21 May 2015
EMA/CHMP/473724/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Imbruvica

International non-proprietary name: IBRUTINIB

Procedure No. EMEA/H/C/003791/II/0001

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

Abbreviation	Definition
ADR	adverse drug reaction
ANC	absolute neutrophil counts
BTK	Bruton's tyrosine kinase
CHMP	Committee for Medicinal Products for Human Use
CDP	cyclophosphamide-doxorubicin-prednisone
CI	confidence interval
CLL	chronic lymphocytic leukemia
CR	complete response
CSR	clinical study report
CT	computed tomography
CYP	cytochrome P450
del 17p	deletion in the short arm of chromosome 17p13.1
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration
Ig	immunoglobulin
IRRC	Independent Response Review Committee
IWWM	International Workshop on Waldenström Macroglobulinemia
LPL	lymphoplasmacytic lymphoma
MAPK	mitogen-activated protein kinase
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MR	minor response
NCCN	National Comprehensive Cancer Network
NF-κB	nuclear factor kappa B
NHL	non-Hodgkin's lymphoma
ORR	overall response rate
PFS	progression-free survival
PR	partial response
REAL	Revised European American Lymphoma
SD	stable disease
SEER	Surveillance, Epidemiology, and End Results
SLL	small lymphocytic lymphoma
SmPC	Summary of Product Characteristics
SMQ	standardized MedDRA query
STAT	signal transducer and activator of transcription 3
TTNT	Time to next therapy
TTP	time-to-progression
ULN	upper limit of normal
US	United States
VGPR	Very good partial response
WHO	World Health Organization
WM	Waldenstrom's Macroglobulinemia

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 NV submitted to the European Medicines Agency on 11 November 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:**
Imbruvica	IBRUTINIB

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

The Marketing authorisation holder (MAH) applied for an extension of indication for Imbruvica for the treatment of adult patients with Waldenström macroglobulinaemia (WM). Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.8 and 5.1 of the SmPC and the Package Leaflet in order to incorporate all information relevant to the WM indication. In addition, some minor editorial corrections have been made in the SmPC.

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/0271/2014 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Imbruvica was designated as an orphan medicinal product EU/3/12/984 - EMA/OD/156/11 on 26 April 2012 and EU/3/13/1115 - EMA/OD/171/12 on 12 March 2013. Imbruvica was designated as an orphan medicinal product in the following indication: Treatment of mantle cell lymphoma and Treatment of chronic lymphocytic leukaemia.

The new indication, which is the subject of this application, falls within a separate orphan designation ‘‘treatment of lymphoplasmacytic lymphoma” EU/3/14/1264 granted on 29/04/2014.

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

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: Filip Josephson Co-Rapporteur: Christian Schneider

Timetable	Actual dates
Submission date	11 November 2014
Start of procedure:	28 November 2014
CHMP Rapporteur Assessment Report	19 January 2015
PRAC Rapporteur Assessment Report	23 January 2015
Committees comments on PRAC Rapp Advice	1 February 2015
PRAC Rapporteur Updated Assessment Report	3 February 2015
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	12 February 2015
CHMP Co-Rapp Assessment Report	17 February 2015
CXMP comments	18 February 2015
CHMP joint Rapporteur and Co-Rapp Assessment Report	20 February 2015
Request for supplementary information (RSI)	26 February 2015
MAH's responses submitted to the CHMP on:	20 March 2015
PRAC Rapporteur Assessment Report	20 April 2015
CHMP Rapporteur Assessment Report	20 April 2015
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	7 May 2015
CHMP Rapporteur updated Assessment Report	13 May 2015
CXMP comments	13 May 2015
Opinion	21 May 2015

2. Scientific discussion

2.1. Introduction

Problem statement

Waldenström macroglobulinaemia is a lymphoproliferative B-cell disorder characterized by infiltration of lymphoplasmacytic cells into the bone marrow and immunoglobulin M (IgM) monoclonal gammopathy. It is considered to be a lymphoplasmacytic lymphoma (LPL) by the Revised European American Lymphoma (REAL) and World Health Organization classification systems. Waldenström macroglobulinemia is a rare type of NHL, accounting for <2% of all NHL subtypes (Leukemia & Lymphoma Society, 2013). It is a disease of the elderly with a median age of 63–68 years with a male predominance (Buske 2013).

The somatic mutation MYD88 L265P is present in >90% of patients with Waldenstrom's macroglobulinemia and supports malignant growth via signalling involving Bruton's Tyrosine Kinase (BTK). WHIM-like mutations in CXCR4 are present in 1/3 of patients with WM, and their expression induces BTK activity and may confer decreased sensitivity to ibrutinib mediated growth suppression in WM cells (Treon et al, 2013).

Clinical manifestations of WM include cytopenias (anaemia) and lymphadenomegaly resulting from infiltration by lymphoplasmacytic cells and IgM paraprotein-related symptoms such as cryoglobulinemia, cold agglutinin syndrome, demyelinating neuropathy, amyloidosis (involving kidneys, heart and nervous system), infections and symptomatic hyperviscosity (visual disturbance, headache, dizziness, altered consciousness, fatigue and weakness).

To establish the diagnosis of WM, it is necessary to demonstrate an IgM monoclonal protein, along with histological evidence of infiltration of the bone marrow by lymphoplasmacytic cells in line with the diagnosis of lymphoplasmacytic lymphoma (Weber et al 2003).

Factors associated with a poor prognosis include advanced age (>65 years); β2-microglobulin >3 mg/L; anemia (hemoglobin ≤11.5 g/dL); thrombocytopenia (platelet count ≤100 x 10^9/L); and IgM monoclonal gammopathy (IgM >7.0 g/dL). Based on these key factors an international prognostic scoring system for newly diagnosed patients with WM was recently developed, indicating that the 5-year survival rates range from 36% to 87% in high- and low-risk patients, respectively (Table 1).

Table 1. Waldenström Macroglobulinemia International Prognostic Scoring System

	Low-risk	Intermediate-risk	High-risk
Number of risk factors	≤1 (excluding age)	2 or age >65 years	>2 risk factors
Percentage of patients	27%	38%	35%
5-year survival rate	87%	68%	36%
Reference: Morel 2009			

Waldenström macroglobulinaemia remains an incurable disease. According to the current European Society for Medical Oncology (ESMO) guidelines (Buske 2013) the first recommendation is to include the patient in a clinical trial, otherwise frontline treatment options include alkylating agents, nucleoside analogues, bortezomib and the monoclonal antibody rituximab. In relapsed disease the choice of the rituximab/chemotherapy depends on the prior regimen. If the patient was treated initially with

rituximab plus alkylating agents, the salvage regimen could be switched to rituximab in combination with nucleoside analogues, rituximab/bendamustine or bortezomib and vice versa.

About the product

Ibrutinib is an inhibitor of Bruton's tyrosine kinase (BTK) that targets the ATP binding domain of BTK and forms a covalent bond with a cysteine residue (Cys-481) in the binding pocket that leads to sustained inhibition of BTK enzymatic activity. BTK has a pivotal role in signalling through the B-cell antigen receptor activating pathways necessary for B-cell activation/proliferation and development in WM (SmPC section 5.1).

The applicant applied for a marketing authorisation for the following indication: "IMBRUVICA is indicated for the treatment of adult patients with Waldenström macroglobulinaemia (WM)."

The recommended indication for approval is:

IMBRUVICA is indicated for the treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy (SmPC section 4.1).

The recommended dose for the treatment of WM is 420 mg (three capsules) once daily until disease progression or no longer tolerated by the patient (SmPC section 4.2).

2.2. Non-clinical aspects

No new clinical data with the exception of ERA have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Introduction

2.2.2. Ecotoxicity / environmental risk assessment

The total consumption of ibrutinib on the EU market within the approved indications (mantle-cell lymphoma, chronic lymphocytic leukemia; MCL/CLL) and the intended indication (WM) has been recalculated, assuming 100% market share within the EU. This recalculation resulted in an estimated consumption volume of 9200 kg/year in the year 2021. Using this updated estimate for the consumption volume of ibrutinib, the calculations in the Environmental Risk Assessment (ERA) have been updated. The changes are related to the increase of the consumption volume due to adding the WM indication and recalculating the volume based on a 100% market share.

Table 2. Summary of changes to Ibrutinib ERA

Section of ERA	Summary of Changes
Summary	The following parameters have been updated: $PEC_{surfacewate}$ $PEC_{groundwater}$ $PEC_{surfacewater}/PNEC_{water}$ $PEC_{surfacewater}/PNEC_{microorganisms}$ $PEC_{groundwater}/PNEC_{groundwater}$ PEC_{soil} $PEC_{sediment}$ $PEC_{soil}/PNEC_{soil}$ $PEC_{sediment}/PNEC_{sediment}$
Paragraph 9.2 Phase I Calculation and Refinement of Predicted Environmental Concentration	The estimated consumption volume has increased from 4370 kg to 9200 kg. This results in a change of the $PEC_{surfacewater}$ from 0.012 µg/L to 0.025 µg/L and in a change of $PEC_{groundwater}$ from 0.003 µg/L to 0.0062 µg/L.
Paragraph 9.4 Outcome of Phase II TIER A Fate and Effect Analysis	The calculations of the risk characterisation ratios PEC/PNEC changed. $PEC_{surfacewater}/PNEC_{water}$ changed from 0.008 to 0.016. $PEC_{surfacewater}/PNEC_{microorganisms}$ changed from 1.2×10^{-7} to 0.25×10^{-6}. $PEC_{groundwater}/PNEC_{groundwater}$ changed from 0.0006 to 0.0013.
Paragraph 10.1.1 Predicted Environmental Concentration in Sludge (PEC_{sludge})	The $PEC_{sludge,\ with\ primary\ settler}$ changed from 0.0642 mg/kg dry sludge to 0.133 mg/kg dry sludge. The $PEC_{sludge,\ without\ primary\ settler}$ changed from 0.084 mg/kg dry sludge to 0.174 mg/kg dry sludge.
Paragraph 10.2: Predicted Environmental Concentration in soil (PEC_{soil})	The PEC_{soil} changed from 0.00015 mg/kg soil to 0.00033 mg/kg soil.
Paragraph 10.3: Predicted Environmental Concentration in sediment ($PEC_{sediment}$)	The $PEC_{sediment}$ changed from 4.0 µg/kg to 8.2 µg/kg.
Paragraph 13.1: Calculation of the ratio $PEC_{soil}/PNEC_{soil}$	The $PEC_{soil}/PNEC_{soil}$ changed from 0.007 to 0.014.
Paragraph 13.2: Calculation of the ratio $PEC_{sediment}/PNEC_{sediment}$	The $PEC_{sediment}/PNEC_{sediment}$ changed from 0.008 to 0.017.
Annex 1: Justification of estimated consumption volume	The information and justification for the estimated consumption volume has been updated including WM indication and assuming a 100% market share.

2.2.3. Discussion on non-clinical aspects

The updated ERA is considered acceptable and it does not change the conclusions drawn from ERA submitted with the initial MAA that ibrutinib is not expected to pose a risk to the environment.

2.2.4. Conclusion on the non-clinical aspects

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

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.

2.3.2. Pharmacokinetics

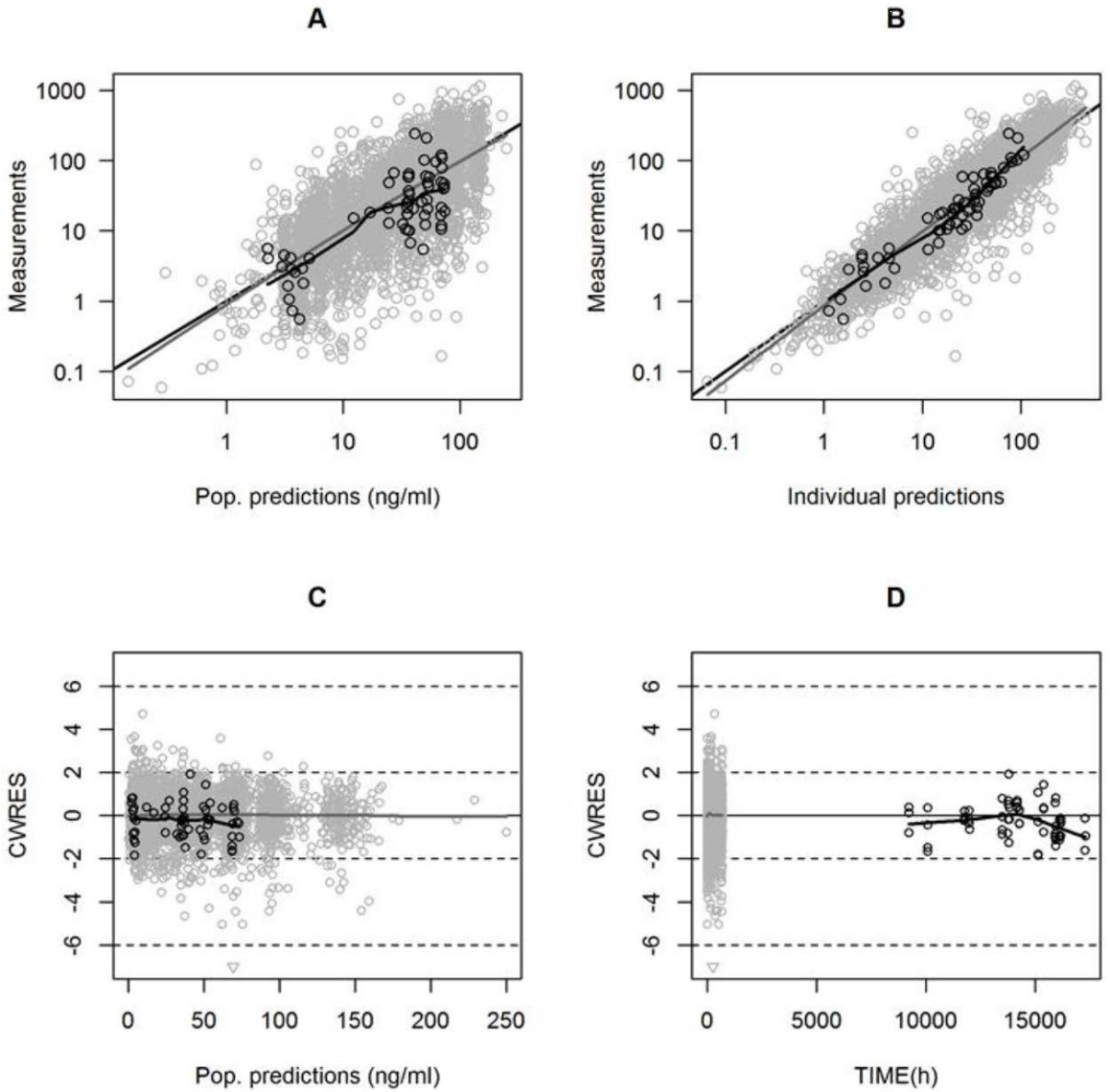
The MAH has submitted an analysis of sparse PK data from the Study 1118E using 62 samples from 16 subjects receiving ibrutinib for WM. Study 1118E was an open Phase 2, multicenter study designed to evaluate the safety and efficacy of ibrutinib in previously treated, relapsed/refractory WM patients. Treatment was administered in 4-week cycles until progression for a total of up to 40 cycles. Subjects received ibrutinib orally at a dose level of 420 mg given once daily with approximately 240 mL of water; each dose of ibrutinib had been taken approximately at the same time each day at least 30 minutes before eating or at least 2 hours after a meal.

Ibrutinib concentrations in plasma were measured liquid chromatography coupled to tandem mass spectrometry method (LC-MS/MS). Plasma samples were extracted using liquid/liquid extraction and subsequently analyzed using a chromatography method. The lower limit of quantification (LLOQ) was 0.500ng/mL, and the validated concentration range was 0.500-100 ng/mL.

Individual empirical Bayes PK parameters for ibrutinib were estimated for the subjects recruited in study 1118E, using the previous population PK model and parameters values (Bayesian feedback). The outcome was qualified using graphical exploration (including goodness of fit (GOF) plots and visual predictive checks (VPC) and calculating the prediction errors (%PE).

