regard to Hepatitis B Virus (HBV) reactivation and infection has been added to the product information. The Package Leaflet has been updated accordingly.

2.8.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed. The justification for not providing a bridging report has been found acceptable.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The results from Study LYM-3002 have provided convincing evidence of clinical efficacy of VcR-CAP in terms of the primary endpoint PFS, compared to R-CHOP in untreated MCL patients unsuitable for haematopoietic stem cell transplantation. The results of PFS (Cut-off 2 December 2013) showed a statistically significant improvement (IRR) for VcR-CAP compared with R-CHOP (HR 0.63, 95% CI 0.50-0.79; p<0.001), with a gain in median PFS of 10.3 months in favour of VcR-CAP. The robustness of the PFS effect is supported by alternative IRC assessment and Investigator assessment and several sensitivity analyses, the results of which were in line with the primary analysis.

The secondary endpoints, including time to progression (30.5 vs 16.1 months), time to next anti-lymphoma treatment (44.5 vs 24.8 months) and treatment free interval (40.6 vs 20.5 months), overall response rates (53.3 % vs. 41.7%), and duration of response rates (42.1 vs. 18.0 months) supported the primary efficacy endpoint and favoured the VcR-CAP arm compared to the R-CHOP arm.

Uncertainty in the knowledge about the beneficial effects

One uncertainty that was identified during the assessment was the specific population included in the pivotal trial (patients who were ineligible to transplantation) and the selected dose however this uncertainty was satisfactorily addressed (see discussion on clinical efficacy).

The pivotal study supporting the MCL indication utilized IV administration of Velcade and no data were provided with SC administration in MCL, however no relevant Velcade PK/PD differences were observed between Velcade administered IV and SC in MM setting (Velcade is currently administered SC both as single agent and combination. Since no significant differences on the Velcade SC bioavailability are expected between MM and MCL patients, it is likely that the lack of data from study LYM-3002 on Velcade SC administration in VcR-CAP regimen have no impact on its overall efficacy. Therefore the SC administration is considered appropriate also for MCL indication and this has been reflected in section 4.2 of the SmPC 3.5 mg vial only (the only strength for which SC is allowed).

Risks

Unfavourable effects

The common chemotherapy backbone of the two regimens and the characteristics of the disease accounted for the most common classes of AEs in both groups in the LYM-3002 study: Hematologic abnormalities were the most common AE class in both groups (86% and 94% respectively in the R-CHOP and VcR-CAP arms), followed by infections and infestations (46% in R-CHOP and 60% in VcR-CAP), gastrointestinal disorders (47% in R-CHOP and 58% in VcR-CAP) and nervous system disorders (46% vs 50%).

More patients in the pooled VcR-CAP arm compared to the pooled R-CHOP group experienced adverse events grade ≥ 3 (92% vs 68% respectively) and serious adverse events (38% vs 31% respectively).

Peripheral sensory neuropathy was confirmed to be a Velcade and Vincristine associated toxicity. Velcade discontinuation due to peripheral neuropathy occurred in 5% of subjects in the pooled VcR-CAP treatment group while Vincristine discontinuation in the pooled R-CHOP treatment group was slightly less frequent (3%).

Myelotoxicity was higher in the pooled VcR-CAP group compared with the pooled R-CHOP group and reflects the higher and more extensive haematological toxicity of Velcade in comparison with Vincristine. Grade ≥ 3 neutropenia rate was 70% in the pooled R-CHOP group and 83% in the pooled VcR-CAP group, and grade ≥ 3 thrombocytopenia rate was 5% in pooled R-CHOP group and 52% in pooled VcR-CAP group. The greater Velcade-related myelotoxicity was clinically reflected in a more intensive supportive treatment with platelet transfusions administered to prevent the number and the severity of bleeding events in the VcR-CAP group (23% of subjects in the pooled VcR-CAP group needed platelet transfusions vs 3% in the pooled R-CHOP group). Platelet transfusions and the transient nature of thrombocytopenia have resulted, despite the high rate of grade ≥ 3 thrombocytopenia in the pooled VcR-CAP group, in a low incidence of all grade bleeding events in both pooled groups (5% in the R-CHOP arm and 6% in the VcR-CAP arm respectively), and a similar incidence of grade ≥ 3 bleeding events was also reported. In light of their efficiency in preventing major bleedings, platelet transfusions should be considered, where clinically appropriated, during VcR-CAP administration. The need of platelet transfusion and of prophylaxis due to neutropenia has been reflected in sections 4.2 and 4.4.of the SmPC.

Herpes zoster-related events were more common in the VcR-CAP group, in spite of antiviral prophylaxis. The already established association between Velcade exposure and herpes zoster reactivation is therefore confirmed. Prophylactic antiviral therapy should be mandatory and this has been adequately reflected in the SmPC (see sections 4.4 and 4.8).

HBV infection with fatal outcomes occurred in 0.8% (n=2) of patients in the non-Velcade treatment group (R-CHOP) and 0.4% (n=1) of patients receiving VcR-CAP. The overall incidence of hepatitis B infections was similar in patients treated with VcR-CAP or with R-CHOP (0.8% vs 1.2% respectively). These data have been adequately reflected in the SmPC (see sections 4.4 and 4.8).

Uncertainty in the knowledge about the unfavourable effects

Even if thrombocytopenia is a known safety concern associated to Velcade use, the grade of thrombocytopenia observed in study LYM-3002 in VcR-CAP group is higher than that expected in the regimens currently employed in the treatment of MCL (as highlighted by the lower platelet transfusions in R-CHOP treated patients). This has been adequately reflected in the SmPC (see section 4.2 and 4.4) and is reflected in the Risk Management Plan.

The treatment with VcR-CAP is also associated with an increased risk of pneumonia compared to R-CHOP in the study LYM-3002. Since the majority of the pneumonia events in study occurred within the context of neutropenia, the use of colony stimulating factors is strongly supported (SmPC sections 4.2, 4.4 and 4.8).

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The proposed combination VcR-CAP showed a significant superiority over R-CHOP in untreated MCL patients unsuitable for haematopoietic stem cell transplantation, with a gain in absolute PFS of 10.3 months. The secondary endpoints, supported the primary efficacy endpoint and favoured the VcR-CAP arm compared to the R-CHOP arm which can translate in a clinically significant benefit and in a better quality of life in patients who are at present destined to receive multiple chemotherapy treatments during their lifetime.

The toxicity associated with VcR-CAP combination although consistent with the known single safety profiles of velcade, rituximab, cyclophosphamide, doxorubicin and prednisone, was also important, including grade ≥ 3 and serious adverse events especially with regard to thrombocytopenia, neutropenia peripheral neuropathy and herpes zoster reactivation.

Benefit-risk balance

In general, the availability of new medicinal products in the first line treatment of MCL in patients suitable or not for an autologous stem cell transplant is considered of great clinical value. The safety profile of VcR-CAP regimen although sufficiently characterized, is significantly higher than that of R-CHOP. In view of the large effect in terms of PFS, the coherent evidence from secondary efficacy endpoints and the lack of significant uncertainty in terms of efficacy or safety, the toxicity profile is considered acceptable. Therefore, the benefit-risk balance for VcR-CAP regimen in the proposed indication is considered positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation requested		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication to include the use of Velcade in combination with rituximab, cyclophosphamide, doxorubicin and prednisone for the treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation; as a consequence, 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet is updated in accordance.

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