Standard of goodness fit are provided below:

Figure 2: Standard Goodness of Fit (GOF) for Ibrutinib PK: NONMEM Bayesian Feedback Run

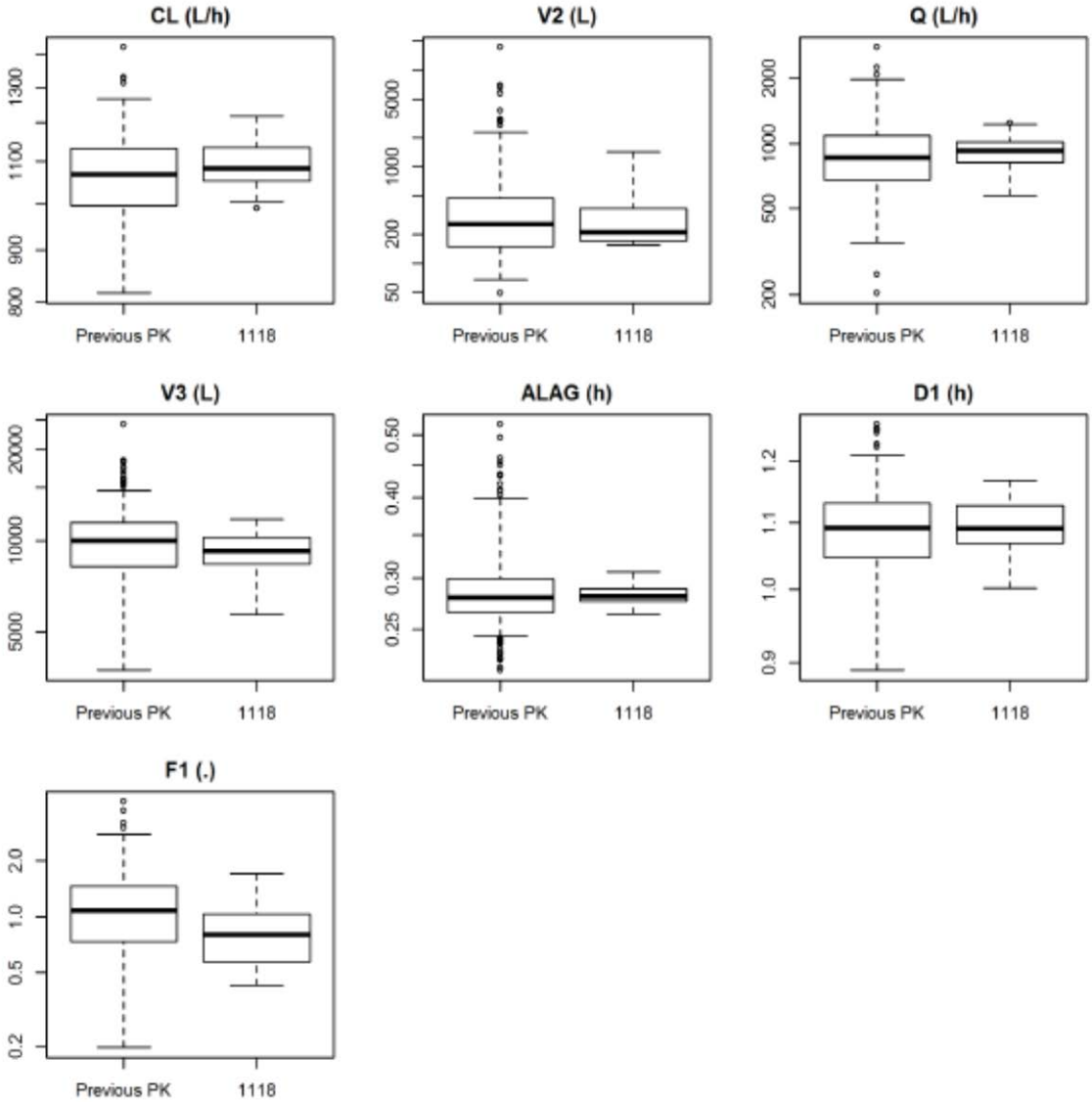


Gray symbols: previous PK assessment; black symbols: Study 1118E data Lines: smoothers.
A: observations [DV] vs population predictions [PRED]; B: observations [DV] vs individual predictions [IPRED]; C: conditional weighted residuals [CWRES] vs population predictions [PRED]; D: conditional weighted residuals [CWRES] vs time.

The distribution of covariates was similar to that reported in the previously reported population PK report model. The GOF plots, the graphical exploration of the empirical Bayes estimates and the VPC plots indicated the absence of bias in the individual predictions. Median PE% was -13.2%, i.e., within the predetermined cut-off value of ±15%.

Comparison of previous PK parameters against data from study 1118E is presented below:

Figure 3: Boxplots of Individual PK Parameters for Ibrutinib: NONMEM Bayesian Feedback Run (Study PCYC-1118E-CA) versus Previous PK Assessment



CL: apparent clearance; V2 apparent central Volume; Q: apparent intercompartmental flow; V3: apparent peripheral Volume; ALAG: lag time; D1: infusion rate (subjects with CO3 [antacid coadministration]=0); F1: apparent bioavailability.
The plots are log-scaled and show the median (thick line), the 1st and 3rd quartiles (box), and outliers (dots). The position of the whiskers (i.e. the lines that go from the ends of the box to the most remote points that are no outliers) are adjusted for unimodal skewness[6] (range=1.5).

2.3.3. Discussion on clinical pharmacology

The approach taken is based on Bayesian feedback of new data to a previously developed PoP-PK model for ibrutinib to demonstrate that these new dataset in WM patient compares well to those estimated from PoP-PK data from previous data. Overall, the approach taken appears justifiable given the scarcity of the new data as estimating standard NC PK parameters is not an option, and the development of a new model is likely futile given the nature of the dataset.

With the limitations linked to the sparse dataset, the updated population pharmacokinetic model indicated no differences between the pharmacokinetics in patients with WM as compared with other B-cell malignancies. There is thus no concern regarding potential differences in interaction risk or how to dose special populations in the new patient population.

2.3.4. Conclusions on clinical pharmacology

Additional clinical pharmacology studies for Imbruvica are not required.

2.4. Clinical efficacy

2.4.1. Dose response studies

Study 04753

Study PCYC-04753 was a Phase 1, open-label, multicenter, dose-escalation study of ibrutinib in subjects with a variety of B-cell malignancies. Four subjects with a diagnosis of previously treated WM were enrolled and treated at 2 different dose levels: 3 subjects received 560 mg/day and 1 subject received 12.5 mg/kg. All 4 subjects were male with a median age of 65 years (range: 54 to 78 years). Median time since initial diagnosis was 102 months (range: 18 to 182 months). Subjects had received a median of 3 prior therapies (range: 1 to 5).

Average dose-normalized ibrutinib exposure based on the AUC was approximately 2 times higher in the 2.5 mg/kg dose cohort compared with the other cohorts in this study. Given the atypically high level of exposure to ibrutinib at the 2.5 mg/kg dose level and the intersubjective variability in plasma levels observed in this study (CV for Cmax: 59% to 136%; CV for AUC: 60% to 107%), there was concern that some subjects in a larger population may experience low exposures and may not achieve the targeted pharmacodynamic effect. Therefore, a dose greater than 2.5 mg/kg was considered necessary to achieve consistent, full BTK occupancy. In Study 04753, the next higher dose level above 2.5 mg/kg demonstrating full occupancy was 5.0 mg/kg (350 mg for a 70 kg individual), where absolute doses ranged from 280 mg/day to 600 mg/day. Taken together, these findings indicated that dose levels >280 mg are likely necessary to achieve full PD effect in the vast majority of subjects.

Efficacy was a secondary objective of this study, with serum IgM reduction being the basis of the response assessment for patients with WM (Kimby 2006). Three subjects had a best response of PR (defined as IgM reduction of at least 50% from baseline) and continued on therapy for more than 3.5 years, and the fourth subject achieved stable disease but discontinued study treatment due to progressive disease after 8 months.

While the number of subjects with WM in the Phase 1 study was small (n=4), the overall safety profile in these subjects was consistent with the safety profile observed in subjects with other B-cell malignancies.

Study 1102

Saturation of the Bruton's Tyrosine Kinase (BTK) binding sites was confirmed at doses of 420 and 840 mg in subjects with CLL/SLL in Study 1102 (a Phase 1b/2, Open-label, non-randomized study in subjects with treatment-naïve and relapsed/refractory CLL/SLL). Although ibrutinib plasma exposures

were higher at 840 mg compared to 420 mg, there were no clinically meaningful advantages with regard to safety, efficacy and PD findings with the higher dose in subjects with CLL/SLL in Study 1102.

The once-daily dosing regimen of 420 mg/day ibrutinib was chosen for Study 1118E, in line with the dose used in subjects with CLL/SLL. Ibrutinib exposure in PK evaluable subjects in Study 1118E (n=16) receiving 420 mg/day was also within range of the exposure observed in subjects with CLL/SLL receiving the same dose level.

2.4.2. Main study

PCYC-1118E

PCYC-1118E was a phase 2, single-arm, multi-centre study of Bruton's Tyrosine Kinase (BTK) inhibitor, ibrutinib, in subjects with previously treated Waldenstrom Macroglobulinemia.

Methods

Study participants

Inclusion criteria

The main criteria for subject inclusion in the study were:

• Clinicopathological diagnosis of WM and meeting criteria for treatment using consensus panel criteria;

• Measurable disease, which was defined as the presence of serum IgM with a minimum IgM level of >2 times the institutional ULN;

• At least 1 prior therapy for WM;

• Eastern Cooperative Oncology Group PS of ≤ 2;

• Age ≥ 18 years;

• Adequate hematologic, renal, and hepatic function;

• No active therapy for other malignancies with the exception of topical therapies for basal cell or squamous cell cancers of the skin.

Exclusion criteria

Key exclusion criteria included anti-coagulation with warfarin therapy and known lymphoma of the central nervous system (CNS), treatment with strong CYP3A4/5 and/or CYP 2D6 inhibitors, and significant cardiovascular disease.

Treatments

Ibrutinib was administered orally at a dose of 420 mg daily in 4-week cycles. Subjects were evaluated for response and tolerance to ibrutinib on the first day of each cycle (4 weeks ±2 days) at Cycle 2, Cycle 3, and thereafter every 3 cycles (12 ±1 week) for a maximum of 40 four-week cycles (ie,

approximately 3 years), or until disease progression. Participants were to be followed for up to two years after removal from or completion of the study, until new treatment or death, whichever occurs first.

Doses were to be withheld for any of the following conditions: Grade 4 ANC (< 500/μL) for > 7 days (neutrophil growth factors are permitted); Grade 3 Platelets (< 50,000/μL) or, in subjects with baseline thrombocytopenia, a platelet decrease of 50-74% from baseline in presence of bleeding; Grade 4 Platelets (< 25,000/μL) or, in subjects with baseline thrombocytopenia, decrease of > 75% from baseline or < 20,000/ μL, whichever is the larger decrease; Grade 3 or 4 nausea, vomiting, or diarrhea (if persistent despite optimal antiemetic and/or antidiarrheal therapy); any other related grade 4 toxicities and any unmanageable non hematologic Grade 3 toxicities.

Objectives

The primary objective of this study was to assess the efficacy in terms of Overall response rate (ORR) (>25% reduction in disease burden), major response rates (>50% reduction in disease burden), and VGPR/CR of ibrutinib in symptomatic WM patients with relapsed/refractory disease.

The secondary objectives were to assess the safety and tolerability of ibrutinib in symptomatic WM subjects with relapsed/refractory disease and to determine Progression free survival (PFS) and Time to next therapy (TTNT) of ibrutinib in symptomatic WM subjects with relapsed/refractory disease.

Outcomes/endpoints

The primary endpoint of the study was the ORR per investigator assessment utilizing the adopted response criteria from the Third International Workshop on WM (see table below). Overall response rate was defined as a response assessment of minor response (MR:25-49% reduction in serum IgM levels) or better. The primary endpoint has also been assessed by IRRC.

Table 3: Tabular Summary of Investigator vs. IRRC Response Criteria for Overall Response Rate- Study 1118E

Response Category	Protocol-Specified Criteria (Investigator Assessment)	IRRC-Specified Response Criteria
Complete response (CR)	Resolution of all symptoms, normalization of serum IgM levels with complete disappearance of IgM paraprotein by immunofixation, and resolution of any adenopathy or splenomegaly	Resolution of all symptoms, normalization of serum IgM levels, required 2 consecutive measurements of IgM and negative serum immunofixation. Resolution of any adenopathy or splenomegaly by central radiology
Very good partial response (VGPR)	≥90% reduction in serum IgM levels	≥90% reduction in serum IgM levels or IgM levels within normal range Required 2 consecutive measurements of IgM
Partial response (PR)	≥50% reduction in serum IgM levels	≥50% reduction in serum IgM levels Required 2 consecutive measurements of IgM
Minor response (MR)	25-49% reduction in serum IgM levels	≥25% reduction in serum IgM levels Required 2 consecutive measurements of IgM

IgM: immunoglobulin M; IRRC: independent response review committee; ORR: overall response rate

Key secondary efficacy endpoints included major response rate (defined as PR or better, where PR was ≥50% reduction in serum IgM levels), duration of response (DOR: defined as time from the date of

initial minor response or better for overall response - or partial response or better for major response - to the date of the earliest occurrence of disease progression or death or date of censoring), time to response (TTR), Progression-Free Survival (PFS: defined as time from the date of first dose to the date of disease progression or death or date of censoring), overall survival (OS: defined as time from Study Day 1 to death or date of censoring) and haemoglobin improvement. For subjects with baseline haemoglobin ≤ 11 g/dL, haemoglobin improvement was defined as an increase to >11 g/dL with at least a 0.5 g/dL improvement or an increase of ≥ 2 g/dL over baseline; for subjects with baseline value > 11 g/dL, haemoglobin improvement was defined as an increase of ≥ 2 g/dL over baseline; sustained haemoglobin improvement was defined as improvement that sustained continuously for ≥ 56 days without blood transfusion or growth factors.

Exploratory efficacy endpoints included the change in serum immunoglobulin M (IgM) as well as the assessments of tumours involvement in the bone marrow, lymphadenopathy and splenomegaly.

Sample size

Assuming the response rate for ibrutinib is 50% in the study population with at least 60 evaluable subjects the study would have at least 80% power to declare that the lower bound of the 2-sided 95% CI for response rate would exceed 32%.

Randomisation

N/A

Blinding (masking)

N/A

Statistical methods

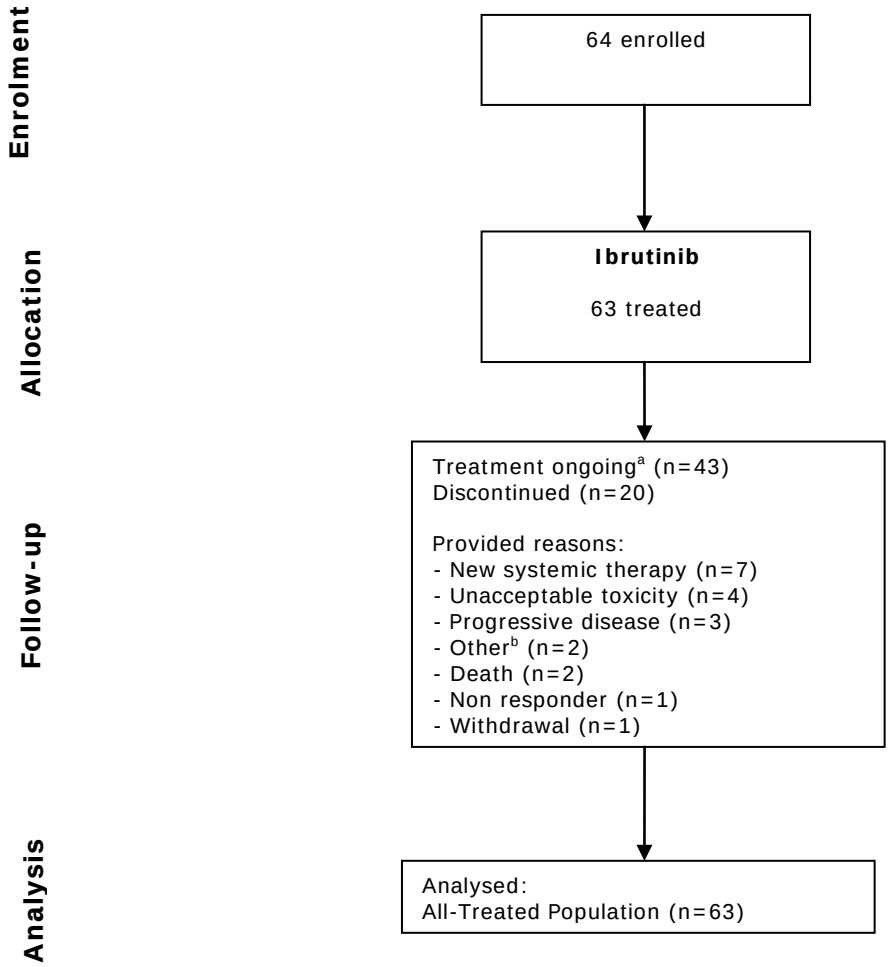
Overall response rate as assessed by investigator, and IRRC assessments, along with their 95% confidence interval (CI) (Clopper-Pearson), were calculated using exact binomial distribution.

Subgroup analyses for ORR were performed for selected baseline characteristics and potential prognostic variables to explore the effect of these factors on clinical benefit in response to ibrutinib. The ORR and its corresponding exact binomial 95% CI were calculated for each subgroup.

An analysis for the primary endpoint, overall response rate (PR or better), was conducted at 6 months.

Results

Participant flow



[b] Cut-off 28-Feb-2014

[b] 1 subject with myelodysplastic syndrome plus 1 with amyloidosis

Recruitment

Subjects were enrolled across 3 sites in the USA. The first patient was enrolled on 18 May 2012.

Conduct of the study

The original protocol was amended 11 times; the main amendments are reported in Table 4.

Table 4: Summary of key Protocol Amendments (Study 1118E)

Date	Change
03 Apr 2012	• Exclusion of participants on warfarin or being treated with strong CYP3A4/5 and/or CYP2D6 inhibitors
02 May 2012	• Revised eligibility criteria for contraceptive methods
18 Jul 2012	• Removal of the restriction to have maximum number of prior treatments given the high level of activity observed in subjects enrolled with multiple prior therapies
31 Oct 2012	• Modification of eligibility criterion for hemoglobin to >8 g/dL
10 Jan 2013	• Increased accrual to 60 participants • Addition of an Independent Review Committee • Addition of recommendations for holding ibrutinib prior to and following surgical procedures
07 May 2013	• Incorporated independent radiology review of all CT scans
09 Jul 2013	• Updated the response criteria for WM according to Sixth IWWM • Included provision for pathology material to be sent to the IPRC for central review
13 Nov 2013	• Clarified duration of ibrutinib hold for surgical procedures to at least 3 to 7 days before and after a procedure.
17 Dec 2013	• Extended the duration of study treatment to 40 cycles • Revised the response criteria to the original response criteria used at study initiation • Resumption of study treatment at the discretion of the investigator if a dose delay of ≥21 days was permitted • Collection of Grade 1 or higher TEAEs in the database

Major protocol deviations are shown in Table 5:

Table 5: Important Protocol Deviations (Study 1118E)

Site	Subject ID	Event Start Date	Classification	Short Summary	DFCI IRB Approval Prior to Event
DFCI	001-010	03-Aug-12	Eligibility	Subject had previous history of non-compliance on a protocol with an oral agent. Per protocol version 3, exclusion criterion 3.2.17, subjects with history of non-compliance are excluded.	Yes
DFCI	001-012	02-Aug-12	Eligibility	Subject received 5 prior therapies. Per protocol version 3, inclusion criterion 3.1.3, more than 4 prior therapies was not permitted. Protocol version 4 was under IRB review at this time which removed the maximum number of prior therapies.	Yes
DFCI	001-012	03-Aug-12	Efficacy	Screening serum IgM result on 03-Aug-12 was not used as baseline result for the study. The value was considered unreliable for the purposes of respose assessment as subject underwent plasmapheresis on 26-Jul-12. Site used serum IgM result from 26-Jun-12 (more than 30 days from study entry) as baseline value for follow up response assessments.	Yes
DFCI	001-015	20-Aug-12	Eligibility	Subject enrolled with screening platelets of 24,000mm^3. Per protocol version 3, inclusion criterion 3.1.6 required platelets >50,000mm^3 for study entry.	Yes
DFCI	001-025	09-Nov-12	Efficacy	Only bone marrow aspirate was collected at screening. Protocol required bone marrow biopsy and aspirate to be performed at screening.	Yes
MSKCC	002-051	15-May-13	Safety	Subject restarted study treatment with platelet count <50,000mm^3. Protocol required resolution to Grade 2 (>50,000mm^3) before restarting.	Yes
DFCI	001-044	03-Dec-13	Withdrawal Criteria	Subject was held from study treatment for 24 days due to adverse event. Per protocol, subject was required to discontinue if held more than 21 days, however, subject continued study treatment following the dose hold.	Yes
STANFORD	003-032	05-Mar-13	Informed Consent	Re-consent obtained by PA-C instead of an MD. Per DFCI policy, only MDs are to conduct ICF process.	No
STANFORD	003-064	10-Jun-13	Informed Consent	Consent changed per Stanford IRB request without approval from DFCI.	No

Baseline data

The baseline demographics and disease characteristics are presented in Table 6 and 7 respectively.

Table 6: Demographics and Baseline Characteristics - All-Treated Population (Study 1118E)

	Ibrutinib N=63
Age (years)[a]	
Mean (standard deviation)	64.5 (10.7)
Median	63.0
Min, Max	44.0, 86.0
Age Group (n, %)	
<65	32 (50.8)
≥65	31 (49.2)
Gender (n, %)	
Male	48 (76.2)
Female	15 (23.8)
Race (n, %)	
White	60 (95.2)
Other	3 (4.8)

max: maximum; min: minimum

[a] Age was defined as year of enrollment - year of birth.

Table 7: Baseline Disease Characteristics- All-Treated Population (Study 1118E)

	Ibrutinib N=63[a]
Months since initial diagnosis[b]	
Mean (standard deviation)	90.3 (71.4)
Median	73.7
Min, Max	6.3, 334.0
IPSSWM risk at baseline (n, %)[c]	
Low	15 (23.8)
Intermediate	27 (42.9)
High	21 (33.3)
Serum IgM (g/L)	
Mean (standard deviation)	37.6 (16.2)
Median	34.9
Min, Max	7.2, 83.9
β2 microglobulin (mg/L)	
Mean (standard deviation)	4.6 (2.4)
Median	3.9
Range	1.4, 14.2
β2 microglobulin (n, %)	
>3 mg/L	43 (68.3)
≤3 mg/L	17 (27.0)
Cytopenia (n, %)	
Any	40 (63.5)
Hgb ≤11 g/dL	38 (60.3)
Platelet ≤100 x 10^9/L	7 (11.1)
ANC ≤1.5 x 10^9/L	3 (4.8)
ECOG performance status (n, %)	
0	47 (74.6)
1	16 (25.4)
Number of prior regimens	
Median	2.0
Min, Max	1.0, 11.0

ANC: absolute neutrophil count; ECOG: Eastern Cooperative Oncology Group; Hgb: hemoglobin; IPSSWM: International Prognostic Scoring System for Waldenstrom's Macroglobulinemia; max: maximum; min: minimum
Note: Baseline is the last measurement prior to study treatment start.
[a] N =60 for β2 microglobulin
[b] Months since initial diagnosis=(First Dose Date – Diagnosis Date)/30.4375.
[c] IPSSWM has the following 5 adverse factors: age >65 years; hemoglobin ≤11.5 g/dL; platelet ≤100 × 10^9/L; β2 microglobulin >3 mg/L; and serum IgM monoclonal protein concentration >70 g/L. Risk-at-baseline categories are defined as follows - low risk: if ≤1 adverse factor except age; intermediate risk: if 2 adverse characteristics or age >65 years; high risk: if >2 adverse characteristics.

Numbers analysed

Table 8: Tabular Summary of Analysis Populations (Study 1118E)

Analysis Population	Definition	Purpose
Enrolled Population	Included all subjects who were confirmed to be eligible and were registered to the protocol through the DFCI QACT.	Summary of subject enrollment
All-Treated Population	Included all enrolled subjects who received at least 1 dose of study drug	Analysis of all efficacy endpoints
Safety Population	Same as All-Treated Population	Analysis of all safety endpoints
IPRC-Evaluable Population[a]	All enrolled subjects who received at least 1 dose of study drug and had not been diagnosed with an alternative diagnosis other than WM by the IPRC	Analysis of all efficacy endpoint

IPRC: independent pathology review committee; WM: Waldenstrom's Macroglobulinemia
[a] Analysis for the IPRC-Evaluable Population was not conducted as it was the same as the All-Treated Population.

Outcomes and estimation

Primary endpoint: Overall Response Rate

Results in term of ORR by Investigator and IRRC assessment (cut-off date 28 February 2014) are presented in Table 9:

Table 9: Overall Response Rate - All-Treated Population (Study 1118E- cut-off date 28 February 2014)

	By Investigator (N=63)	By IRRC (N=63)
Best response - n (%)		
Complete response (CR)	0 (0.0%)	0 (0.0%)
Very good partial response (VGPR)	9 (14.3%)	7 (11.1%)
Partial response (PR)	35 (55.6%)	32 (50.8%)
Minor Response (MR)	11 (17.5%)	13 (20.6%)
Stable disease (SD)	7 (11.1%)	9 (14.3%)
Progressive disease (PD)	1 (1.6%)	1 (1.6%)
Not Evaluable (NE)	0 (0.0%)	1 (1.6%)
Not Done (ND)	0 (0.0%)	0 (0.0%)
Overall response rate (CR+VGPR+PR+MR) - n (%)	55 (87.3%)	52 (82.5%)
95% CI [1]	(76.5%, 94.4%)	(70.9%, 90.9%)
p-value [2]	<.0001	<.0001
Major response rate (CR+VGPR+PR) - n (%)	44 (69.8%)	39 (61.9%)
95% CI [1]	(57.0%, 80.8%)	(48.8%, 73.9%)
p-value [2]	<.0001	<.0001

The updated results of ORR (cut-off date 19 December 2014) are presented in Table 10.

Table 10: Overall Response Rate, All-Treated Population (Study 1118E-cut-off date 19 December 2014)

Investigator Assessment (updated data) N=63	
Best response - n (%)	
Complete response (CR)	0
Very good partial response (VGPR)	10 (15.9)
Partial response (PR)	36 (57.1)
Minor Response (MR)	11 (17.5)
Stable disease (SD)	5 (7.9)
Progressive disease (PD)	1 (1.6)
Not Evaluable	0
Not Done	0
Overall response rate (CR+VGPR+PR+MR) - n (%)	57 (90.5)

Key secondary endpoints

The results of the analyses (cut-off date 28 February 2014) for the secondary endpoints (per investigator and IRRC assessmnet) are presented in Table 11.

Table 11: Secondary Endpoints, All-Treated Population (Study 1118E, cut-off date 28 February 2014)

	Investigator Assessment	IRRC Assessment
Major response rate		
N	63	63
(CR+VGPR+PR) - n (%)	44 (69.8)	39 (61.9)
Duration of overall response (months)		
N	55	52
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.03[b], 18.79[b]	2.43, 18.79[b]
Kaplan-Meier estimate of event-free rate at 18 months	86.1%	80.9%
Time to overall response (months)		
N	55	52
Median (range)	1.0 (0.69-13.37)	1.0 (0.69-13.37)
Progression-free survival (months)		
N	63	63
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.76, 19.94[b]	0.03[b], 19.94[b]
Kaplan-Meier estimate of PFS rate at 18 months[a]	83.2%	79.5%
Overall survival (months)		
N	63	--
Median (95% CI)	NE (NE, NE)	--
Min, Max	3.55, 21.09[b]	--
Kaplan-Meier estimate of overall survival at 18 months	92.7%	--

IRRC=Independent Response Review Committee; NE=not estimable
[a] PFS is calculated as the number of months from the date of first dose to the date of disease progression or death or date of censoring.
[b] Indicates censored observation

According to the Investigator Assessment, at the 18-month landmark, 86.1% (CI: 65.7%, 94.8%) of all responders (MR or better) remained alive and progression-free per investigator assessment, and the median duration of overall response was not reached. Per IRRC assessment, 80.9% of responders remained alive and progression-free at the 18-month landmark (CI: 64.9%, 90.2%); the median duration of overall response was not reached. The corresponding figures for major responders are 82.4% (CI: 58.1%, 93.3%) and 86.7% (CI: 67.9%, 94.9%), respectively.

Per investigator assessment, the median time to overall response was 1.0 month (range: 0.69 to 13.37 months), while the median time to major response was 1.6 months (range: 0.72 to 13.67 months).

Per IRRC assessment, the median time to overall response was 1.0 months (range: 0.69 to 13.37 months), while the median time to major response was 1.2 months (range: 0.72 to 13.37 months).

Sustained (≥8 weeks) improvement in haemoglobin levels was noted in 59% of patients overall and in 82% of patients with ≤11 g/dL at baseline.

The results of the updated analyses (cut-off date 19 December 2014) for the secondary endpoints (per investigator assessment) are presented in Table 12.

Table 12: Secondary Endpoints, All-Treated Population (Study 1118E, cut-off date 19 December 2014)

Investigator Assessment (updated data)	
Major response rate	
N	63
(CR+VGPR+PR) - n (%)	46 (73.0)
Duration of overall response (months)	
N	57
Median (95% CI) Min, Max	NE (NE, NE) 0.03, 29.04
Kaplan-Meier estimate of event-free rate at 18 months	73.7%
Time to overall response (months)	
N	57
Median (range)	1.0 (0.69-16.36)
Progression-free survival (months)	
N	63
Median (95% CI)	NE (NE, NE)
Min, Max	0.76, 29.73
Kaplan-Meier estimate of PFS rate at 18 months	80.0%
Overall survival (months)	
N	63
Median (95% CI)	NE (NE, NE)
Min, Max	3.55, 30.75
Kaplan-Meier estimate of overall survival at 18 months	95.2%

Exploratory analyses

Reductions in serum IgM of ≥25% were observed in 89% of subjects. Levels continued to decrease up to cycle 12 (median serum IgM value: 10.5 g/dL).

Concerning the exploratory evaluation of the extent of WM in other compartments, in the bone marrow an Independent pathology review showed improvement from baseline in cellularity in 39 of 54 subjects (72.2%), the median percentage of tumour involvement by cellularity at baseline was 60.0% and decreased to 30.0% by Cycle 12.

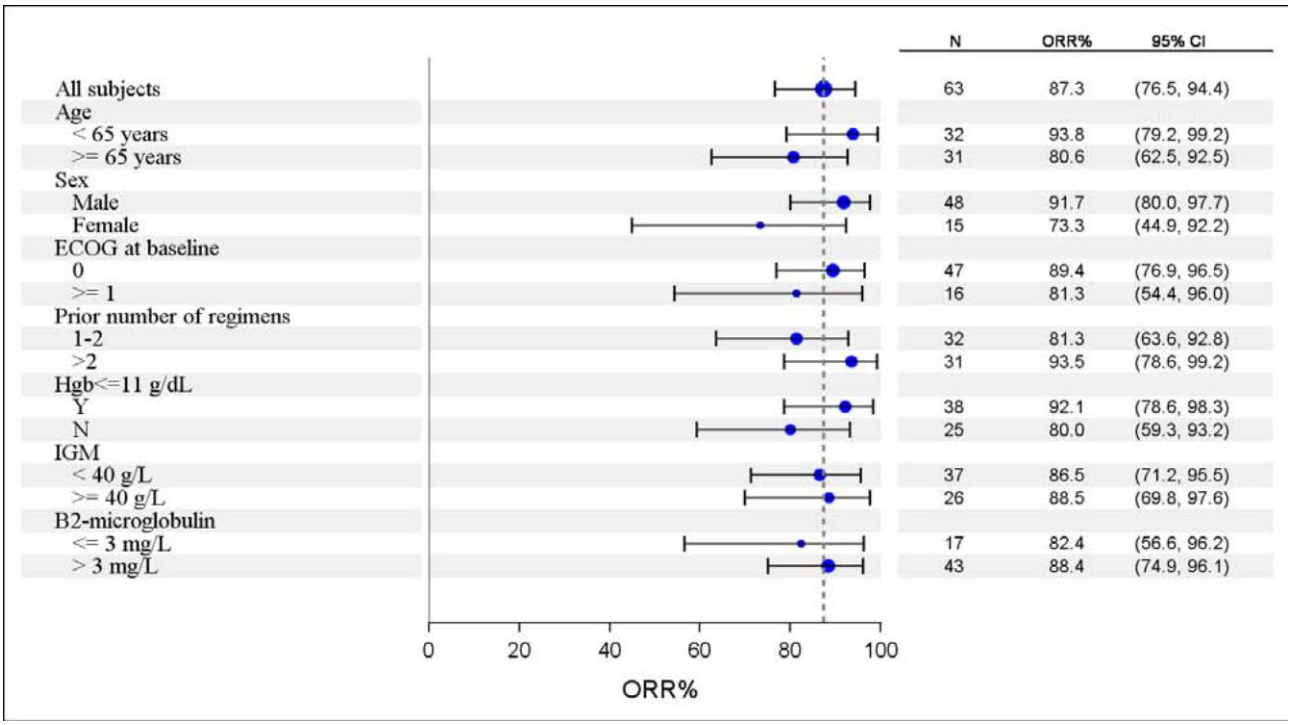
Reduction in adenopathy was observed in 38 (84%) of the patients who had complete follow-up scans available (45/50), as assessed by the Independent Radiology Review. Approximately 89% of subjects (32 of 36 evaluable) with major response were reported with any reduction of adenopathy and 4 of these subjects reported increased adenopathy.

Out of 26 subjects (41%) with splenomegaly at baseline, 25 had follow-up scans available and reduction in splenomegaly was observed in 24 of these (96%), as assessed by the Independent Radiology Review. Approximately 95% of subjects (20 of 21) with major response were reported with reduction/normalisation in spleen size. Any reduction in splenomegaly was reported for all 4 categorical non-responders.

Ancillary analyses

Figure 4 shows the ORR amongst all subgroups examined:

Figure 4: Subgroup Analysis of Overall Response Rate by Investigator Assessment - All-Treated Population (Study 1118E)



The Major Response Rate was investigated amongst subgroups by Investigator and IRRC assessment, results are reported in Figure 5 and Figure 6, respectively.

Figure 5: Subgroup Analysis of Major Reponse by Investigator – All-Treated patients (Study 1118E)

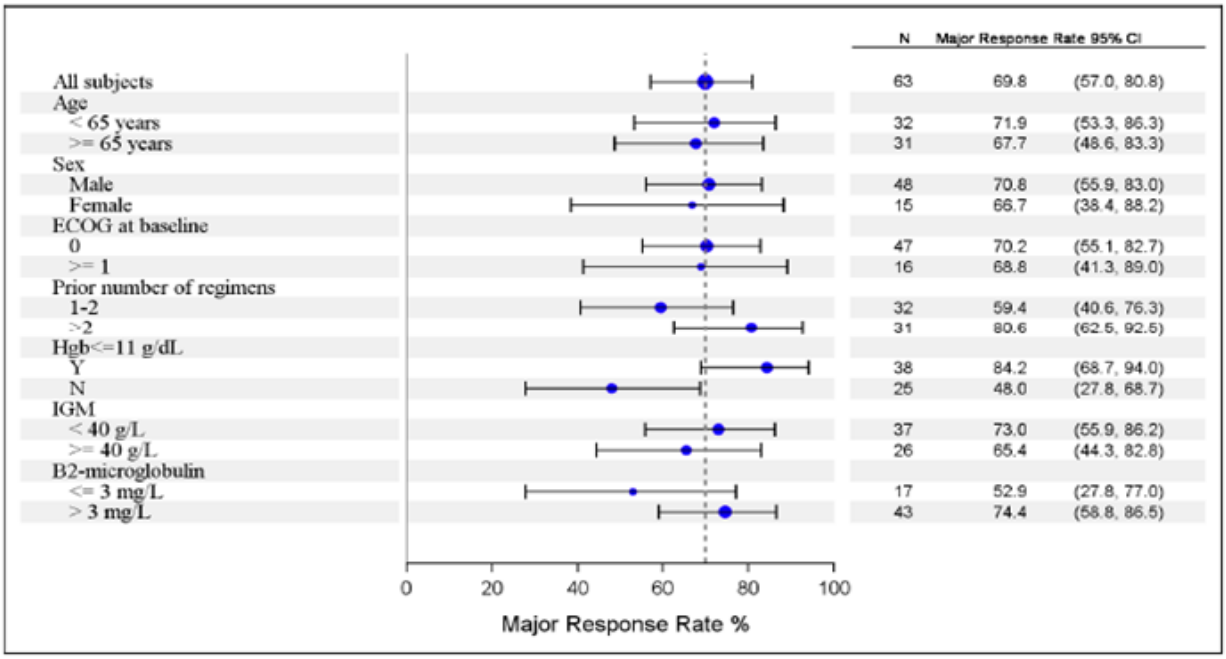
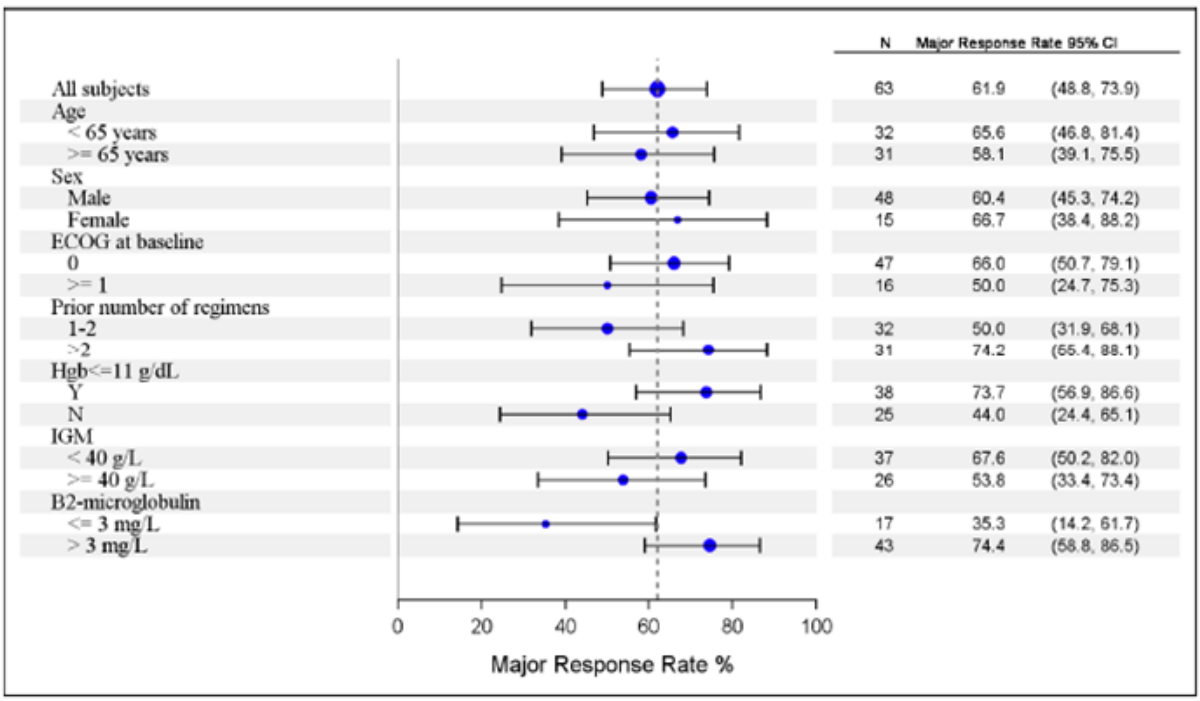


Figure 6: Subgroup Analysis of Major Reponse by IRRC – All-Treated patients (Study 1118E)



Response data by mutation status has been obtained for Study 1118E (Table 13).

Table 13: Response Rates by Mutation Status, All-Treated Population (Study 1118E)

	MYD88 N=55	WT N=7
ORR	52 (94.5%)	5 (71.5%)
CR	0	0
VGPR	9 (16.4%)	1 (14.3%)
PR	35 (63.6%)	1 (14.3%)
MR	8 (14.5%)	3 (42.9%)
Major response[a]	44 (80%)	2 (28.6%)
SD	3 (5.5%)	1 (14.3%)
PD	0	1 (14.3%)

CR=complete response; MR=minor response; ORR=overall response rate; PD=progressive disease; PR=partial response; SD=stable disease, WT=wild type, VGPR=very good partial response

[a] Major response = PR or better.

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 14. Summary of Efficacy for trial 1118E

Title: Phase 2 Study of Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib , in Waldenstrom's Macroglobulinemia			
Study identifier	PCYC-1118E (1118E)		
Design	Phase-2, single-arm, multi-centre		
	Duration of main phase:		40 four-week cycles
Hypothesis	Exploratory		
Treatments groups	Ibrutinib		420 mg daily per OS in 4-week cycles for a maximum of 40 four-week cycles (ie, approximately 3 years), or until disease progression; 63 treated patients
Endpoints and definitions	Primary endpoint	Overall Response Rate (ORR) per Investigator Assessment	minor response (MR: 25-49% reduction in serum IgM levels) or better (per Investigator Assessment)
	Secondary endpoint	Progression Free Survival (PFS)	time from the date of first dose to the date of disease progression or death or date of censoring

	Secondary endpoint	Haemoglobin improvement	Proportion of patients with a sustained (⩾ 8 weeks) improvement in haemoglobin levels For subjects with baseline haemoglobin ⩽ 11 g/dL, haemoglobin improvement was defined as an increase to >11 g/dL with at least a 0.5 g/dL improvement or an increase of ⩾ 2 g/dL over baseline; for subjects with baseline value > 11 g/dL, haemoglobin improvement was defined as an increase of ⩾ 2 g/dL over baseline; sustained haemoglobin improvement was defined as improvement that sustained continuously for ⩾ 56 days without blood transfusion or growth factors.
Database lock	28 February 2014		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	All-Treated population		
Descriptive statistics and estimate variability	Treatment group	Ibrutinib	
	Number of subjects	63	
	ORR n (%)	55 (87.3%)	
	95% CI	(76.5%, 94.4%)	
	PFS (rate at 18 months)	83,2%	
	Haemoglobin improvement n (%)	59%	

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

N/A

Clinical studies in special populations

N/A

Supportive studies

- **Historical Data**

Single-Agent Therapy Studies

To compare the results from Study 1118E with those of other available single-agent therapies for WM, a comprehensive review of clinical studies with single-agent therapies in subjects WM (treatment-naïve as well as relapsed or refractory disease) was conducted and is summarized in Table 15 and Figure 7.

Table 15: Summary of Efficacy in WM (Single-Agent Studies)

Agent Primary author	Population/N	Median Prior Therapies n (range)	Characteristics at Baseline						Major RR (≥PR) (%)	ORR (≥MR) (%)	DOR (months)	Median PFS/TTP (months) All-treated
			Age (med)	% male	IgM (g/L)	Hg (g/L)	Platelets (10^9/L)	β2-m (mg/L)				
Ibrutinib Study 1118E	R/R (n=63)	2 (1-11)	63	76.2	34.9	10.5	11.1% <100	3.9	69.8	87.3	Med. not reached; 18-mo. DOR rate: 86.1%	Med. not reached; 18-mo. PFS rate: 83.2%
Rituximab												
Dimopoulos 2002	R/R (n=12) TN (n=15)	26% ≥3 prior	72	67%	33.5	44% <100	15% <100	37% ≥4.0	44	NR	NR	16 (TTP)
Gertz 2004	TN (n=34) R/R (n=35)	0 NR	68.6	52%	44	9.6	197.5	3.5	35.3 20	52.9 51.4	27 NR	NR
Treon 2005	TN (n=12) R/R (n=17)	1 (0-2)	65	NR	35.6	NR	185	NR	48.3	65.5	18+ (≥PR) 20+ (≥MR)	17 (TTP) 14 (TTP)
Chlorambucil												
LeBlond 2013[c]	TN (n=170)	0	67.8	67%	27.4	9.9	204	3.6	35.9	NR	21.3	27.1 (PFS)
Fludarabine												
LeBlond 2001	R/R (n=46)	1 (no range)[a]	64	73.9%	36.3	107	188	2.6	30	NR	19	NR-
LeBlond 2013[c]	TN (n=169)	0	68.2	67%	28.0	9.9	229	3.2	45.6	NR	38.5	37.8 (PFS)
Cladribine												
Dimopoulos 1995	R/R (n=46)	≥1	60	45.6%	42% >20	52% <100	NR	42% ≥4.0	43	NR	NR	12 (PFS)
Bortezomib												
Chen 2007	TN (n=12) R/R (n=15)	0 2 (1-2)	65	52%	37.6	10.8	259	NR	44	78	10 (1.4-14.9)	16.3 (PFS)
Treon 2007	TN (n=1) R/R (n=26)	2 (0-3)	62	66.7%	46.6	NR	225	NR	48.1	85	NR	6.6 (TTP)
Everolimus												
Treon 2011c (abstract)	TN (n=33)	0	62	NR	44.4	10.8	NR	3.0	42.4	66.7	NR	NR
Ghobrial 2014	R/R (n=61)	3 (1-11)	63	83%	35.1	11.4	242	63% >3.0	50	73	Not reached (3-68)	21 (PFS) 25 (TTP)
Ofatumamab												
Furman 2011 (abstract)	TN (n=9) R/R (n=28)	0 3 (1-5)	63	59.4%	31.1	9.8	NR	NR	35	59	NR	NR
Alemtuzumab[b]												
Treon 2011a	TN (n=5) R/R (n=23)	0 2 (1-5)	59.5	64.3%	35.1	NR	232	3.1	80 29	100 76	NR-	14.5 (combined TTP)

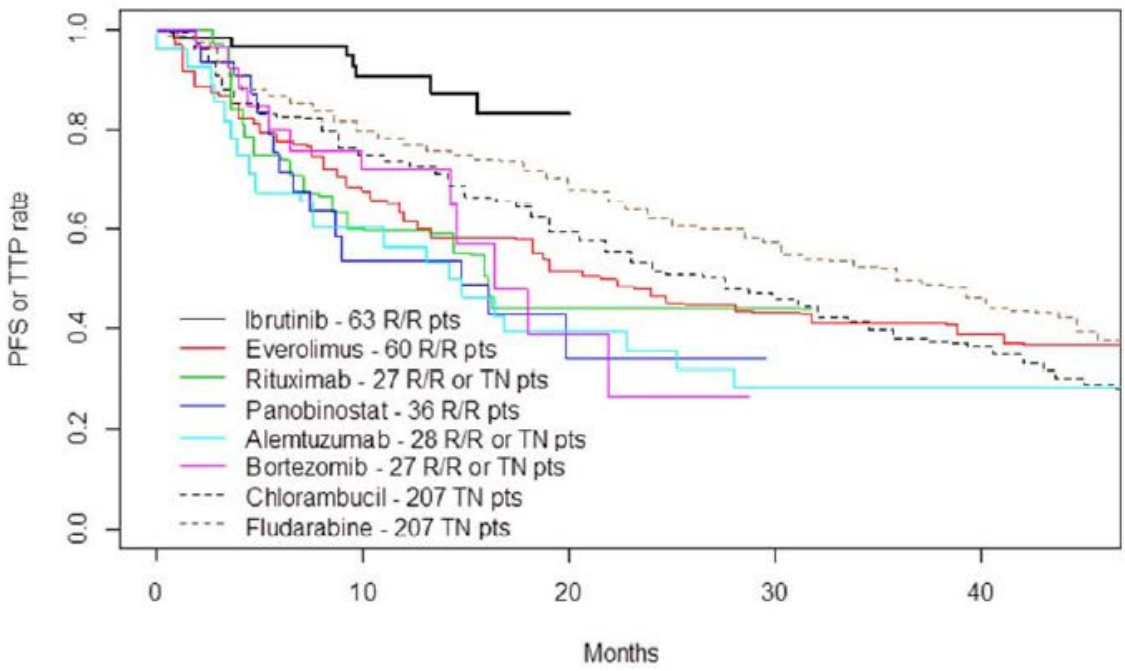
DOR=duration of response; Hg=hemoglobin; IgM=immunoglobulin; med=median; mo=month; MR=minor response; NR=not reported; ORR=overall response rate; PFS=progression-free survival; PR=partial response; R/R=relapsed/refractory; RR=response rate; TN=treatment-naive; TTP=time to progression

[a] Subjects in this study had to be in first relapse or primary refractory.

[b] No longer commercially available in the EU for non-Hodgkin Lymphoma

[c] Baseline characteristics represent all subjects in the treatment arm, not exclusively subjects with WM.

Figure 7: Historical Comparison of Progression-Free Survival in Patients with WM (Single-Agent Use)



Combination Therapy Studies

A comprehensive review of published clinical studies with combination therapies in subjects with WM showed generally high response rates, comparable to ibrutinib (Dimopoulos 2013; Leblond 2001; Tedeschi 2012; Treon 2011b; Treon 2009a, 2009b; Treon 2014).

There is only 1 reported randomized, controlled study conducted with combination therapy in the relapsed setting. In this, study, 92 subjects with relapsed WM, were randomly assigned to fludarabine or cyclophosphamide-doxorubicin-prednisone (CDP) chemotherapy. Partial responses were observed in 30% of subjects treated with fludarabine compared with only 11% in those treated with CDP (Leblond 2001). A study of bendamustine plus rituximab in the treatment of 30 subjects with relapsed or refractory WM resulted in an ORR of 83.3%; the median estimated PFS time was 13.2 months. In addition, 26.6% of subjects required dose reduction and/or truncation of therapy and 46.7% (14 of 30) of subjects completed all 6 planned cycles of bendamustine (Treon 2011b).

The majority of combination therapy studies in WM were conducted in the treatment-naïve setting. In a study of dexamethasone, rituximab, and bortezomib in subjects with treatment-naïve WM, the ORR was 85% and the rate of treatment discontinuation due to adverse events was 27%.

A study of carfilzomib, rituximab, and dexamethasone in 31 treatment-naïve subjects produced an 87% ORR, but only 32% of subjects received treatment for the total of 14 induction and maintenance cycles initially planned (Treon 2014). Treatment discontinuation or dose reduction was necessary for 30.2% (13 of 43) of subjects treated with rituximab and fludarabine. Specifically, treatment with rituximab was discontinued in 9% of subjects due to toxicity and in 21% of subjects with fludarabine (Treon 2009a). In a further study, 32.6% (14 of 43) of subjects treated with rituximab in combination with fludarabine and cyclophosphamide discontinued due to toxicity (Tedeschi 2012).

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The application in WM is based on the results obtained in the Study 1118E, a Phase II, single arm, multicentre study that recruited 63 patients with previously treated WM. Ibrutinib dose selection was not based on a MTD determination (as this was never reached); the selection of the 420-mg, once-daily dose regimen of ibrutinib for the treatment of adult subjects with WM was based on the dose-finding 04753 study, a Phase I, open-label, multicentre, dose escalation study of ibrutinib in B-cell malignancies including 4 WM patients. The justification of the 420 mg once-daily dose was considered acceptable.

The median age of the study population was 63 years with approximately half of the population below the 65 years of age cut-off, with older age defining an adverse factor in the prognostic score. Although this median age corresponds to a slightly lower age at diagnosis than recently reported for WM overall (63-68 years), the reported age span at diagnosis varies considerably among published reports. The 1118E study population is considered representative for the general WM population with previously treated disease.

The primary endpoint (ORR per investigator assessment utilizing response criteria adopted from the third IWWM) and the independent review sensitivity analysis were considered appropriate for a single arm trial in this setting.

Efficacy data and additional analyses

In the primary analysis, the ORR (including MR) per investigator assessment, was 87.3% (CI: 76.5%, 94.4%) with the predominant response category being PR, 56%; best response of VGPR was reached in 14% of patients, giving a major response rate of 70%. Progressive disease was reported for 1 patient.

The primary endpoint, ORR by investigator, was also assessed by an independent review committee for which response notably demanded confirmatory data; the concordance rate was 95%. According to IRRC assessment, the ORR was 82.5% (CI: 70.9%, 90.9%), with 2 fewer VGPRs, 3 fewer PRs, 2 more MRs and 2 more SDs, and the major response rate was 62%. Thus, the result of this sensitivity analysis was considered to be supportive of the primary endpoint.

Follow-up was relative short at the CSR cut-off of 28 February 2014, 14.8 months, with high censoring rates for time-dependent outcomes and consequently immature data. However, updated analyses were submitted corresponding to a median duration of treatment increase from 11.7 months to 19.1 months. In the updated data (cut off: 19 Dec 2014) the ORR has increased from 87.3% to 90.5% (95% CI: 80.4%, 96.4%) with one more patients reaching PR and VGPR, respectively, giving a major response rate of 73% (69.8% at the previous cut-off); PD was still observed in 1 patient.

Results in terms of Response Rate have been provided in a small subgroup of patients from Study 1118E, comparing subjects with MYD88 mutation (N=55) versus wild type group (N=7). The ORR was 94.5% for the MYD88 group versus 71.5% of the wild type group; Overall and the depth of response (major response) was 94.5% and 80% in the MYD88 group versus 71.5% and 28.6% in the wild type group, respectively, showing that there might be a trend for a higher ORR and deeper responses in the mutated group. The CHMP recommended the MAH to submit the results of the MYD88 L265P mutation analyses. Furthermore, since the WHIM-like CXCR4 mutation can promote resistance to ibrutinib and is

the 2nd most frequent mutation described in WM the CHMP recommended the MAH to evaluate the potential prognostic and/or predictive value WHIM-like CXCR4 mutations.

During the assessment the CHMP raised a major objection about the indication needing to be further discussed, with reference to first line setting. Based on historical comparisons of results obtained with ibrutinib in the R/R (Refractory/Relapsed) setting with efficacy and safety/tolerability for single drugs and combination therapies in the first line setting, the indication has been revised to include adult patients with Waldenstrom's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy. The restricted indication was considered acceptable as there is no reason to expect inferior efficacy or a worse safety profile in the first line setting, and for the group of patients unsuitable for chemo-immunotherapy, limited treatment options are currently available.

Study PCYC-1127, a randomized, double-blind, placebo-controlled, phase 3 study of ibrutinib or placebo in combination with rituximab in subjects with Waldenström's macroglobulinemia, is currently ongoing and the CHMP recommended the MAH to submit the CSR.

Regarding the secondary endpoints, the medians for DOR, PFS and OS have not been reached; updated KM estimates at 18 months showed a decrease of event-free rate to 73.7% (86.1%) and PFS to 80% (83.2%), and an increase of OS to 95.2% (92.7%). With the new cut-off (19 Dec 2014), haemoglobin improvement has been achieved in 4 more patients in the all-treated population, 65% (59% in the previous cut off), and in 1 more patient in subjects with a baseline haemoglobin level ≤11 g/dL, 84% (82% in the previous cut off).

2.4.4. Conclusions on the clinical efficacy

Study 1118E provided convincing evidence of clinical efficacy of ibrutinib in terms of the primary endpoint with support of secondary outcomes in adult patients with Waldenstrom's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy.

2.5. Clinical safety

The evaluation of Imbruvica safety derives from the Study 1118E (data cut off: 28 February 2014, N=63) and the integrated safety data of the 420 patients who received ibrutinib in studies 1112 (a randomised, ongoing, Phase III study comparing ibrutinib to ofatumumab in patients with CLL or SLL, N=195), 1102 (a non-randomised, open-label study conducted in patients with CLL/SLL, N=51), 1104 (a non-randomised, open-label study in MCL patients, N=111) and 1118E. The posology administered was 560 mg daily in MCL patients and 420 mg daily in CLL and WM subjects.

An analysis of the long-term safety (cut-off 10 March 2014) of ibrutinib in 198 subjects who received monotherapy with the longest treatment duration and follow-up is based on integrated data from Studies 1102, 04753, and 1103 (an open-label, ongoing, extension study with 119 patients already treated with ibrutinib); the long-term safety population of 198 patients includes 4 subjects with WM. The cumulative number of patients in the long-term safety population who received treatment with ibrutinib for ≤ 1 year was 198, for >1 to 2 years was 125, for >2 to 3 years was 99, and for >3 years was 65.

Patient exposure

The ibrutinib exposure in 1118E Study and in the integrated safety data is summarised in Table 16.

Table 16: Ibrutinib exposure (Safety Population)

	Study 1118E (N=63)	Label Pool[a] (N=420)
Treatment Duration (months)		
n	63	420
Mean (SD)	13.0 (5.10)	14.1 (7.16)
Median	11.7	15.2
Min, Max	0.5, 21.1	0.2, 30.3
≤6 Months	5 (7.9%)	82 (19.5%)
>6-12 Months	28 (44.4%)	60 (14.3%)
>12-24 Months	30 (47.6%)	242 (57.6%)
>24-36 Months	0	36 (8.6%)
Total Cumulative Dose Received (g)		
n	63	420
Mean (SD)	157.0 (69.16)	182.3 (102.46)
Median	149.1	187.7
Min, Max	6.3, 268.8	2.5, 486.1
Average Daily Dose (mg/day)		
n	63	420
Mean (SD)	390.6 (60.68)	428.2 (74.65)
Median	416.0	419.1
Min, Max	158.1, 420.0	140.7, 566.7

Max = maximum; Min = minimum; SD = standard deviation.
N = number of subjects in the analysis population.
[a] Pooled data from Studies 1112 (ibrutinib treated), 1102 (51 previously-treated subjects treated with 420 mg/day), 1104, and 1118E.

Concerning the long-term safety analysis, at the time of the data cut-off (10 March 2014) the median duration of ibrutinib exposure was 24.1 months (range: 0.2 to 52.5). The median treatment duration for the ≤ 1, >1 to 2, and >2 to 3 year exposure periods was the same (12.0 months); for the >3 years exposure period was 5.5 months. Among the four patients with WM, the duration of ibrutinib exposure ranged from 8.0 to 46.5 months (as of the data cut-off date). Three patients are currently remaining on treatment.

Adverse events

An overview of Treatment-Emergent Adverse Events is shown in Table 17 and Table 18.

Table 17: Overview of Treatment-emergent Adverse Events (Safety Population)

	Study 1118E (N=63) n (%)	Label Pool[a] (N=420) n (%)
Subjects with any TEAE	63 (100.0)	419 (99.8)
Grade ≥3	32 (50.8)	288 (68.6)
Subjects with any treatment-related TEAE[b]	42 (66.7)	357 (85.0)
Grade ≥3	18 (28.6)	160 (38.1)
Subjects with any TEAE leading to discontinuation of study drug	6 (9.5)	50 (11.9)
Subjects with any serious TEAE	24 (38.1)	226 (53.8)
Grade ≥3	23 (36.5)	205 (48.8)
Treatment-related serious TEAEs[b]	9 (14.3)	90 (21.4)
Fatal TEAE	1 (1.6)	38 (9.0)

TEAE = treatment-emergent adverse event.
N = Number of subjects in specified treatment arm of safety population. %=100*n/N.
Adverse events that started or worsened from the first dose date of study drug up to 30 days after the last dose of study drug and all possibly related or related AEs are considered treatment emergent (TEAE).
[a] Pooled data from Studies 1112 (ibrutinib treated), 1102 (51 previously-treated subjects treated with 420 mg/day), 1104, and 1118E.
[b] Possibly related or related to study drug per investigator's judgment.

Table 18: Treatment-emergent Adverse Events (Any Grade) by System Organ Class and Preferred Term with Subject Incidence ≥ 10% (Safety Population)

System Organ Class Preferred Term	Study 1118E (N=63) n (%)	Label Pool[a] (N=420) n (%)
Subjects with any TEAE	**63 (100.0)**	**419 (99.8)**
Blood and Lymphatic Disorders	25 (39.7)	218 (51.9)
Neutropenia	16 (25.4)	91 (21.7)
Thrombocytopenia	11 (17.5)	75 (17.9)
Anaemia	10 (15.9)	87 (20.7)
Gastrointestinal Disorders	50 (79.4)	346 (82.4)
Diarrhoea	23 (36.5)	213 (50.7)
Nausea	13 (20.6)	120 (28.6)
Stomatitis	9 (14.3)	55 (13.1)
Gastrointestinal reflux disease	8 (12.7)	28 (6.7)
Vomiting	6 (9.5)	75 (17.9)
Constipation	5 (7.9)	82 (19.5)
Abdominal pain	4 (6.3)	49 (11.7)
General Disorders and Administration Site Conditions	21 (33.3)	275 (65.5)
Fatigue	13 (20.6)	150 (35.7)
Oedema peripheral	4 (6.3)	78 (18.6)
Pyrexia	4 (6.3)	93 (22.1)
Infections and Infestations	46 (73.0)	340 (81.0)
Upper respiratory tract infection	12 (19.0)	109 (26.0)
Sinusitis	12 (19.0)	71 (16.9)
Folliculitis	7 (11.1)	23 (5.5)
Pneumonia	5 (7.9)	56 (13.3)
Urinary tract infection	5 (7.9)	55 (13.1)
Injury, Poisoning, and Procedural Complications	13 (20.6)	133 (31.7)
Contusion	7 (11.1)	66 (15.7)
Metabolism and Nutrition Disorders	6 (9.5)	161 (38.3)
Decreased appetite	3 (4.8)	58 (13.8)
Musculoskeletal and Connective Tissue Disorders	28 (44.4)	225 (53.6)
Muscle spasms	13 (20.6)	72 (17.1)
Arthropathy	8 (12.7)	8 (1.9)
Arthralgia	3 (4.8)	71 (16.9)
Myalgia	3 (4.8)	47 (11.2)
Back pain	1 (1.6)	48 (11.4)
Pain in extremity	0 (0.0)	43 (10.2)
Nervous System Disorders	26 (41.3)	183 (43.6)
Dizziness	9 (14.3)	63 (15.0)
Headache	8 (12.7)	61 (14.5)
Respiratory, Thoracic and Mediastinal Disorders	26 (41.3)	235 (56.0)
Epistaxis	12 (19.0)	48 (11.4)
Cough	8 (12.7)	91 (21.7)
Dyspnoea	3 (4.8)	67 (16.0)
Skin and Subcutaneous Tissue Disorders	29 (46.0)	250 (59.5)
Pruritus	7 (11.1)	32 (7.6)
Rash	7 (11.1)	48 (11.4)
Petechiae	3 (4.8)	50 (11.9)
Vascular Disorders	6 (9.5)	77 (18.3)
Hypertension	5 (7.9)	47 (11.2)

N = number of subjects in the analysis population.
Events are listed within each SOC in order of descending frequency in the Study 1118E population.
[a] Pooled data from: Studies 1112 (ibrutinib treated), 1102 (51 previously-treated subjects treated with 420 mg/day), 1104, and 1118E.

TEAEs of Grade 3 or 4 in severity by Preferred Term are reported in Table 19.

Table 19: Treatment-emergent Adverse Events of Grade 3 or 4 by Preferred Term with Subject Incidence of ⩾2% (Safety Population)

Preferred Term	Study 1118E (N=63) n (%)	Label Pool[a] (N=420) n (%)
Subjects with any Grade 3 or Grade 4 TEAE	**31 (49.2)**	**250 (59.5)**
Neutropenia	11 (17.5)	73 (17.4)
Thrombocytopenia	8 (12.7)	38 (9.0)
Pneumonia	2 (3.2)	31 (7.4)
Anaemia	2 (3.2)	25 (6.0)
Atrial fibrillation	2 (3.2)	19 (4.5)
Febrile neutropenia	2 (3.2)	16 (3.8)
Pyrexia	2 (3.2)	7 (1.7)
Abdominal pain	1 (1.6)	9 (2.1)
Cellulitis	1 (1.6)	10 (2.4)
Dehydration	1 (1.6)	9 (2.1)
Hypertension	1 (1.6)	22 (5.2)
Diarrhoea	0	16 (3.8)
Dyspnoea	0	9 (2.1)
Fatigue	0	13 (3.1)
Hyperuricaemia	0	9 (2.1)
Hyponatraemia	0	9 (2.1)
Urinary tract infection	0	13 (3.1)

TEAE = treatment-emergent adverse event
N = number of subjects in the analysis population.
Events are listed in order of descending frequency in the Study 1118E population.
[a] Pooled data from: Studies 1112 (ibrutinib treated), 1102 (51 previously-treated subjects treated with 420 mg/day), 1104, and 1118E.

An overview of TEAEs in the long-term safety analysis is shown in Table 20 and Table 21.

Table 20: Overall Safety Summary (Long-term Safety Population)

	Long-term Safety Population[a]				
	Ibrutinib Exposure Period				Total
	>0-1 Year (N=198) n (%)	>1-2 Years (N=125) n (%)	>2-3 Years (N=99) n (%)	>3 Years (N=65) n (%)	(N=198) n (%)
Any Grade ≥3 TEAE	115 (58.1)	65 (52.0)	53 (53.5)	28 (43.1)	148 (74.7)
Any Related Grade ≥3 TEAE[b]	43 (21.7)	15 (12.0)	14 (14.1)	4 (6.2)	56 (28.3)
Any Serious TEAE	95 (48.0)	42 (33.6)	20 (20.2)	13 (20.0)	123 (62.1)
Any Grade ≥3 serious TEAE	80 (40.4)	38 (30.4)	18 (18.2)	11 (16.9)	109 (55.1)
Related Serious TEAE	15 (7.6)	1 (0.8)	2 (2.0)	1 (1.5)	19 (9.6)
Grade ≥3 related serious TEAE	13 (6.6)	1 (0.8)	2 (2.0)	1 (1.5)	17 (8.6)
TEAE Leading to Study Drug Discontinuation	21 (10.6)	1 (8.8)	4 (4.0)	0	33 (16.7)
TEAE Leading to Dose Reduction	4 (2.0)	3 (2.4)	2 (2.0)	0	6 (3.0)
Fatal TEAEs	11 (5.6)	6 (4.8)	2 (2.0)	0	19 (9.6)

TEAE = treatment-emergent adverse event
N = number of subjects who were treated in each exposure year. n = number of subjects who experienced any specified events within each exposure year. If a subject discontinued treatment at an exposure year end and had TEAE within 30 days after last dose at the beginning of the next exposure year, the TEAE is counted back to the last exposure year. % = 100*n/N. 1 year = 365 days.
[a] Pooled data from Study 04753 and Study 1102 subjects integrated with their extension Study 1103 data.
[b] Possibly related or related to study drug per investigator's judgment.

Table 21: Prevalence of Treatment-emergent Adverse Events of Grade 3 or Higher in ⩾5.0 % of Subjects in Any Exposure Period or Overall (Long-term Safety Population)

	Long-Term Safety Population[a]				
	Ibrutinib Exposure Period				Total
System Organ Class Preferred Term	>0-1 Year (N=198) n (%)	>1-2 Years (N=125) n (%)	>2-3 Years (N=99) n (%)	>3 Years (N=65) n (%)	(N=198) n (%)
Subjects with any TEAE	**115 (58.1)**	**65 (52.0)**	**53 (53.5)**	**28 (43.1)**	**148 (74.7)**
Pneumonia	17 (8.6)	9 (7.2)	7 (7.1)	6 (9.2)	32 (16.2)
Hypertension	12 (6.1)	15 (12.0)	20 (20.2)	9 (13.8)	29 (14.6)
Neutropenia	17 (8.6)	7 (5.6)	3 (3.0)	4 (6.2)	24 (12.1)
Thrombocytopenia	10 (5.1)	3 (2.4)	4 (4.0)	1 (1.5)	15 (7.6)
Diarrhoea	6 (3.0)	3 (2.4)	2 (2.0)	1 (1.5)	10 (5.1)
Lymphocyte count decreased	0	2 (1.6)	6 (6.1)	3 (4.6)	7 (3.5)

N = number of subjects who were treated in each exposure year. n = number of subjects who experienced any specified events within each exposure year. If a subject discontinued treatment at an exposure year end and had a TEAE within 30 after the last dose at the beginning of the next exposure year, the TEAE is counted back to the last exposure year. % =100* n/N. 1 year = 365 days
Events are sorted by system organ class alphabetically and decreasing frequency of preferred term in the Total column.
[a] Pooled data from Study 04753 and Study 1102 subjects integrated with their extension Study 1103 data.

Adverse Events of special interest

Haemorrhage

In study 1118E, 44.4% of the patients experienced a haemorrhagic TEAE of any grade. The most common haemorrhagic events (≥5%) of any severity were epistaxis (19.0%), contusion (11.1%), and purpura (6.3%). One (1.6%) patient with von Willebrands disease experienced a major haemorrhagic event consisting of a non-fatal, Grade 3, post-procedural haematoma that was assessed as possibly related to study treatment; the event occurred in association with a bone marrow biopsy, reoccurred at a later time-point at the same site and ibrutinib was discontinued. All other haemorrhagic events in this study were Grade 1 or 2.

In the label pool, 49.3% experienced a haemorrhagic TEAE of any severity. The most common of these events (≥5%) were contusion (15.7%), petechiae (11.9%), epistaxis (11.4%) and increased tendency to bruise (9.3%). Grade 3 or 4 haemorrhagic events were experienced by 3.6% of the patients in the label pool. Grade 3 or 4 events experienced by more than one patient were subdural hematoma (five patients, 1.2%) and haematuria (two patients, 0.5%). Nineteen patients experienced major haemorrhagic events: post procedural haematoma (1), ecchymosis (1), epistaxis (1), haematuria (2), lower gastrointestinal haemorrhage (1), post procedural haemorrhage (1), splenic haematoma (1), spontaneous haematoma (1), subdural haematoma (8), traumatic haematoma (1) and vitreous haemorrhage (1).

In 6 of the 8 cases of subdural haematoma there was a fall or head trauma or both prior to the event, five of the eight patients had concomitant anticoagulants, in all but three cases the level of platelets was ≥ 100. All but one case did eventually resolve, in the latter case ibrutinib was continued. In two cases there were no fall or head injuries. None of the eight cases was fatal.

In the long-term safety analysis one major haemorrhagic event (subdural haematoma reported during the third year of exposure) was fatal; this subject experienced bilateral subdural hematomas in the setting of severe thrombocytopenia, 30 days after his last dose of ibrutinib which had been discontinued due to disease progression.

Infections

Treatment-emergent adverse events classified in the SOC “infections and infestations” were reported for 73.0% of subjects in Study 1118E. The most commonly reported PTs included sinusitis (19.0%), upper respiratory tract infection (19.0%), folliculitis (11.1%), pneumonia (7.9%), urinary tract infection (7.9%), and influenza (6.3%). Infections of Grade 3-4 severity were observed in 14.3% of the patients and pneumonia was the most common type of infection of Grade 3-4 severity (eg, pneumonia, pneumonia haemophilus and pneumonia influenzal). In addition, other Grade- 3 infections reported by a single patient each included cellulitis, herpes zoster disseminated, influenza, pleural infection, streptococcal endocarditis and superinfection bacterial. Serious infectious events were reported in 17.5% of the patients. None were fatal. None of the infections resulted in treatment discontinuation or dose reduction, and no atypical infections were reported.

According to the long-term safety analysis, 5 subjects died due to infections: two (1.0%) subjects during the first year of exposure (pneumonia events), 2 (1.6%) subjects during the second year of exposure (sepsis and pneumonia events), and 1 (1.0%) subject during the third year of exposure (pneumonia). Overall, 33.8% of subjects in the long-term safety population experienced a Grade 3 or higher infectious TEAEs (23.2% for ≤ 1 year, 21.6% for >1 to 2 year, 14.1% for >2 to 3 year, and 12.3% for >3 year exposure periods). The most common (≥ 3%) Grade 3 or higher infections were

pneumonia (16.2%), cellulitis (3.5%), and sepsis (3.5%). The prevalence of serious TEAEs in the SOC Infections and Infestations for the long-term safety population was 23.7% for ≤ 1 year, 20.8% for >1 to 2 year, 11.1% for >2 to 3 year, and 12.3% for >3 year exposure periods. Infectious TEAEs led to ibrutinib discontinuation in 3.0% of subjects during the first year of exposure and 3.2% of subjects during the second year; no subject with >2 years of ibrutinib exposure were discontinued due to an infectious TEAE.

Cytopenias

A comparison between WM (Study 1118E) and CLL/SLL/MCL (Label Pool) patients in terms of haematologic TEAEs is reported in Table 22.

Table 22: Summary of Hematologic Treatment-emergent Adverse Events (Safety Population)

	Study 1118E (N=63) n (%)	Label Pool[a] (N=420) n (%)
Neutropenia		
Any grade TEAE	16 (25.4)	91 (21.7)
Grade 3 or 4 TEAE	11 (17.5)	73 (17.4)
Serious TEAE	1 (1.6)	5 (1.2)
TEAE leading to dose reduction	1 (1.6)	9 (2.1)
TEAE leading to treatment discontinuation	0	1 (0.2)
Anemia		
Any grade TEAE	10 (15.9)	87 (20.7)
Grade 3 or 4 TEAE	2 (3.2)	25 (6.0)
Serious TEAE	0	6 (1.4)
TEAE leading to dose reduction	0	1 (0.2)
TEAE leading to treatment discontinuation	0	0
Thrombocytopenia		
Any grade TEAE	11 (17.5)	75 (17.9)
Grade 3 or 4 TEAE	8 (12.7)	38 (9.0)
Serious TEAE	2 (3.2)	4 (1.0)
TEAE leading to dose reduction	3 (4.8)	3 (0.7)
TEAE leading to treatment discontinuation	1 (1.6)	1 (0.2)
Febrile neutropenia		
Any grade TEAE	2 (3.2)	17 (4.0)
Grade 3 or 4 TEAE	2 (3.2)	16 (3.8)
Serious TEAE	1 (1.6)	12 (2.9)
TEAE leading to dose reduction	1 (1.6)	2 (0.5)
TEAE leading to treatment discontinuation	0	0

TEAE = treatment-emergent adverse event
N = number of subjects in the analysis set
[a] Pooled data from: Studies 1112 (ibrutinib treated), 1102 (51 previously-treated subjects treated with 420 mg/day), 1104, and 1118E.

In the long-term safety population, the prevalence of Grade 3 or higher TEAEs in terms of Blood and Lymphatic System Disorders remained stable during the second and third year of exposure (19.7% for ≤ 1 year, 11.2% for >1 to 2 year, 11.1% for >2 to 3 year, and 7.7% for >3 year exposure periods). One subject was discontinued due to thrombocytopenia occurred during the first year of exposure.

Cardiac Arrhythmias

Cardiac arrhythmias including atrial fibrillation (7.9%), sinus tachycardia and sinus bradycardia (1.6% each), were reported in the 1118E study. No cases of atrioventricular block or atrial flutter were reported.

In the label pool, cardiac arrhythmia TEAEs reported in ≥1% of the 420 subjects treated with ibrutinib were atrial fibrillation (8.1%), sinus tachycardia (1.9%), sinus bradycardia (1.2%), and atrial flutter (1.0%).

Grade 3 or higher treatment-emergent cardiac arrhythmias reported overall in ≥ 1% of subjects in the long-term safety population were atrial fibrillation (4.5%) and atrial flutter (1.0%).

Atrial Fibrillation and Atrial Flutter

Atrial fibrillation was reported for 5 patients in the 1118E study whereof three Grade 1-2 and two Grade 3. For 3 subjects, these events were reported as related to ibrutinib. Review of the medical history of the 5 patients with atrial fibrillation revealed that 3 out of the 5 patients had a prior history of atrial fibrillation. Discontinuation of ibrutinib therapy was reported for one patient with Grade-2 atrial fibrillation which worsened to Grade-3 atrial fibrillation and led to treatment discontinuation. None of the TEAEs of atrial fibrillation in Study 1118E were fatal.

In the label pool, atrial fibrillation and atrial flutter TEAEs of any grade were reported in 34 (8.1%) and 4 (1.0%) patients respectively. A total of 37 patients experienced a TEAE of atrial fibrillation and/or atrial flutter in the label pool (one patient experienced both TEAEs) whereof Grade 3 or 4 TEAEs of atrial fibrillation/atrial flutter were reported in 20 (54 %) patients respectively. None of the events of atrial fibrillation/flutter were fatal. Serious TEAEs of atrial fibrillation were reported in 20 patients while atrial flutter was serious in one patient. In two of the 37 patients (5.4%) atrial fibrillation and/or flutter events led to a dose reduction or treatment discontinuation.

In the long-term safety population the prevalence of Grade 3 or higher atrial fibrillation was 2.0% for ≤ 1 year, 2.4% for >1 to 2 year, 0% for >2 to 3 year, and 3.1% for >3 year annual exposure periods. The prevalence of Grade 3 or higher atrial flutter was 0%, 0.8%, 1.0% during the first, second, and third year of exposure, respectively, and 0% during the >3 year exposure period. Serious TEAEs of atrial fibrillation occurred in 5.6% of subjects overall, with a prevalence rates of 3.0%, 2.4%, and 0% during the first, second, and third year of exposure, respectively, and 3.1% during the >3 years exposure period. Serious TEAEs of atrial flutter occurred in 1.0% of subjects overall, with a prevalence of 0%, 0.8%, and 1.0% of subjects in the first, second and third years of exposure, and 0% during the >3 year annual exposure period. Treatment-emergent events of atrial fibrillation or atrial flutter were not fatal in any subject in the long-term safety population and no subject discontinued study treatment due to these events.

Tumor Lysis Syndrome (TLS)

No cases of TLS were reported in Study 1118E.

Four of the 420 patients (1.0%) in the label pool experienced TLS, each in the setting of disease progression. Events were assessed as Grade 3 or 4 in severity for three of these patients, one of which was serious (0.2%). None of the events of TLS were fatal, and none led to a reduction in the ibrutinib dose or treatment discontinuation.

Hypersensitivity

No cases of anaphylactic reactions were reported among patients treated with ibrutinib in Study 1118E or in the larger label pool.

Hypersensitivity-like AE terms such as hypersensitivity, drug hypersensitivity, urticaria, angioedema, swelling of face, and lip swelling were reported at low rates in the label pool (≤1.2%), but were not reported in any subject in Study 1118E. Most of these TEAEs were Grade 1 or 2 in severity, and for only 1 subject (0.2%) was a hypersensitivity-like TEAE assessed as Grade 3 or 4 (angioedema in label

pool). The patient had a history of multiple food and drug allergies, including anaphylaxis, and experienced four episodes of worsening angioedema during the study.

Eye Disorders

In the 1118E study, TEAEs in the SOC "eye disorders" were observed in 19.0% of subjects. The two most common eye disorders were conjunctival hemorrhage and vision blurred (4.8% each). Retinal hemorrhage was reported for one patient. Each of these events was Grade 1-2 in severity. Retinal detachment, which occurred in two patients (3.2%, was of Grade-3 severity in one subject. None of the events in the "eye disorders" SOC were serious nor did they require treatment discontinuation or dose reduction for resolution.

Other Malignancies

Table 23: Incidence of Other Malignancies of Any Grade (Safety Population)

Preferred Term	Study 1118E (N=63)	Label Pool[a] (N=420)
Subjects With Any Other Malignancy Events	**9 (14.3)**	**49 (11.7)**
Skin Cancer	7 (11.1)	34 (8.1)
Basal cell carcinoma	4 (6.3)	16 (3.8)
Squamous cell carcinoma	2 (3.2)	15 (3.6)
Penile squamous cell carcinoma	1 (1.6)	2 (0.5)
Bowen's disease	0	2 (0.5)
Malignant melanoma	0	1 (0.2)
Skin cancer	0	1 (0.2)
Squamous cell carcinoma of skin	0	1 (0.2)
Other	2 (3.2)	16 (3.8)
B-cell lymphoma	1 (1.6)	1 (0.2)
Myelodysplastic syndrome	1 (1.6)	1 (0.2)
Bladder cancer	0	1 (0.2)
Colon adenoma	0	1 (0.2)
Gastrointestinal carcinoma	0	2 (0.4)
Lung adenocarcinoma metastatic	0	1 (0.2)
Lung adenocarcinoma stage I	0	1 (0.2)
Malignant histiocytosis	0	1 (0.2)
Metastatic neoplasm	0	1 (0.2)
Peripheral T-cell lymphoma unspecified	0	1 (0.2)
Prostate cancer	0	1 (0.2)
Sarcoma	0	1 (0.2)
Soft tissue neoplasm	0	1 (0.2)
Squamous cell carcinoma of lung	0	1 (0.2)
Sweat gland tumour	0	1 (0.2)
Thyroid neoplasm	0	1 (0.2)

N = number of subjects in the analysis set
All malignancies during the study are included regardless if within or beyond 30 days of last dose.
Events are listed in order of descending frequency in the Study 1118E population.
[a] Pooled data from: Studies 1112 (ibrutinib treated), 1102 (51 previously-treated subjects treated with 420 mg/day), 1104, and 1118E.
Source: Mod5.3.5.3/ISS/Tab2.10.1.

Gastrointestinal Disorders

In Study 1118E, the MedDRA SOC Gastrointestinal Disorders was associated with the highest incidence of TEAEs (79.4%), with events of diarrhea (36.5%), nausea (20.6%), stomatitis (14.3%), and gastroesophageal reflux disease (12.7%) being the most common. For one patient the GI TEAE was assessed as severe (Grade 3 abdominal pain). There were no Grade 4 reports. None of the GI TEAEs reported in study 1118E led to treatment discontinuation.

As in study 1118E, the SOC Gastrointestinal Disorders was associated with the highest incidence of TEAEs (82.4%) in the label pool, but relatively few patients had Grade 3 (n=35, 8.3%). There were no

Grade 4 events reported. Grade 3 GI TEAEs reports included diarrhea (16 subjects, 3.8%), abdominal pain (9 subjects, 2.1%), nausea (5 subjects, 1.2%), and stomatitis (2 subjects, 0.5%). Notable Grade 3 GI TEAEs reported in a single patient in the label pool included colitis, intestinal obstruction, and small intestinal obstruction. For one patient, the GI TEAE was fatal (ileus paralytic). Three patients (0.7%) had GI TEAEs that led to discontinuation of ibrutinib treatment; for two patients, the event was severe (diarrhea). There were two patients with reports of pancreatitis-related TEAEs in the label pool (pancreatitis, pancreatitis chronic). One of the events of pancreatitis was considered serious but did not result in ibrutinib discontinuation.

Renal Events

In study 1118E, TEAEs of any grade in the MedDRA SOC Renal and Urinary Disorders were reported in 3 subjects (4.8%) consisting of single reports of hematuria, renal failure acute, and urinary tract pain (1.6% each). Each of the TEAEs was assessed as Grade 1 or 2 and none were reported as serious or resulted in a dose reduction or treatment discontinuation.

In the label pool, TEAEs of any grade were reported in a higher proportion of subjects (15.7%) compared with study 1118E although the most common events were similar for the two safety populations. The most common TEAEs (≥ 2%) in the label pool were pollakiuria (3.6%), dysuria (2.9%), hematuria (2.9%), and renal failure acute (2.9%). Grade 3 or 4 TEAEs (3.3%) as well as serious events (2.4%) were infrequent in the label pool, of which renal failure acute (5 five patients [1.2%], 4 events were serious) was the most common severe and serious event. For one patient, the renal event (renal failure acute) was fatal. No TEAE resulted in a reduction of the ibrutinib dose or treatment discontinuation.

Hepatic Events

One patient (1.6%) in study 1118E had a hepatobiliary TEAE. The event, cholecystitis, was reported as a nonfatal, serious event. The reported event did not result in a reduction of the dose or treatment discontinuation.

In the label pool, TEAEs of any grade in the MedDRA SOC Hepatobiliary Disorders were reported in 3.8% of subjects, with hyperbilirubinemia (1.9%) and cholecystitis (1.0%) being the only events in this SOC reported in 1% or more of the patients. For three patients (0.7%), the hepatobiliary TEAEs were assessed as Grade 3 or 4 in severity, and these events consisted of single patients with hyperbilirubinemia, cholecystitis, and cholestasis (0.2% each). No patient had a fatal hepatobiliary event. Serious hepatobiliary TEAEs were reported in 3 (0.7%) patients (2 reports of cholecystitis; 1 report of cholestasis). One (0.2%) patient experienced a hepatic TEAE that resulted in a reduction of the dose (hepatic function abnormal) while no patient experienced a hepatobiliary TEAE that resulted in discontinuation of ibrutinib treatment.

Hypertension

Hypertension was reported as a treatment-emergent adverse event for 5 subjects (7.9%) in Study 1118E; the event was assessed as Grade 3 in severity for 1 subjects. Among the 420 subjects treated with ibrutinib in the label pool, hypertension was reported in 47 (11.2%) subjects; the event was assessed as Grade 3 or 4 in severity for 22 (5.2%) of these subjects. In addition, a treatment-emergent adverse event of blood pressure increased was reported for 3 subjects (0.7%), 1 of which was assessed as Grade 3 or 4. One subject (0.2%) in the label pool required an ibrutinib dose reduction as a result of an adverse event of hypertension. Thus, albeit that the absolute numbers of subjects experiencing treatment-emergent hypertension was relatively low, there appears to be no

increase in the frequency of treatment-emergent hypertension in Study 1118E when compared to rates expected based on previous experience with ibrutinib.

Serious adverse event / deaths / other significant events

Serious Adverse Events

Treatment-emergent Serious Adverse Events by SOC, Preferred Term and Severity are shown in Table 24.

Table 24: Serious Treatment-emergent Adverse Events (Any Grade) with Subject Incidence ≥ 1% (Safety Population)

System Organ Class Preferred Term	Study 1118E (N=63) n (%)	Label Pool[a] (N=420) n (%)
Subjects with any Serious TEAE	**24 (38.1)**	**226 (53.8)**
Blood and Lymphatic Disorders	4 (6.3)	31 (7.4)
Thrombocytopenia	2 (3.2)	4 (1.0)
Febrile neutropenia	1 (1.6)	12 (2.9)
Neutropenia	1 (1.6)	5 (1.2)
Anaemia	0	6 (1.4)
Cardiac Disorders	2 (3.2)	36 (8.6)
Atrial fibrillation	1 (1.6)	20 (4.8)
Sinus tachycardia	1 (1.6)	1 (0.2)
Gastrointestinal Disorders	0	25 (6.0)
Diarrhoea	0	6 (1.4)
Abdominal pain	0	5 (1.2)
General Disorders and Administration Site Conditions	4 (6.3)	34 (8.1)
Pyrexia	3 (4.8)	15 (3.6)
Chills	1 (1.6)	2 (0.5)
Malaise	1 (1.6)	2 (0.5)
Non-cardiac chest pain	0	4 (1.0)
Hepatobiliary Disorders	1 (1.6)	3 (0.7)
Cholecystitis	1 (1.6)	2 (0.5)
Infections and Infestations	11 (17.5)	111 (26.4)
Pneumonia	2 (3.2)	38 (9.0)
Cellulitis	1 (1.6)	8 (1.9)
Herpes zoster disseminated	1 (1.6)	2 (0.5)
Influenza	1 (1.6)	1 (0.2)
Pleural infection	1 (1.6)	1 (0.2)
Pneumonia haemophilus	1 (1.6)	1 (0.2)
Pneumonia influenzal	1 (1.6)	1 (0.2)
Pneumonia viral	1 (1.6)	2 (0.5)
Streptococcal endocarditis	1 (1.6)	1 (0.2)
Upper respiratory tract infection	1 (1.6)	3 (0.7)
Lower respiratory tract infection	0	5 (1.2)
Lung infection	0	6 (1.4)
Sepsis	0	6 (1.4)
Sinusitis	0	4 (1.0)
Urinary tract infection	0	10 (2.4)

Injury, Poisoning, and Procedural Complications	1 (1.6)	17 (4.0)
Post-procedural haematoma	1 (1.6)	1 (0.2)
Subdural haematoma	0	7 (1.7)
Metabolism and Nutrition Disorders	1 (1.6)	8 (1.9)
Dehydration	1 (1.6)	4 (1.0)
Neoplasms Benign, Malignant, and Unspecified (incl. polyps)	2 (3.2)	33 (7.9)
B-cell lymphoma	1 (1.6)	1 (0.2)
Myelodysplastic syndrome	1 (1.6)	1 (0.2)
Mantle cell lymphoma	0	11 (2.6)
Nervous System Disorders	1 (1.6)	10 (2.4)
Syncope	1 (1.6)	2 (0.5)
Renal and Urinary Disorders	0	10 (2.4)
Renal failure acute	0	5 (1.2)
Respiratory, Thoracic, and Mediastinal Disorders	1 (1.6)	16 (3.8)
Pleural effusion	1 (1.6)	3 (0.7)
Dyspnoea	0	4 (1.0)

TEAE = treatment-emergent adverse event.
N = number of subjects in the analysis population.
Events are listed within each SOC in order of descending frequency in the Study 1118E population.
[a] Pooled data from: Studies 1112 (ibrutinib treated), 1102 (51 previously-treated subjects treated with 420 mg/day), 1104, and 1118E.

Deaths

In Study 1118E, one patient died due to worsening of pleural effusion 22 days after the last dose of study drug. The condition was attributed to disease progression.

In the label pool, TEAEs with a fatal outcome were reported for 38 subjects (9.0%) and were considered events related to disease progression and infections. Adverse events leading to death in more than 1 subjects in the label pool included MCL (8 subjects, all with MCL at baseline), pneumonia (including *Pneumocystis jirovecii* pneumonia; 6 subjects), Richter's syndrome (3 subjects, all with CLL at baseline), sepsis or neutropenic sepsis (4 subjects), cardiac arrest (2 subjects), and CLL (2 subjects, both with CLL at baseline). The primary cause of death for other subjects included events considered to be related to their underlying oncologic disease, sudden death, systemic inflammatory response syndrome, renal or respiratory failure, or shock.

Laboratory findings

An overview of the main haematologic and chemistry laboratory abnormalities is reported in Table 25 and Table 26, respectively:

Table 25: Haematology Worst Treatment-Emergent Laboratory Abnormalities (Safety Population)

		Study 1118E (N=63)		Label Pool[a] (N=420)	
	Direction of Toxicity	Any Grade n (%)	Grade 3+4 n (%)	Any Grade n (%)	Grade 3+4 n (%)
Hemoglobin	Low	8/63 (12.7)	5/63 (7.9)	146/399 (36.6)	9/399 (2.3)
Platelets	Low	27/63 (42.9)	8/63 (12.7)	229/379 (60.4)	39/379 (10.3)
Absolute neutrophil count	Low	28/63 (44.4)	12/63 (19.0)	209/402 (52.0)	104/402 (25.9)

CLL = chronic lymphocytic leukemia; CTCAE = Common Terminology Criteria for Adverse Events; IWCLL = International Workshop on Chronic Lymphocytic Leukemia; SLL = small lymphocytic lymphoma
N = number of subjects who received at least 1 dose of ibrutinib in each analysis population.
Toxicities were graded using the IWCLL 2008 guidelines for CLL/SLL and CTCAE version 4.03 for other histology types. Abnormalities worsened after first dose of study treatment up to 30 days after the last dose of study drug were included in this table.
[a] Pooled data from Studies 1112 (ibrutinib treated), 1102, 1104 (51 previously-treated subjects treated with 420 mg/day), and 1118E.

Table 26: Worst Postbaseline Chemistry Toxicity Grade (Any Grade) (Safety Population)

		Study 1118E (N=63)		Label Pool[a] (N=420)	
	Direction of Toxicity	Any Grade	Grade 3+4	Any Grade	Grade 3+4
Alanine aminotransferase (U/L)	High	4/63 (6.3)	0/63 (0.0)	56/419 (13.4)	0/419 (0.0)
Alkaline phosphatase (U/L)	High	6/63 (9.5)	0/63 (0.0)	72/419 (17.2)	3/419 (0.7)
Aspartate aminotransferase (U/L)	High	5/63 (7.9)	0/63 (0.0)	70/419 (16.7)	0/419 (0.0)
Bilirubin (µmol/L)	High	7/63 (11.1)	0/63 (0.0)	62/418 (14.8)	3/418 (0.7)
Creatinine (µmol/L)	High	13/63 (20.6)	0/63 (0.0)	78/419 (18.6)	0/419 (0.0)
Creatinine clearance (mL/min)	Low	13/62 (21.0)	0/62 (0.0)	102/418 (24.4)	5/418 (1.2)
Potassium (mmol/L)	High	3/63 (4.8)	0/63 (0.0)	35/419 (8.4)	1/419 (0.2)
	Low	4/63 (6.3)	1/63 (1.6)	49/419 (11.7)	6/419 (1.4)
Sodium (mmol/L)	High	12/63 (19.0)	0/63 (0.0)	71/419 (16.9)	0/419 (0.0)
	Low	6/63 (9.5)	1/63 (1.6)	75/419 (17.9)	19/419 (4.5)

N = number of subjects with baseline and at least 1 post-baseline test
Treatment-emergent laboratory abnormalities were defined as abnormalities worsened after first dose of study treatment up to 30 days after the last dose of study drug.
[a] Pooled data from Studies 1112 (ibrutinib treated), 1102 (51 previously-treated subjects treated with 420 mg/day), 1104, and 1118E.

Safety in special populations

Age

Close to 50% of the patients in the 1118E study were ≥ 65 years of age. In the ≥ 65 years subgroup, 58.1% of subjects experienced Grade 3 or higher TEAEs *versus* 43.8% in the younger subgroup; concerning serious TEAEs and TEAEs leading to discontinuation, the percentage was 48.4% vs 28.1% and 12.9% vs 6.3%, respectively.

Neutropenia was the only Grade 3 or 4 TEAE experienced by a higher proportion (absolute difference ≥ 10% higher) of patients in one age subgroup *versus* the other one and was reported by 25.0% of subjects <65 years of age compared to 9.7% of those aged ≥ 65 years.

AEs according to age-groups in Study 1118E and in the pooled safety population are shown in Table 27 and Table 28, respectively:

Table 27: Overall Summary of Treatment-emergent Adverse Events by Age Categories; Safety Population (Study 1118E)

	1118E			
	Age <65	Age 65 - 74	Age 75 - 84	Age 85+
Population: Safety	32	20	8	3
Subjects with any treatment-emergent adverse events	32 (100.0%)	20 (100.0%)	8 (100.0%)	3 (100.0%)
Fatal	0	1 (5.0%)	0	0
Serious	9 (28.1%)	8 (40.0%)	4 (50.0%)	3 (100.0%)
Withdrawal	2 (6.3%)	3 (15.0%)	1 (12.5%)	0
CNS (confusion/extrapyramidal)	0	0	0	0
AE related to fall	1 (3.1%)	0	1 (12.5%)	0
Cardiac disorder (SOC)	4 (12.5%)	3 (15.0%)	3 (37.5%)	0
Cerebrovascular events (SMQ)	0	1 (5.0%)	0	0
Infections	21 (65.6%)	17 (85.0%)	6 (75.0%)	2 (66.7%)

Note: Percentages calculated with the number of safety population in each age group as denominator.

Table 28: Overall Summary of Treatment-emergent Adverse Events by Age Categories; Safety Population (Label Pool)

	Label pool*			
	Age <65	Age 65 - 74	Age 75 - 84	Age 85+
Population: Safety	174	160	81	5
Subjects with any treatment-emergent adverse events	174 (100.0%)	159 (99.4%)	81 (100.0%)	5 (100.0%)
Fatal	7 (4.0%)	15 (9.4%)	10 (12.3%)	0
Serious	62 (35.6%)	84 (52.5%)	44 (54.3%)	4 (80.0%)
Withdrawal	7 (4.0%)	20 (12.5%)	12 (14.8%)	0
CNS (confusion/extrapyramidal)	2 (1.1%)	4 (2.5%)	3 (3.7%)	0
AE related to fall	3 (1.7%)	10 (6.3%)	5 (6.2%)	0
Cardiac disorder (SOC)	21 (12.1%)	28 (17.5%)	19 (23.5%)	0
Cerebrovascular events (SMQ)	2 (1.1%)	6 (3.8%)	2 (2.5%)	0
Infections	129 (74.1%)	125 (78.1%)	56 (69.1%)	3 (60.0%)

Note: Percentages calculated with the number of safety population in each age group as denominator.
* Pooled data from: Study 1112 (ibrutinib treated), 1102 (51 previously-treated subjects treated with 420mg/day), 1104 and 1118E.

Safety related to drug-drug interactions and other interactions

N/A

Discontinuation due to adverse events

TEAEs leading to discontinuation and dose reduction are summarised in Table 29 and Table 30, respectively.

Table 29: Treatment-emergent Adverse Events Leading to Treatment Discontinuation in ⩾1% of Subjects (Safety Population)

System Organ Class Preferred Term	Study 1118E (N=63) n (%)	Label Pool[a] (N=420) n (%)
Subjects with any TEAE Leading to Discontinuation	**6 (9.5)**	**50 (11.9)**
Atrial fibrillation	1 (1.6)	2 (0.5)
B-cell lymphoma	1 (1.6)[b]	1 (0.2)
Myelodysplastic syndrome	1 (1.6)	1 (0.2)
Pleural effusion	1 (1.6)	1 (0.2)
Post procedural haematoma	1 (1.6)	1 (0.2)
Thrombocytopenia	1 (1.6)	1 (0.2)
Pneumonia	0	7 (1.7)
Sepsis	0	4 (1.0)
Subdural haematoma	0	5 (1.2)

TEAE = treatment-emergent adverse event
N = number of subjects in the analysis set.
Events are listed in order of descending frequency in the Study 1118E population.
[a] Pooled data from: Studies 1112 (ibrutinib treated), 1102 (51 previously-treated subjects treated with 420 mg/day), 1104, and 1118E.
[b] This event was further described as disease transformation to B-cell lymphoma with blastic morphology

Table 30: Treatment-emergent Adverse Events Leading to Dose Reduction in ⩾1% of Subjects (Safety Population)

Preferred Term	Study 1118E (N=63) n (%)	Label Pool[a] (N=420) n (%)
Subjects with any TEAE Leading to Dose Reduction	**7 (11.1)**	**39 (9.3)**
Thrombocytopenia	3 (4.8)	3 (0.7)
Febrile neutropenia	1 (1.6)	2 (0.5)
Neutropenia	1 (1.6)	9 (2.1)
Pruritus	1 (1.6)	1 (0.2)
Stomatitis	1 (1.6)	1 (0.2)
Tenosynovitis	1 (1.6)	1 (0.2)
Diarrhoea	0	8 (1.9)

TEAE = treatment-emergent adverse event.
N = number of subjects in the analysis set.
Events are listed in order of descending frequency in the Study 1118E population.
[a] Pooled data from: Studies 1112 (ibrutinib treated), 1102 (51 previously-treated subjects treated with 420 mg/day), 1104, and 1118E.

Post marketing experience

N/A

2.5.1. Discussion on clinical safety

The safety evaluation includes a total of 420 patients that constitutes the integrated dataset (label pool) which includes the 63 WM patients in the pivotal 1118E study, 195 CLL/SLL patients from Study 1112, 51 CLL/SLL patients from Study 1102 and 111 MCL subjects from Study 1104. The median duration of exposure to ibrutinib in the 1118E study, was about 12 months with a median average daily dose of 416 mg/day and 14.1 months in the pooled data with a median average daily dose of 419 mg/day.

All patients in study 1118E reported at least one TEAE. The highest incidence was reported for gastrointestinal disorders (79 %) and the most common TEAEs included diarrhoea (37 %), neutropenia (25 %), nausea, fatigue, and muscle spasms (21 % each), epistaxis, sinusitis and upper respiratory tract infection (19 % each), thrombocytopenia (18 %), and anaemia (16 %). TEAEs in Infections and Infestations were also reported in a high proportion (73 %). The most common included sinusitis and upper respiratory tract infection and folliculitis. Both the WM disease in itself and ibrutinib (by way of action) may contribute to the increase in susceptibility for infections.

For both the WM and CLL populations, an informative overview of the prevalence of the most commonly reported TEAEs illustrated by histograms have been provided by the MAH (data not shown). For the WM population as opposed to the CLL population, events of diarrhoea decrease over time and fatigue remain at the same low level throughout the treatment periods. There were no obvious accumulation/increases over time in regard to the WM population and overall no concern was raised. Any discrepancies between the two populations are considered related to the differences in disease characteristics between the two populations.

About 50 % of the patients in the 1118E study reported any Grade 3 or 4 events. The most frequently reported Grade 3-4 TEAEs were hematologic events including neutropenia (18 %) and thrombocytopenia (13 %). Cumulatively, infectious events (including pneumonia and other respiratory events) were also frequently reported Grade 3-4 TEAEs (14 %). Serious TEAEs were reported for 38 % of the patients.

In the 1118E study one patient died while on study however this was attributed to disease progression.

About 10 % of the patients in the 1118E study experienced TEAEs leading to discontinuation of study drug and 11 % had TEAEs leading to dose reduction whereof four patients with Grade ≥ 3. Although recognising the relatively high proportions of TEAEs, serious TEAEs and Grade≥ 3 events reported in the study, the proportion of patients that discontinued was considered low. Seven patients in study 1118E and 6 in the CLL population reported events leading to dose reductions and all of them recovered/resolved. In the CLL population all events leading to dose reductions recovered/resolved except for one case of conjunctivitis.

In study 1118E, 44% of the patients experienced a haemorrhagic TEAE of any grade. The most common were epistaxis (19 %), contusion (11 %), and purpura (6 %). One patient (with Von Willebrand disease) experienced a major haemorrhagic event consisting of a non-fatal, Grade 3, post-procedural haematoma (bone marrow biopsy).

In the label pool, 49 % experienced a haemorrhagic TEAE of any severity. The most common of these events were contusion (16 %), petechiae (12 %), epistaxis (11 %) and increased tendency to bruise (9 %). Grade 3 or 4 haemorrhagic events were experienced by 3.6%. A total of eight cases were reported of subdural haematoma whereof six cases were related to a fall/ head trauma. After review of study narratives it appeared that several were associated with fall/ trauma, however an adequate

account of events of fall occurring in the WM study as well as for the CLL population has been provided and no concern has been evoked.

Cases of leukostasis have previously been reported in association with ibrutinib. There were however, no cases reported in the 1118E study.

Atrial fibrillation/ flutter have been reported in association with ibrutinib. The clinical relevance is however un-clear, but there were overall few discontinuations/ dose reductions due to these events and atrial fibrillation/ flutter are adequately highlighted in the SmPC section 4.4 with recommendations and measures to be considered/ taken.

No new safety concerns with regard to hepatic, renal or laboratory observations have been identified.

Based on the data from the long term safety population (198 patients) after a median of 2 years of follow up, it appears that there is no evidence of any cumulative toxicity.

In general no new ADRs have been included in the SmPC however based on the updated pooled analysis the frequencies of the following ADRs have been revised: epistaxis, skin infections and urinary tract infection.

2.5.2. Conclusions on clinical safety

From the safety perspective, the safety profile of ibrutinib in patients with WM is overall consistent with what is already known in ibrutinib treated patients with CLL/SLL and MCL. No new safety signal has been evoked. No significant tolerability issues in the WM population as compared to the overall integrated dataset including CLL/SLL and MCL patient populations have been identified. In addition, data from the long-term safety population is not indicative of any cumulative toxicity.

It is concluded that ibrutinib has an acceptable safety profile to support the extension of the indication to include WM.

2.5.3. PSUR cycle

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.6. 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 4.0 is acceptable, barring any amendments to the safety specification that may be necessary in the light of questions on clinical safety raised by CHMP.

No new safety concerns were identified during the evaluation of this application but the safety specification of the RMP was updated with information on the epidemiology of Waldenström macroglobulinemia (WM) and with the findings from clinical trials in WM patients (4 subjects with WM from Study PCYC-04753and 63 subjects with WM from Study 1118E).

No new pharmacovigilance activities have been proposed in this RMP update.

Finally, no significant changes to the risk minimisation measures have been proposed in this update.

As requested, TLS has been moved from an Important Potential Risk to an Important Identified Risk.

TLS is included in section 4.4 of the SmPC as well as listed in section 4.8 as an adverse reaction. Based on the risk assessment, the MAH believes that the wording included in the SmPC along with the pharmacovigilance plan and monitoring through routine pharmacovigilance activities are sufficient to manage the risk. No additional risk-minimisation activities are proposed. This is supported.

Relevant sections of the proposed RMP version 4.1 have been satifactorily updated and the RMP is therefore acceptable.

The CHMP endorsed the PRAC advice without further changes.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC.

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been submitted which was acceptable based on the limited PI changes.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Based on the results of the primary endpoint (cut-off date 28 February 2014 corresponding to a median follow-up of 14.8 months) Overall Response Rate was 87.3% (CI: 76.5%, 94.4%) with the predominant response category being PR, 56%; no CR was obtained. The median time to overall response was 1.0 month (range: 0.69 to 13.37 months). These data were supported by the IRRC assessment.

Furthermore, a sustained (≥8 weeks) improvement in haemoglobin levels, a clinically highly relevant outcome, was reported in 59% of patients overall and in 82% of patients with ≤11 g/dL at baseline. Kaplan-Meier estimate of Progression Free Survival rate was 83.2%. Preplanned subgroup analyses generally showed a reasonably consistent treatment effect across the variables studied.

Uncertainty in the knowledge about the beneficial effects

One uncertainty was about the generalizability of the results to a broader setting, i.e. first line. The assessment of ibrutinib in naïve patients was based only on historical comparisons. However, the observed ORR of 87.3%, as reported in the 1118E study, is reassuring in terms of activity, and numerically superior in inter-study comparisons with most published studies investigating other

monotherapy agents in previously treated and/or naive patients. Furthermore, the presence of the MYD88 L265P mutation in both untreated and previously treated WM patients, supporting the mechanistic rationale for treatment with ibrutinib in the treatment-naive setting.

Risks

Unfavourable effects

The highest TEAE incidence in the Study 1118E was reported for gastrointestinal disorders (79 %) and the most common TEAEs included diarrhoea (37 %), neutropenia (25 %), nausea, fatigue, and muscle spasms (21 % each), epistaxis, sinusitis and upper respiratory tract infection (19 % each), thrombocytopenia (18 %), and anaemia (16 %).

Almost 50 % of the patients reported any Grade 3 or 4 events. The most frequently reported being hematologic events (neutropenia [18 %] and thrombocytopenia [13 %]). One death occurred while on study which was attributed to disease progression.

About 10 % patients experienced TEAEs leading to discontinuation of study drug and seven (11 %) had TEAEs leading to dose reduction whereof four patients with Grade ≥ 3. Although recognizing the relatively high proportions of TEAEs, serious TEAEs and Grade≥ 3 events reported in the 1118E study, patients that discontinued and /or had dose reductions due to TEAEs are considered low.

Uncertainty in the knowledge about the unfavourable effects

No new uncertainties in the knowledge about the unfavourable effects have emerged. Previously known uncertainties including other malignancies, cardiac safety and long term safety are to be addressed in future study updates and within the RMP.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The observed effect in terms of the primary endpoint supported by secondary outcome measures in the pivotal study is clearly of importance for WM patients. An ORR of 87.3%, as reported in the 1118E study, when combined with a sustained improvement of the haemoglobin level in 59% of patients overall, is reassuring in terms of activity, and numerically superior in inter-study comparisons with most published studies investigating other monotherapy agents in previously treated and/or naive patients.

The safety profile of ibrutinib in patients with WM is overall consistent with what is already known in ibrutinib treated patients with CLL/SLL and MCL and no new safety signal has been evoked.

Table 30: Effects Table (data cut-off: 28 February 2014)

Effect	Description	Unit	Ibrutinib	Historical control	Uncertainties / Strength of evidence	References
Favourable Effects						
ORR	Proportion of patients with a minor response or better	%	87.3 (76.5, 94.4)	51-76[1]	Single-arm study; small number of patients (n=63); limited follow-up	Efficacy results: see Tables 11-12. Historical comparison :

Effect	Description	Unit	Ibrutinib	Historical control	Uncertainties / Strength of evidence	References
PFS	18-month progression-free survival	%	83.2	N/A (median 12-21 months)[1]	(median=14.8 months); median duration of response not reached.	see Table 15 and Fig. 7
Haemoglobin Improvement	Proportion of patients with a sustained (≥ 8 weeks) improvement in haemoglobin levels	%	59	N/A		
Unfavourable Effects						
Thrombocytopenia	Incidence of serious TEAE	%	1.0	N/A	The safety profile of ibrutinib in patients with WM is consistent with what is already known in ibrutinib-treated patients with CLL/SLL and MCL	Results are based on the integrated safety data of the 420 patients who received ibrutinib in studies 1112, 1102, 1104, and 1118E; see clinical safety section
Neutropenia	Incidence of serious TEAE	%	2.9	N/A		
Atrial fibrillation	Incidence of serious TEAE	%	4.8	N/A		
Pneumonia	Incidence of serious TEAE	%	9.0	N/A		
Cellutitis	Incidence of serious TEAE	%	1.9	N/A		

Abbreviations: ORR: overall response rate; PFS: progression-free survival; TEAE: treatment-emergent adverse events; WM: Waldenstöm macroglobulineria; CLL: chronic lymphocytic leukemia; SLL: small lymphocytic lymphoma; MCL: mantle cell lymphoma.

Notes: [1] Overall response rate across different trials in relapsed/refactored population (see Table 15).

Benefit-risk balance

The efficacy of ibrutinib in the target population is considered clinically relevant and, in the view of the safety profile, the benefits are considered to outweigh the combined risks and uncertainties. Therefore, the benefit-risk balance is considered positive.

Discussion on the Benefit-Risk Balance

Considering the current treatment landscape and general outcomes in WM, the positive B/R based on reassuring activity and durable responses were reported with ibrutinib in the single-armed 1118E study, with no new major safety or tolerability issues identified, it is sufficient to justify the positive benefit/risk of ibrutinib for the treatment of previously treated WM. The inclusion also of first-line treatment for patients unsuitable for chemo or immunotherapy was based on historical comparisons of results obtained with ibrutinib in the R/R setting with efficacy and safety/tolerability for single drugs and combination therapies in the first line setting. Reference is also made to the presence of the MYD88 L265P mutation in both untreated and previously treated WM patients, supporting the mechanistic rationale for treatment with ibrutinib in the treatment-naive setting. There is no reason to expect inferior efficacy or a worse safety profile in the first line setting for the group of patients unsuitable for chemo or immunotherapy for whom no satisfactory treatment options are currently available.

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 approved		Type
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

Extension of Indication to add treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC and the Package Leaflet have been updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC. Furthermore, an updated RMP version 4.0 was approved as part of the application.

The requested variation proposed amendments to the SmPC and Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to add treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC and the Package Leaflet have been updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC. Furthermore, an updated RMP version 4.0 was approved as part of the application.

Summary

Please refer to the Scientific Discussion Imbruvica-H-C-3791-II-01

Attachments / annexes

1. SmPC and Package Leaflet (changes highlighted) as adopted by the CHMP on 21 May 2015.
2. Rapporteurs initial Assessment Report dated 19 January 2015
3. Co - Rapporteurs initial Assessment Report dated 17 February 2015
4. CHMP Request for supplementary information as agreed by the CHMP on 12 February 2015
5. Joint Rapporteur/Co-Rapporteur Assessment Report on the responses provided by the applicant, dated 20 February 2015
6. PRAC Rapporteur´s RMP Updated Assessment Report dated 20 April 2015, adopted by PRAC on 07 May 2015

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